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REVIEW

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Cite this: *RSC Adv.*, 2020, **10**, 36031

Microwave assisted synthesis of five membered nitrogen heterocycles

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Received 11th June 2020
Accepted 2nd September 2020

DOI: 10.1039/d0ra05150k

rsc.li/rsc-advances

Our continuously changing environment demands sensible and sustainable chemistry. Consequently, organic synthesis started to follow green chemistry principles in recent years. It is observed that microwave (MW) radiation has been widely used as a source of energy in organic synthesis in the past decade. The MW heating approach has evolved into a new green method in organic synthesis since it provides short reaction time, high yields, and high product purities along with a decrease in the rate of by-product formation. Solvent-free reaction protocols worked well under MW irradiation. All these features make MW assisted organic synthesis an environment-friendly approach. In organic synthesis, heterocycles are vital targets especially nitrogen-containing ones because of their prominent presence in natural products and widespread applications in pharmaceutical industries. Five membered nitrogen heterocycles include pyrroles, oxazoles, pyrrolidones, *etc.* among which pyrroles are the most important ones due to their potent biological properties. Even though there are a variety of reaction protocols for the synthesis of pyrroles, a significant development materialized in MW assisted synthesis of pyrroles in the past few years. In this review, we focus on the developments in MW assisted synthesis of pyrroles and other five-membered nitrogen heterocycles.

1 Introduction

Heterocycles are vital targets in organic synthesis especially nitrogen containing ones because of their notable presence in natural products and their wide variety of applications in pharmaceutical industries. Nitrogen containing five membered heterocycles include pyrroles, pyrrolidines, oxazoles, indoles, pyrazoles *etc.* Among which pyrrole was found to be the most important one.

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Pyrroles are nitrogen containing five membered heterocycles whose structural moiety appears in a variety of pharmaceuticals and a large number of biologically active natural products, and also acts as the key factor throughout the total synthesis of these molecules.[1] The major part of porphyrin rings is pyrrole and its derivatives which act as building blocks in chlorophyll, heme, vitamin B_{12}, and bile pigments.[2] Pyrrole containing pharmaceutical compounds acts as fungicides, antibiotics, anti-inflammatory drugs,[3] cholesterol reducing drugs, anti-tumor agents,[4] anti-microbial[5] and many more. Not only in pharmaceuticals but also in polymer chemistry, pyrroles are used as an efficient catalyst for polymerization process, used as corrosion inhibitor,[6] preservative, solvent for resin, terpenes, in metallurgical process.[7] In recent years pyrroles and its derivatives are successfully implemented as organic conducting materials also.[8]

There are a variety of protocols available for the synthesis of pyrroles. Paal–Knorr synthesis, Knorr synthesis, Hantzsch pyrrole synthesis are some of them. The major disadvantages regarding these protocols are they are carried out in presence of acid catalyst in organic solvent medium and the protocols are time consuming ones. Since the constantly changing environment demands a sensible and sustainable chemistry organic synthesis also started to follow green principles. As part of that microwave irradiation introduced in place of conventional heating technique.

Microwave irradiation, one of the most effective nonconventional activation methods, has been illuminating organic synthesis over the last 30 years.[9] Substantial deceleration of reaction time (hours to minutes) and greater yield rendered this alternative heating source an attractive chemical synthesis method. This thermal control provides fine tuning of the parameters of the reaction and less chemical waste. Advantages such as elimination of side reactions and cost-effective response have also increased the popularity of microwave-assisted reactions. The first microwave-irradiated synthetic reaction was reported in 1969, but experiments performed by Gedye and Giguere made it more popular.[10] The interaction of microwave energy with organic molecule is due to dielectric heating and the efficient interaction of polar molecules such as ethanol, water, acetonitrile, *etc.* with microwaves leads to rapid heat generation. The convection mode of microwave heating increases the reaction rate whereas the external heating source of traditional heating slows down the transfer of energy and hence the reaction rate.[11] Usual domestic ovens were used in the early stages of microwave irradiated chemical synthesis while nowadays we have sophisticated monomods and multimodes.

The major advantages of implementing microwave heating over conventional heating technique are shorter reaction time,

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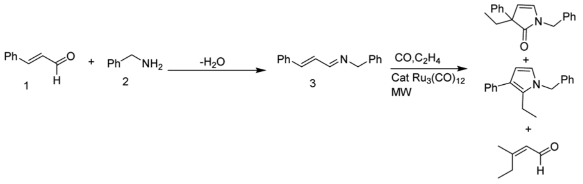
higher yield under milder reaction conditions, neat reactions worked well under microwave irradiation, higher purity of the products formed, and suppression in the rate of by-product formation. All these features make microwave assisted reactions more towards a greener and environment-friendly process.

In the past few years microwave irradiation is found to be applied in the synthesis of nitrogen containing five membered heterocycles in a large scale. And it is observed that most of these protocols were carried out either in water or under solvent-free conditions. Here, in this review we summarize the developments in microwave assisted synthesis of pyrroles, pyrrolidine, indoles, quinoline and its derivatives in the past five years.

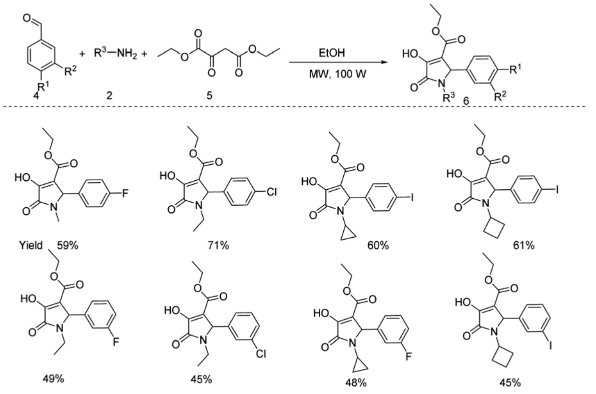
2. Microwave assisted synthesis of pyrrole and derivatives

Feller and Imhof developed a microwave mediated Ru catalyzed four component (primary amine **2** and α,β-unsaturated aldehyde **1** with ethylene and carbon monoxide) reaction pathway for the synthesis of substituted pyrroles and chiral γ-lactams (Scheme 1).[12] As compared to the conventional heating method, this protocol took lesser reaction time and the precatalyst ($Ru_3(CO)_{12}$) loading was also found to be lower.



