Microwave-assisted synthesis of nitrogen-containing heterocycles

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In the recent years, microwave (MW) radiation is widely used as a source of heating in organic synthesis. Since the discovery of the MW heating approach, MW-assisted reaction has emerged as a new green-method in organic synthesis as it provides spectacular accelerations, higher yields under milder reaction conditions, and higher product purities, and it reduces pollution of the environment through the use of solvent-free reaction protocols. N-containing heterocycles hold a special place among pharmaceutically significant natural products and synthetic compounds needed for any developed human society. Therefore, organic chemists have been engaged in extensive efforts to produce these compounds following various greener techniques, primarily to circumvent growing environmental concerns. In this review, we discuss only the MW-assisted synthesis of N-containing heterocyclic compounds.

Keywords: green chemistry; microwave-assisted synthesis; N-containing heterocycles

1. Introduction

Heterocycles form by far the largest of the classical divisions of organic chemistry. Heterocycles are essential building blocks that are frequently used in the pharmaceutical; more than 95% of pharmaceuticals contain at least one heterocyclic fragment [1]. They also have application in a wide variety of industries including cosmetics, reprography, information storage, plastics, solvents, antioxidants, and vulcanization accelerators [2,3].

Amongst the heterocycles, N-based heterocycles have been the object of considerable focus, because N-containing heterocycles are structural components of many bioactive natural products such as vitamins, hormones, antibiotics, alkaloids, glycosides, and many more compounds which are of significance for human and animal health [4]. Many natural drugs such as quinine, papaverine, emetine, theophylline, atropine, codeine, morphine, and reserpine are N-containing heterocycles [1,5]. Therefore, N-containing heterocycles are especially considered “privileged” structures for the synthesis and development of new drugs [6,7]. Traditional methods of organic synthesis are orders of magnitude too slow to satisfy the demand for these compounds [8,9]. It is therefore easy to understand why the development of new methods for the synthesis of complex heterocyclic compounds continues to drive the field of synthetic organic chemistry.

Green or sustainable chemistry has now become a subject of intensive research [10–13]. The concept of “green chemistry” emerged in the early 1990s [12] and is now widely adopted to meet the fundamental scientific challenges to protect the human health and environment while simultaneously achieving commercial viability [3,14]. Nonclassical methods following the principles of green chemistry [9] reduce or even eliminate the generation of hazardous substances [12–15] as well as eliminate the use of conventional volatile organic solvents. There have been tremendous successes in the synthesis of numerous numbers of heterocyclic compounds and in the development of new processes under clean, environmentally benign methodologies that are sustainable for the long term.

Microwave (MW) is one of the potential green chemistry techniques used during the recent years [16]. The ability of MW-assisted organic synthesis to rapidly synthesize organic compounds is of significant benefit for library generation. Moreover, it allows modifications in selectivity (chemo-, regio-, and stereo-selectivity) and solvent-, catalyst-free conditions [17]. This review outlines the use of MW, highlights the importance of a number of N-containing heterocycles, and summarizes some advances in their synthesis under MW irradiation through recent selected examples.

2. MW irradiation

A nonclassical heating technique using microwaves (MWs), termed “Bunsen burner of the 21st century”, is rapidly becoming popular and is dramatically
reducing reaction times [14]. The rate of acceleration observed in MW irradiation is due to material–wave interactions leading to dielectric heating. MW consists of an electric and magnetic field and thus represents electromagnetic energy. This energy can act as a nonionizing radiation that causes molecular motions of ions and rotation of the dipoles, but does not affect molecular structure [14]. The applied MW field causes the molecules, on average, to temporarily spend slightly more time orienting themselves in the direction of the electric field rather than in other directions. When the field is removed, thermal agitation returns the molecules to a disordered state in the relaxation time and thermal energy is released. Hence this phenomenon relies on the ability of a substance (solvent or reactant) to absorb MWs and convert them into heat [18]. This internal heating is much more homogeneous than the classical heating.

Synthesis of various N-containing heterocycles utilizing MW irradiation are now discussed under the following headings.

### 2.1. Pyroles

Pyroles are heterocycles of great importance because pyrrole is a basic substructure of numerous biologically active alkaloids and pharmaceutical products [19,20]. Classically, pyroles were synthesized by various methods viz. Knorr pyrole synthesis [21], Paal–Knorr synthesis [22], Hantzsch pyrole synthesis [23], etc.

Aydogan et al. [19] carried out the reaction of cis-1,4-dichloro-2-butene 1 with various amine compounds 2, amino alcohols, and amino acid esters without solvent under MW irradiation on silica gel for 2–4 min, and N-substituted homochiral pyrole derivatives 3 (11 examples) were obtained in good yield (49–69%) instead of the expected 3-pyrrolines (Scheme 1).

Heating an aniline 4 with 2,5-dimethoxypyrazinium 5 in water (0.64 M) in a MW reactor at 150˚C for 30 min resulted in the formation of the corresponding pyroles 6 (10 examples) in water in 81–99% yield (Scheme 2). Wilson et al. [20] reported this simplified approach to the uncatalyzed Paal–Knorr condensation.

Jayagobi et al. [24] have reported the synthesis of pyrano[4,5-\(c\)]pyrroles 10(a) and 10(b) by one-pot intramolecular Knoevenagel-Hetero Diels-Alder reaction of alkenyl aldehyde 7 with barbituric acid 8 in excellent yield (80%) under MW heating (Scheme 3) in 2 min in toluene. Traditional method in refluxing toluene in the presence of ethylene diaminediacetate (EDDA) provides 67% yield in 6 h.

Deb et al. [25] have reported synthesis of ring-fused pyrrole 13 in a single operation by the reaction of 1,3-diketone 11 and cyclic aniline 12 under MW irradiation at 280˚C in the presence of 0.5 equivalent of p-toluenesulphonic acid (p-TSA) with 53% yield (Scheme 4) in 10 min.

Ligand-free 5-endo-dig cyclization of homopropargyl azide 14 in the presence of 20 mol% ZnCl\(_2\) (1.0 M in ether) in CH\(_2\)Cl\(_2\) at 105˚C provided pyroles 15 (eight examples) in high to moderate yield (91–41%) [26] in 40–60 min (Scheme 5). Conventional heating also furnished the same product but at 75˚C for 16 h.

Portela-Cubillo et al. [27] investigated iminyl radical generation and cyclization using the set of functionalized O-phenyl oxime ethers 17 promoted by MWs to produce dihydropyrrole 21 (four examples) in 68–82% yield (Scheme 6). Reaction took place at 160˚C for 15 min with one equivalent of ionic liquid 1-ethyl-3-methyl-1H-imidazol-3-ium hexafluorophosphate (emimPF\(_6\)). However, it was difficult to...
furnish the conventional thermolyses of \( O \)-phenyl oxime ethers as reaction times had to be long, the products were not cleanly formed and yields were disappointingly low.

### 2.2. Indole and its derivatives

Indole nuclei are broadly found in a large amount of synthetic and natural products. Indole is a popular component of fragrances and the precursor to many pharmaceuticals [28]. Classically, indoles have been synthesized by various methods [29,30]. The use of more environmental friendly protocols for the synthesis of indole derivatives has been reported which are mentioned below.

A series of novel 2-aryl-3,4-dihydro-2\( H \)-thieno[3,2-\( b \)]indoles 24 (22 examples) have been synthesized by Karthikeyan and his co-workers [29] regioselectively

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**Scheme 3.** Synthesis of pyrano[4,5-\( c \)]pyrroles by one-pot intramolecular Knoevenagel hetero-Diels-Alder reaction reaction under MW heating.

**Scheme 4.** Synthesis of ring-fused pyrrole under MW irradiation.

**Scheme 5.** Synthesis of pyroles by 5-endo-dig cyclization of homopropargyl azide.

**Scheme 6.** Synthesis of dihydropyrrole using \( O \)-phenyl oxime ethers.
in excellent yields (85–98%) under MW irradiation (Scheme 7) at 90°C in 3–6 min. 24 were also obtained under conventional condition in refluxing ethanol but completed in 30–70 min.

The synthesis of indoles 27 (six examples) which begins with the intermediates 26 prepared from the corresponding commercially available aldehydes 25 (Scheme 8) was accomplished by Lehmann et al. [30]. Formation of indoles took place with 99.9% yield at 200 W, 200°C, and 15-min irradiation time. The existing methods for the synthesis of these compounds afford only relatively low to modest yields (53–79%) in several hours.

Borthakur et al. [31] recently described this formation of various 5-hydroxybenzol[g]indole 31 (12 examples) at 140°C for 5 min in 80% yield (Scheme 9).

Bhella et al. [32] recently reported monomode MW-assisted regio- and stereo-selective 1,3-dipolar cycloadditions of C-(3-indolyl)-N-phenylnitrone 32 with olefinic dipolarophiles 33 to afford the formation of isoxazolidines 34 (six examples) in high yields (87%) in 5 min (Scheme 10).

The same group [32] extended their investigations on 1,3-dipolar cycloadditions of nitrone 32 to allenic esters 35 (two examples) under MW irradiation in solvent-free conditions which afforded potentially biologically active bis-indole derivatives 36 in high yields (84–90%) in 3 min (Scheme 11).