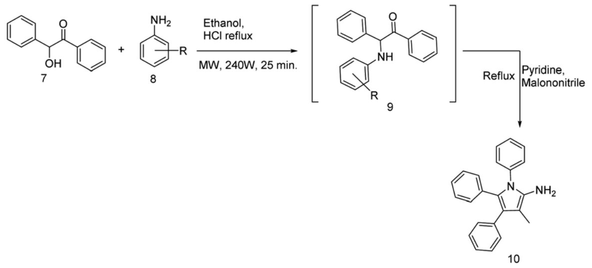
Scheme 1 Microwave assisted ruthenium catalysed synthesis of pyrroles.

A new methodology for microwave assisted multicomponent reaction for the synthesis of substituted pyrrole derivatives **6** from sodium diethyl oxaloacetate **5**, aromatic aldehydes **4** and primary amines **2** was reported by Komiotis and coworkers (Scheme 2).[13] They studied the scope of this reaction in a variety of substrate molecules under optimized reaction conditions (sodium diethyl oxaloacetate (1 equiv.), amine (1 equiv.) and aldehyde (1 equiv.) in ethanol under MW, 100 W) and obtained average to good yields. From the pharmacological studies conducted, they found that some of the substituted pyrroles show excellent cytostatic and antiviral activities.



Scheme 2 Three-component reaction between sodium diethyl oxaloacetate, amines and aromatic aldehydes under MW irradiation for the synthesis of pyrrole.

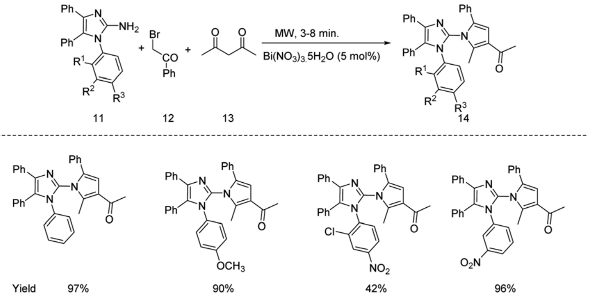
Vyankatesh and coworkers designed a new microwave assisted protocol for the synthesis of 2-amino-4,5-diphenylpyrrole-3-carbonitriles **10** from a heterocyclic compound with substituted anilines **8** (Scheme 3).[14] Under optimized reaction conditions (benzoin **7** (2.12 g, 0.01 mol), **8** and conc. HCl (6–8 drops), ethanol (40 mL), malononitrile (1.66 mg, 0.01 mol), pyridine (1.5 mL), MW, 240 W, 25 min), they explored the applications and limitations of this protocol and obtained good yields. From the pharmacological studies they found that some of the pyrrole derivatives show excellent *in vitro* anti-inflammatory activity.



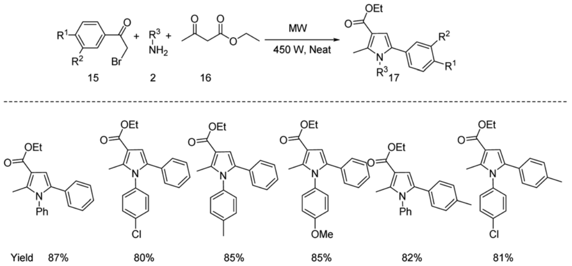
Scheme 3 Microwave assisted protocol for the synthesis of 2-amino-4,5-diphenylpyrrole-3-carbonitriles.

There are few reports on synthesis of pyrrole using enaminones (*in situ* generated) with phenacyl bromide **12**, recently in 2018 Chawla *et al.* designed a new methodology for the microwave assisted synthesis of imidazole substituted pyrroles through a one pot synthesis (Scheme 4).[15] Under the optimized reaction conditions they studied a number of substrates and obtained good to excellent yields.

In 2015 Zhang and coworkers developed an efficient microwave assisted three component (**2**, α-bromoacetophenone **15** and ethyl acetoacetate **16**) one-pot synthesis of *N*-substituted 2-



Scheme 4 Microwave assisted synthesis of imidazole substituted pyrroles.



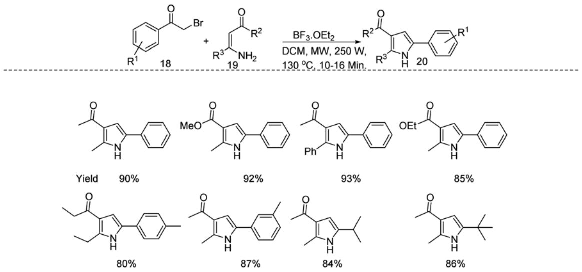
Scheme 5 Microwave assisted one-pot three component (amine, α-bromoacetophenone and ethyl acetoacetate) synthesis of *N*-substituted 2-methyl-1*H*-pyrrole-3-carboxylate derivatives.

methyl-1*H*-pyrrole-3-carboxylate derivatives **17** (Scheme 5).[16] Here substituted phenacyl bromides are used for studying the scope of the reaction. This protocol is both catalyst- and solvent-free and the substrate scope studies are carried out under the optimized reaction conditions (**15** (1.0 mmol), **16** (2.5 mmol) and **2** (1.0 mmol), MW, 450 W, Neat) in various amines, different α-bromoacetophenone and ethylacetoacetate and obtained good yields.

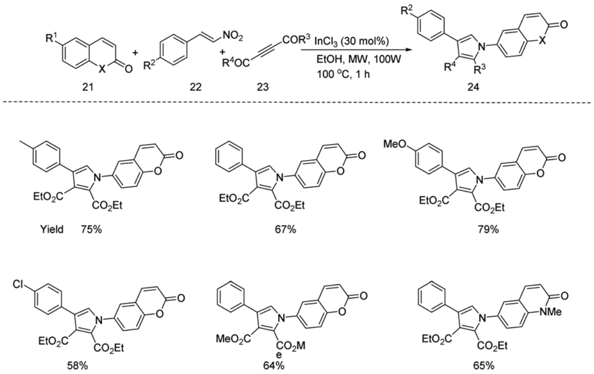
In that same year similar kind of a protocol was reported by Reddy and coworkers. They proposed a new protocol for microwave assisted synthesis of trisubstituted pyrroles **20** from substituted β-amino unsaturated ketone **19** and substituted phenacyl bromide **18** (Scheme 6).[17] The applications and limitations of this protocol was studied in a variety of substrate molecules under the optimized reaction conditions (**19** (1 mmol) and boron trifluoride diethyl etherate (10 mol%), DCM (5 mL), **18** (1 mmol), MW, 10–16 min, 130 °C, 250 W) and obtained good to excellent yields.

A new microwave assisted protocol for the synthesis of 6-(pyrrolyl)coumarin/quinolone derivatives **24** through an indium(III) catalysed one pot three component reaction (6-amino coumarin/quinolones **21**, dialkyl acetylene dicarboxylates **23**, and β-nitrostyrenes **22**) (Scheme 7) was reported by Ansary *et al.*[18] They applied this protocol under optimized reaction condition (**21** (100 mg, 1.0 equiv.), **22** (1.2 equiv.), **23** (1.2 equiv.), EtOH (2 mL) and $InCl_3$ (30 mol%), MW 100 W, 1 h) in a number of different substrates and obtained good yields.

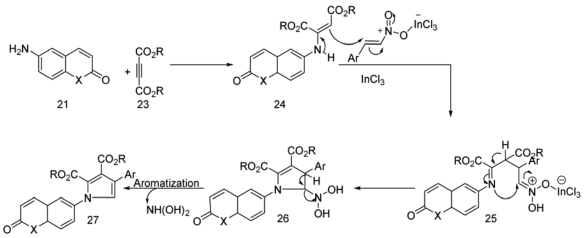
The proposed mechanism evolves nucleophilic addition **21** to the **23** leading to the formation of the enamine followed by a indium(III) catalysed Michael type reaction between enamine and β-nitrostyrene, which leads to the formation of an intermediate (Scheme 8). This would be followed by an intermolecular cyclization and aromatization generating the desired 6-(pyrrolyl) coumarin/quinolone derivatives.



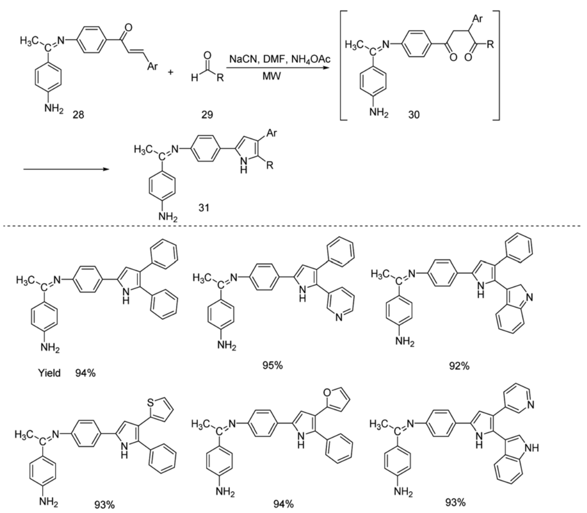
Scheme 6 Microwave assisted synthesis of trisubstituted pyrroles from substituted β-amino unsaturated ketone and substituted phenacyl bromide.



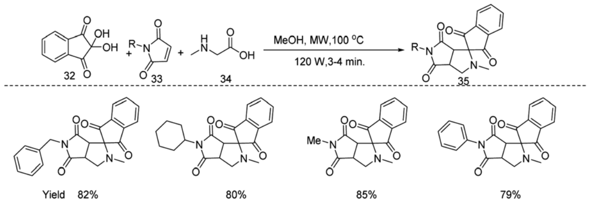
Scheme 7 Microwave assisted protocol for the synthesis of 6-(pyrrolyl) coumarin/quinolone derivatives through an indium(III) catalysed one pot three component reaction.



Scheme 8 Proposed mechanism for the formation of 6-(pyrrolyl) coumarin/quinolones. This figure has been adapted from ref. 18 with permission from John Wiley and Sons, copyright 2020.



Scheme 9 Microwave assisted synthesis of pyrroles from chalcones with different aldehydes and ammonium acetate in the presence of sodium cyanide.



Scheme 10 Microwave assisted one pot stereoselective synthesis of dihydro-2′*H*-spiro[indene-2,1′-pyrrolo[3,4-*c*]pyrrole]-tetraone derivatives.

Younis *et al.* designed an efficient synthesis of pyrrole derivatives *via* solvent-free reaction of chalcones **28** with different aldehydes **29** and ammonium acetate in the presence of sodium cyanide in a one-pot under microwave irradiation (Scheme 9).[19] In comparison to the conventional methods, the major advantages of this protocol are high yield, short reaction time and easy purification of product by non-chromatographic methods. Some of the synthesized compounds showed significant antitumor activities. They have studied the possibility and limitations of this protocol in a variety of molecules under optimized conditions and obtained excellent yields.

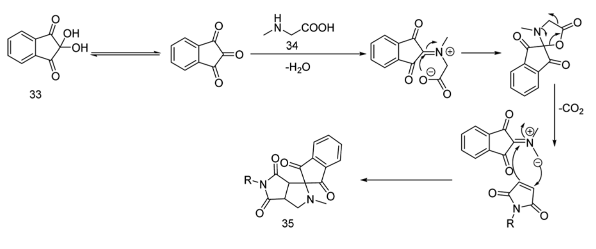
Perumal and coworkers proposed a new microwave assisted one pot stereoselective synthesis of dihydro-2′*H*-spiro[indene-2,1′-pyrrolo[3,4-*c*]pyrrole]-tetraone derivatives **35** (Scheme 10).[20] They explored the scope of this three component 1,3-dipolar cycloaddition reaction under the optimized reaction conditions (3-(4-1-(aryl/alkyl)-1*H*-pyrrole-2,5-dione) **33** (1 mmol), ninhydrin **32** (1 mmol), sarcosine **34** in methanol at 100 °C, 120 W and 1 bar pressure) employing a series of maleimides differing in the aryl part and obtained good yields. From the pharmacological studies, they found that some of these compounds show AChE inhibition and antimycobacterial activities.

The proposed mechanism goes through the generation of azomethine ylides *in situ* from **32** and **34**, followed by 1,3-dipolar cycloaddition with a number of **33** (Scheme 11).

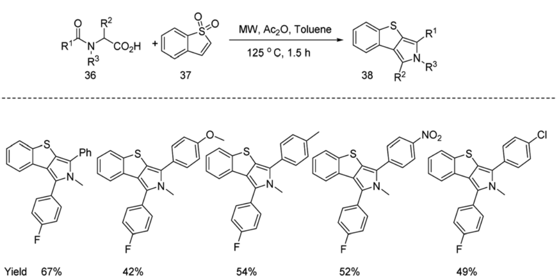
Dürüst and coworkers designed a new protocol for the microwave assisted synthesis of benzothiophene-fused pyrrole derivatives **38** through cycloaddition and metal-free Pummerer-type sulfone deoxygenation pathway (Scheme 12).[21] The applications and limitations of this protocol was explored under the optimized reaction condition (*N*-acylated amino acid derivatives **36** (0.500 mmol), benzo[*b*]thiophene 1,1-dioxide **37** (0.167 mmol), Ac_2O (0.2 mL), toluene (3 mL), MW, 125 °C, 1.5 h) and obtained moderate yields in a variety of substrate molecules.

Zanatta and coworkers developed a new microwave assisted regioselective synthesis of polyfunctionalized 3-ferrocenyl-1*H* pyrroles **39** from pentane-2,4-dione or non-symmetrical 1,3-dicarbonyl compounds **38** and ferrocenyl vinyl azide **37** (Scheme 13).[22] The scope of this reaction was explored under the optimized conditions (**37** (0.5 equiv.) and **38** (0.55 equiv.), DCE (5 mL), MW, 100 °C, 30 min) and obtained moderate yields (32–75%) of the products. When compared to the acidic, basic or metal-catalyzed methodologies for polysubstituted pyrrole synthesis, the present synthetic route is mild, quick, simple, and it furnishes new functionalized tetrasubstituted-pyrroles in short reaction time (30 min).

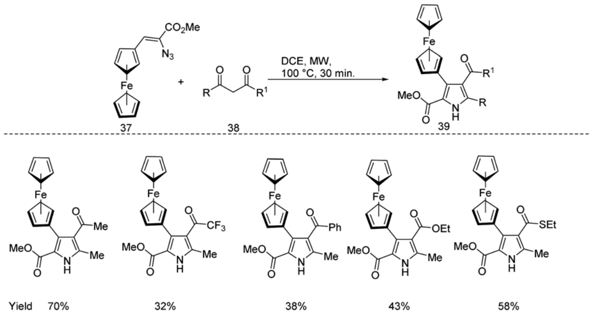
Dumitrescu *et al.* developed a new simple and clean strategy for the synthesis of the derivatives of pyrrolo[1,2-*c*]quinazolines



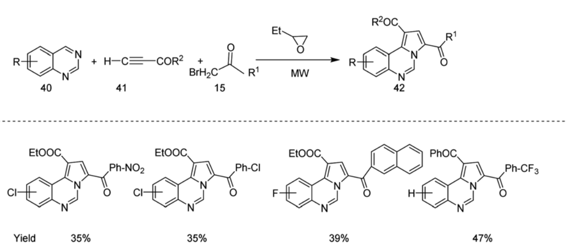
Scheme 11 Proposed mechanism for the formation of dihydro-2′*H*-spiro[indene-2,1′-pyrrolo[3,4-*c*]pyrrole]-tetraone derivatives. This figure has been reproduced from ref. 20 with permission from Elsevier, copyright 2020



Scheme 12 Microwave assisted synthesis of benzothiophene-fused pyrrole derivatives.



Scheme 13 Microwave assisted regioselective synthesis of polyfunctionalized 3-ferrocenyl-1*H* pyrroles from pentane-2,4-dione or non-symmetrical 1,3-dicarbonyl compounds and ferrocenyl vinyl azide.

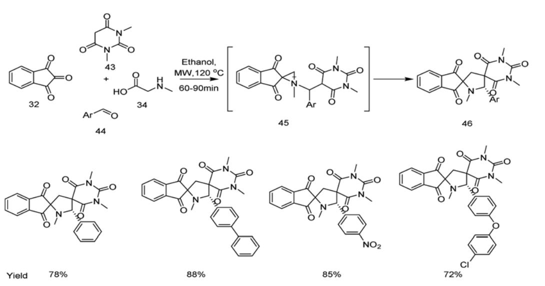


Scheme 14 Microwave assisted synthesis of derivatives of pyrrolo[1,2-*c*]quinazolines.

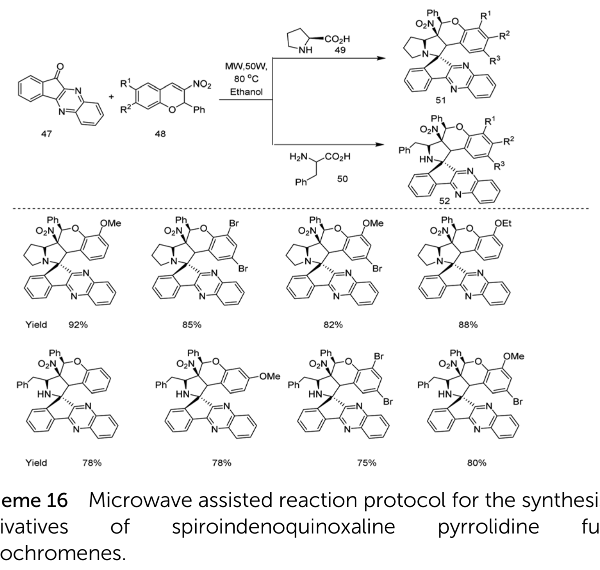
which follows a three component, one pot synthesis protocol under microwave irradiation(Scheme 14).[23] The three components are **15**, quinazolines **40** and electron deficient nonsymmetrically substituted alkynes **41**. The synthesis was carried out through a 1,3-dipolar cycloaddition of quinazolinium *N*-ylides. The applicability of the reaction was studied under optimized conditions (**15** (2 mmol), **40** (2 mmol) **41** (2.2 mmol), and 1,2-epoxybutane (18 mL) under MW irradiation) in a number of substrates and obtained moderate to good yields of the product.

3. Microwave assisted synthesis of pyrrolidines

Narayanarao and coworkers designed a new protocol for the microwave mediated synthesis of regioselective diisospiropyrrolidine analogs (Scheme 15).[24] The protocol was carried out through an efficient one-pot four-component tandem reaction in the presence of four common reactants (substituted benzaldehyde **44**, *N*,*N*-dimethylbarbituric acid **43**, ninhydrin **32**, sarcosine **34**) and magnesium silicate nanoparticles (NPs) in ethanol under microwave irradiation. Some of the diisospiropyrrolidines synthesized show antiproliferative and antibacterial activity. A wide range of diisospiropyrrolidine analogs were synthesized under the optimized condition (**32** (1 mmol), **34** (1.2 mmol), **43** (1.2 mmol), $MgSiO_3$ NPs (10 mol%), ethanol (10 mL) treated under MW irradiation at 120 °C for 60–90 min)



Scheme 15 Microwave mediated synthesis of regioselective diisospiropyrrolidine analogs.



Scheme 16 Microwave assisted reaction protocol for the synthesis of derivatives of spiroindenoquinoxaline pyrrolidine fused nitrochromenes.

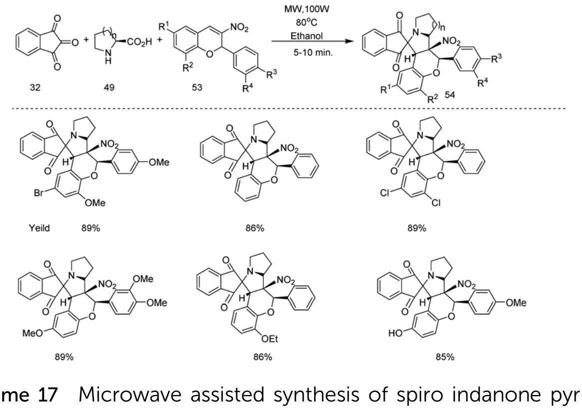
Nayak *et al.* worked on synthesising different spiro pyrrole derivatives through cycloaddition of various dipolarophiles with azomethine ylides generated from methyl glycine or related amino acids.

In 2019 they designed a new autocatalytic, simple, clean, one pot, three component (indenoquinoxalone **47**, L-proline **49**/L-phenyl alanine **50** and 3-nitro-2*H*-chromene **48**) microwave assisted reaction protocol for the synthesis of derivatives of spiroindenoquinoxaline pyrrolidine fused nitrochromenes (Scheme 16).[25] Compared to the conventional heating protocol, the microwave assisted pathway is much better affording high yields of the products, mild reaction condition, high regioselectivity, and operational simplicity to assemble complex structural entity in a single operation with good to excellent yield. The reaction mechanism involves a 1,3-dipolar cycloaddition of azomethine ylides generated *in situ* by the condensation of α-amino acids (**49** and **50**) and **47** with **48** as dipolarophile. The scope of this protocol was investigated in a variety of substrates under optimized conditions and compared with the conventional heating method which revealed that the microwave assisted reactions offered excellent yields.

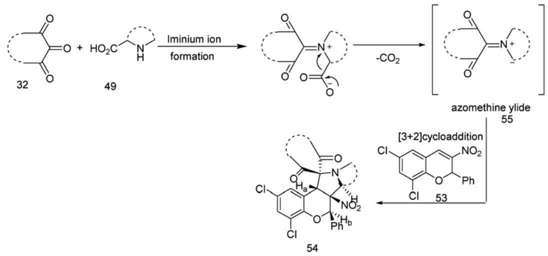
Before that in the same year they proposed a microwave assisted reaction protocol for the synthesis of spiro indanone pyrrolidine/piperidine fused nitrochromene derivatives **54** (Scheme 17).[26] It is a one pot, three component (2-phenyl-3-nitrochromenes **53**, indane-1,3-dione **32**, and proline/pipecolic acid **49**) reaction and from the substrate scope studies under optimized condition (**49** (1 mmol), **53** (1 mmol), **32** (1 mmol) in EtOH (2 mL), MW irradiation (100 W power) at 80 °C for 5–10 min) it is clear that microwave assisted reaction is more regiospecific and diastereospecific, affording high yield in less reaction time as compared to the conventional heating method.

The proposed mechanism goes through a 1,3-dipolar cycloaddition in which 2-phenyl-nitrochromene dipolarophiles react with azomethine ylides **55**, generated *in situ* by the condensation of dicarbonyl compound **32** and secondary amino acid **49** (Scheme 18).

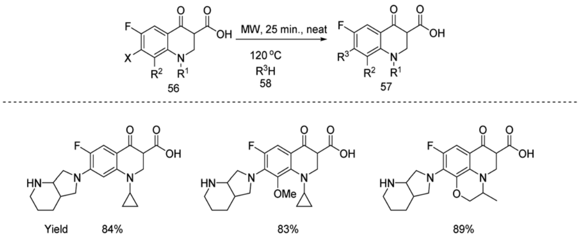
Hakimi *et al.* developed a new microwave assisted solvent-free methodology for the synthesis of different antibacterial



Scheme 17 Microwave assisted synthesis of spiro indanone pyrrolidine/piperidine fused nitrochromene derivatives.



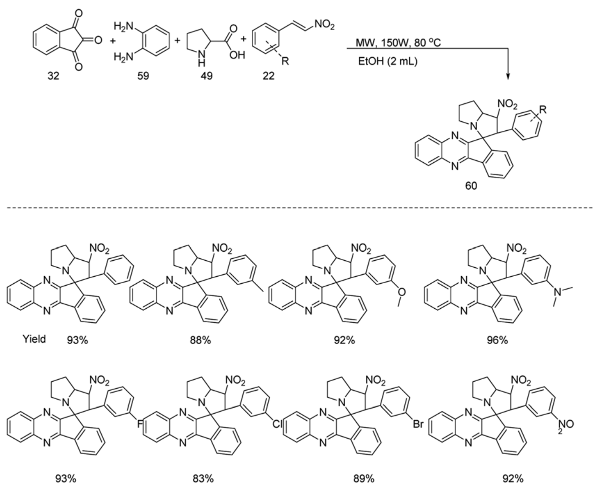
Scheme 18 Proposed plausible mechanism. This figure has been adapted/reproduced from ref. 26 with permission from John Wiley and Sons, copyright 2020.



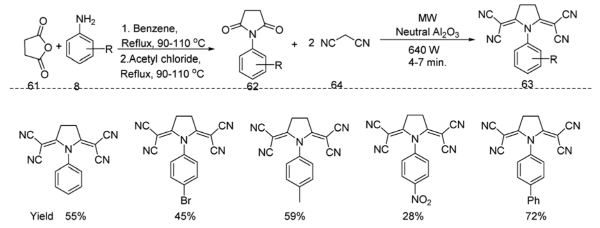
Scheme 19 Microwave assisted solvent-free methodology for the synthesis of different antibacterial fluoroquinolone compounds from 7-halo-6-fluoroquinolone-3-carboxylic acids with a variety of amines.

fluoroquinolone compounds **57** from 7-halo-6-fluoroquinolone-3-carboxylic acids **56** with a variety of amines **58** through direct amination (Scheme 19).[27] From the substrate scope studies carried out under the optimized reaction conditions (**56** (1 g, 3.5 mmol), **58** (0.6 g, 5.25 mmol), MW, 25 min, 150 °C, Neat) the products were formed in excellent yields.

Trivedi *et al.* designed a four component (ninhydrin **32**, phenylenediamine **59**, proline **49**, and nitrostyrene derivatives **22**) reaction for the synthesis of spiroindeno[1,2-*b*]quinoxaline-11,3′-pyrrolizines **60** through a microwave assisted protocol and studied their AChE inhibitory activity (Scheme 20).[28] Under the optimized reaction condition (**32** (0.2 mmol), **59** (0.2 mmol), **49** (0.2 mmol) and **22** (0.2 mmol) in EtOH (2 mL), MW irradiation, 80 °C, 150 W) the scope of the one pot four-component 1,3-dipolar cycloaddition was explored which afforded the products in excellent yields as compared to the conventional method. Pharmacological studies revealed that some of the compounds synthesized could be used as potential AChE inhibitors.



Scheme 20 Four component reaction for the synthesis of spiroindeno[1,2-*b*]quinoxaline-11,3′-pyrrolizines.



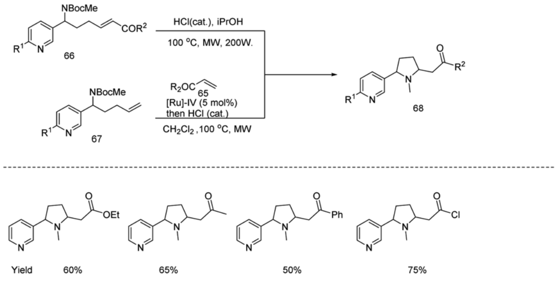
Scheme 21 Microwave assisted synthesis of a number of malononitrile derivatives of substituted *N*-phenylpyrrolidine-2,5-diones.

Rajput *et al.* designed a new solvent-free protocol for the microwave assisted synthesis of a number of malononitrile derivatives of substituted *N*-phenylpyrrolidine-2,5-diones **63** from substituted *N*-phenylpyrrolidine-2,5-dione **61** and dicyanomethane **64** in presence of succinic anhydride, benzene and acetyl chloride (Scheme 21).[29] They studied the scope of the reaction under the optimized reaction conditions (malononitrile derivatives (5 mmol), *N*-phenyl succinimides **62** (10 mmol), **64** (2 g) in neutral Al_2O_3 (2 g), MW, 640 W, 4–7 min, Neat) and obtained average yields. Pharmacological studies showed that most of the synthesised molecules exhibit antimicrobial activities.

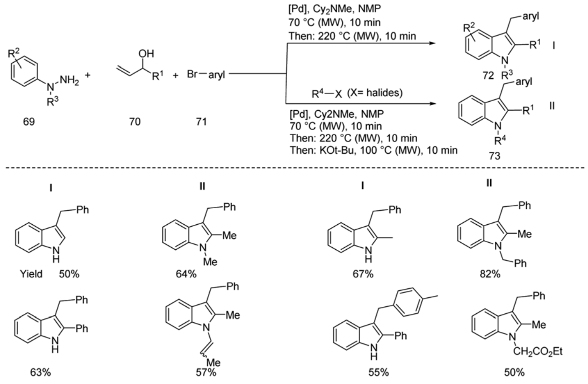
Joseph and coworkers developed a microwave assisted protocol for the synthesis of a series of 2,5-disubstituted pyrrolidines **68** through an efficient telescoped cross-metathesis/cyclizing aza-Michael addition involving *N*-heteroaromatic olefinic derivatives (Scheme 22).[30] This strategy was successfully applied for the preparation of original nicotine–lobeline, nicotine–pelletierine and lobeline–nicotine–epibatidine hybrids under optimized reaction conditions and obtained 50–70% yields.

4. Microwave assisted synthesis of indoles

Müller and coworkers designed a microwave assisted three-component Heck isomerization–Fischer indolization (HIFI)



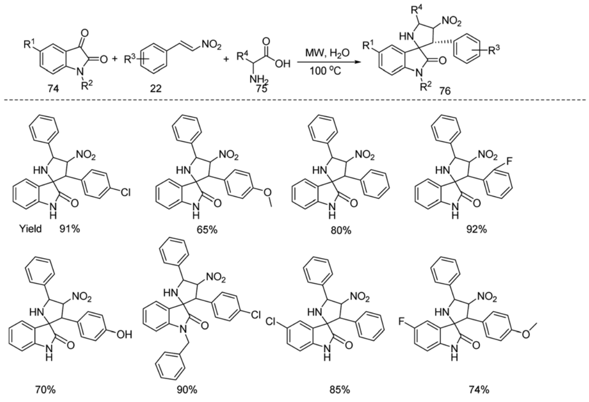
Scheme 22 Microwave assisted protocol for the synthesis of a series of 2,5-disubstituted pyrrolidines.



Scheme 23 Microwave assisted three-component Heck isomerization–Fischer indolization (HIFI) and the four-component Heck isomerization–Fischer indolization–alkylation (HIFIA) for the synthesis of 3-arylmethylindoles and 1-alkyl-3-benzylindoles.

and the four-component Heck isomerization–Fischer indolization–alkylation (HIFIA) for the synthesis of 3-arylmethylindoles **73** and 1-alkyl-3-benzylindoles **72** respectively from (hetero)aryl bromides **71**, allyl alcohols **70**, hydrazines **69** and alkyl bromides (Scheme 23).[31] They studied the applications and limitations of this protocol under the optimized reaction conditions (Three-Component Heck Isomerization–Fischer Indolization (HIFI) for the synthesis of 3-arylmethylindoles: **71** (1 mmol), **70** (1.1 equiv.), Pd$_2$(dba)$_3$ (0.5 mol%) CataCXium Ptb (2 mol%), Cy$_2$NMe (1.1 equiv.), NMP, 70 °C, 10 min then hydrazines (1 equiv.), 220 °C MW, 10 min. Four-Component Heck Isomerization–Fischer Indolization Alkylation (HIFIA) for the synthesis of 1-alkyl-3-benzylindoles: bromobenzene (1 mmol), Pd$_2$(dba)$_3$ (0.5 mol%), CataCXium Ptb (2.0 mol%), allyl alcohol (1.1 equiv.), Cy$_2$NMe (1.1 equiv.), NMP (0.5 mL), 70 °C, MW, 10 min then PhNHNH$_3$Cl (1 equiv.), 220 °C, MW, 10 min followed by addition of *t*-BuOK (5 equiv.), RX 7 (3 equiv.), then heat at 100 °C, MW, 10 min) and obtained moderate to good yields.

Meshram *et al.* developed an ecofriendly one-pot three-component (isatin **74**, β-nitrostyrene **22** & benzyl amine/α-amino acids **75**) microwave assisted, aqueous phase, catalyst-free protocol for the synthesis of functionalized spirooxindoles **76** (Scheme 24).[32] The protocol allows easy construction of a variety of spirooxindoles in moderate to good yields under the optimised reaction conditions (**74** (1 mmol), **75** (1.2 mmol), **22** (1 mmol), water (2 mL), MW, 100 °C, 10 min) with good diastereoselectivity starting from readily available precursors. The newly synthesised molecules showed antimicrobial activity against *Escherichia coli*, *Candida tropicalis*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*.



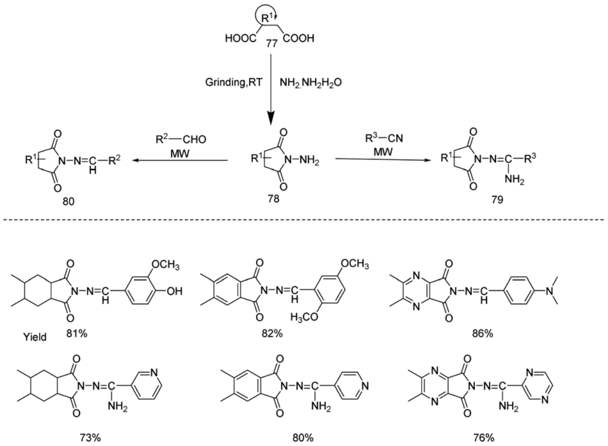
Scheme 24 Microwave assisted three component synthesis of functionalized spirooxindoles.

A simple nature friendly, cleaner, faster, and better yielding, multicomponent reaction protocol for the synthesis of a series of 3-(3′-pyrrolyl)-2-oxindoles containing phenothiazine, pyrrole or triazole like heterocyclic moieties under both conventional and microwave heating conditions has been reported.[33] Comparison of both conventional and microwave heating methodologies revealed that the microwave assisted protocol gave the highest yields.

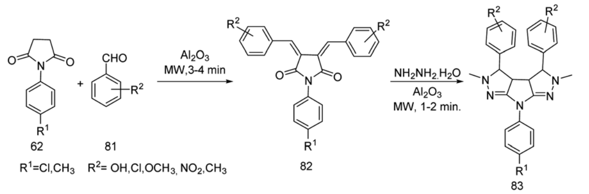
Sondhi *et al.* designed a simple and eco-friendly reaction protocol for the synthesis of azomethine and amidine derivatives of isoindole and pyrrolopyrazine from different dicarboxylic acids **77** (*cis* cyclohexane 1,2-dicarboxylic acid, phthalic acid and pyrazine 2,3-dicarboxylic acid) and hydrazine hydrate (Scheme 25).[34] First of all 2-aminohexahydro-1*H*-isoindole-1,3(2*H*)-dione, 2-amino-1*H*-isoindole-1,3(2*H*)-dione and 6-amino-5*H*-pyrrolo[3,4-*b*]pyrazine-5,7(6*H*)-dione were generated from dicarboxylic acids and hydrazine hydrate through grinding followed by microwave irradiation with aldehydes and different pyridines to generate the corresponding azomethine and amidine derivatives of isoindole and pyrrolopyrazine with excellent yields. Pharmacological studies revealed that the newly synthesised compounds possess both good anti-inflammatory and anti-cancer activity.

5. Microwave assisted synthesis of fused pyrazoles and isoxazoles

Patel and Rajput successfully conducted synthesis and microbial evaluation of hexahydro-2*H*-pyrrolo[2,3-*c*:5,4-*c*′]dipyrazole



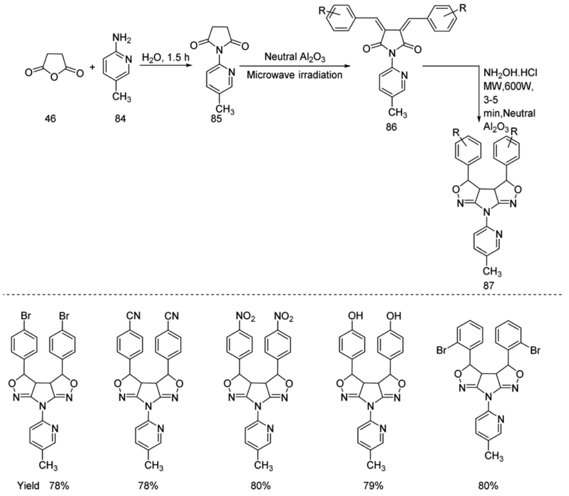
Scheme 25 Microwave assisted synthesis of azomethine and amidine derivatives of isoindole and pyrrolopyrazine from different dicarboxylic acids.



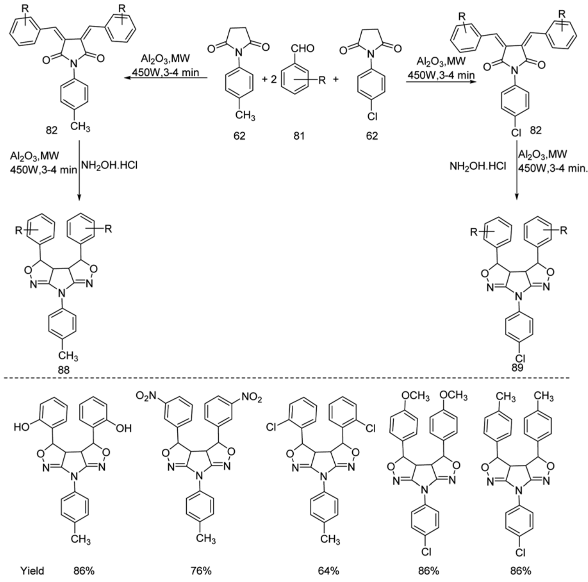
Scheme 26 Synthesis of hexahydro-2*H*-pyrrolo[2,3-*c*:5,4-*c*′]dipyrazoles from chalcone through a microwave mediated protocol.

derivatives **83** from chalcone through a microwave mediated protocol (Scheme 26).[35] The methodology is a one pot solvent-free synthetic pathway in which 1-*p*-tolylpyrolodine-2,5-dione and 1-*p*-chloropyrolodine-2,5-dione **62** react with substituted benzaldehydes **81** upon microwave irradiation in presence of neutral alumina affording both (3*Z*,4*Z*)-3,4-bis(benzylidene)-1-(4-chlorophenyl)pyrrolidine-2,5-dione and (3*Z*,4*Z*)-3,4-bis(benzylidene)-1-(*p*-tolylphenyl)pyrrolidine-2,5-dione. Further treatment with hydrazine hydrate in presence of neutral alumina upon irradiation under microwave results in the formation of dipyrazole derivatives. From the microbial evaluation it is clear that 7-(4-chlorophenyl)-3,3*a*,3*b*,4,5,7-hexahydro-2*H*-pyrrolo [2,3-*c*:5,4-*c*′] dipyrazole-3,4-diyl-diphenol exhibited bacterial activity against *P. aeruginosa*.

Rajput *et al.* developed a new series of bis-isoxazoles **87** by the reaction of *N*-5-methyl pyridine succinimide **84** and substituted benzaldehyde under microwave irradiation in presence of neutral alumina under neat conditions (Scheme 27).[36] First, chalcones were synthesized as an intermediate that undergo ring closure with hydroxyl amine hydrochloride under microwave irradiation in presence of neutral alumina resulting in the formation of bis-isoxazole derivatives. The substrate scope studies carried out under optimized conditions (bis-chalcone (0.1 mol) and hydroxyl amine hydrochloride (0.2 mol) in neutral Al_2O_3 (1 g) MW, 600 W, 3–5 min) on a wide variety of substrates showed that the products were formed in good to excellent yields.



Scheme 27 Microwave assisted synthesis of bis-isoxazoles by the reaction of *N*-5-methyl pyridine succinimide and substituted benzaldehyde.



Scheme 28 Microwave assisted synthesis of 7*H*-pyrrolo[2,3-*c*:5,4-*c*′] diisoxazole derivatives.

Patel and Rajput successfully synthesized 7*H*-pyrrolo[2,3-*c*:5,4-*c*′]diisoxazole derivatives using a microwave oven in minimum time compared to the conventional methods through a solvent-free methodology (Scheme 28).[37] From the microbial studies carried out on the substrates obtained under the optimized conditions (for synthesis of chalcone: **62** (10 mmol), neutral alumina (2–2.5 grams) **81** (20 mmol), MW 450 W, 3–4 min), for the synthesis of 7*H*-pyrrolo[2,3-*c*:5,4-*c*′]diisoxazole derivatives: bis-chalcone derivatives (10 mmol), neutral alumina (2–2.5 grams), hydroxylamine hydrochloride (2 mol), MW, 450 W, 4–6 min, it was found that some of the synthesized compounds showed antibacterial and antifungal activity.

6 Conclusions

The short review based on the recent developments in the area of microwave assisted synthesis of nitrogen containing five membered heterocycles summarizes the synthesis of pyrroles, pyrrolidines, fused pyrazoles, fused isoxazoles and indoles. Some of these syntheses occurred in aqueous medium while some others were carried out under solvent-free conditions. As compared to other synthetic protocols, microwave assisted ones were found to be cleaner with short reaction time. The high purity and higher yield of products under milder reaction conditions make these protocols environmentally friendly.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

SS and KRR thank the Council of Scientific and Industrial Research (CSIR), New Delhi-India and the University Grants Commission (UGC), New Delhi-India for the CSIR and UGC research fellowships, respectively. GA thanks the Kerala State Council for Science, Technology and Environment (KSCSTE-Trivandrum), for financial support in the form of research grant (Order No. 341/2013/KSCSTE dated 15.03.2013). The authors are also thankful to EVONIK Industries, Germany for financial support (ECRP 2016 dated 6.10.2016).

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