Carpita et al. [33] reported differently substituted indoles 38 (22 examples) via MW-assisted cycloisomerization in water of 2-alkynylanilines 37 which is promoted by catalytic amounts of neutral or basic salts or by stoichiometric weak organic bases in good to high yields (45–66%) without any added metal catalyst in 15–30 min, and did not take place by applying conventional heating (Scheme 12). Earlier, the same group [34] produced similar indoles in moderate to good yields (16–77%) from same reactants 37 under MW irradiation in water without any added metal catalyst, acid, or base in 0.25–1.5 h.

A MW-assisted, one-pot, three-component coupling reaction for the synthesis of 2,3-disubstituted indoles 42 has been developed by Chen et al. [35] (Scheme 13). This reaction was carried out in two steps under standard Sonogashira coupling conditions which afforded a variety of 2,3-disubstituted indoles (24 examples) in 40–80 min in moderate to excellent yields (60–91%).

Waldmann et al. [36] described a silver-catalyzed and MW-assisted one-pot cascade reaction sequence that gives access to different alkaloid-inspired polycyclic scaffold classes including fascaplysin-type alkaloids 49 (52%) and analogs thereof 48 (53%; Scheme 14).

### 2.3 Imidazoles

Imidazole derivatives have attracted considerable attention in recent years as these are endowed with a wide range of pharmaceutical activities [6,37]. The application of imidazoles as 1,3-disubstituted imidazole salts as ionic liquids are also well known [37]. Classically, imidazoles have been synthesized by various methods [38–41].

The MW-mediated preparation of lophine (2,4,5-triphenylimidazole) 53 has been described by Crouch et al. [42] as shown in Scheme 15. When the homogenous mixture of equal molar quantities of benzaldehyde 51, benzil 52, glacial acetic acid, and
Scheme 9. Synthesis of 2-(p-tolyl)-3-morpholino-5-hydroxybenzo[g]indoles.

Scheme 10. Reaction of C-(3-indolyl)-N-phenylnitrone with olefinic dipolarophiles under MW heating.

Scheme 11. Reaction of 1,3-dipolar cycloadditions of nitrone and allenic esters under MW irradiation.

Scheme 12. MW-assisted catalytic cycloisomerization of 2-alkynylaniline derivatives.

Scheme 13. Synthesis of 2,3-disubstituted indoles under standard Sonogashira coupling conditions.
ammonia was irradiated to raise the temperature from room temperature to 120°C over 10 min and then to 125°C over five more minutes, compound 53 was obtained in 90%. The existing methodology requires gram quantities of reagent, large quantities of solvent, and reaction times of greater than 1 h.

Later, Xia et al. [43] reported a MW-assisted three-component synthesis of various 2,4,5-trisubstituted imidazoles 54 (14 examples) with good to excellent yields (74–93%) in ionic liquid 1-methyl-3-heptyl-imidazolium tetrafluoroborate ([HeMIM]BF₄), without solvent and additional acid (Scheme 16). The reaction time was dramatically reduced from several hours in conventional heating to just a few minutes under MW irradiation.

Wolkenberg et al. [44] described a simple, high-yielding (80–99%) synthesis of 2,4,5-trisubstituted imidazoles 57 from 1,2-diketones 56 and aldehydes 55 in the presence of NH₄OAc under MW irradiation at 180°C for 5 min (Scheme 17). Classical methods require harsh reaction conditions (150–200°C, 4–6 h) and suffer from low yields (40–90%), mixtures of products, and lack of generality. These compounds have utility in expedient preparations of the imidazolium alkaloid lepidiline B6 and the platelet aggregation inhibitor trifenagrel.

Sparks and his co-workers [45] have discovered an efficient MW-assisted, one-pot, two-step synthesis of 2,4,5-triarylimidazoles 60 (15 examples) from ketooximes 58 and aldehydes in moderate (17–37%) to good yields (40–63%) via cyclization to the N-hydroxyimidazole (Scheme 18). The novel thermally induced N–O reductive bond cleavage step takes place upon MW irradiation at 200°C for 20 min, whereas conventional methods require 2 days.

4,5-Diaryl-2-sydnonyl-1-substituted imidazoles 65 (16 examples) have been prepared by Shih et al. [46] by the one-pot condensation of 3-(4-ethoxyphenyl)-4-formylsydnone 61, benzil derivatives 62, and ammonium acetate, under MW irradiation (Scheme 19). The use of MW heating reduces reaction time (52–85% yield in 30–90 min) compared to classical heating at 90–110°C (46–77% yields in 1–3 days). When primary amines 63 added, similar treatment produced 64 (eight examples) in 2–3 h with 45–60% yields. Conventional heating also affords 64, but in 2–3 days with 20–34% yield.

2-Imidazolines 69 have been synthesized by Hoz et al. [47]. MW-assisted cyclization of nitriles 66 with ethylenediamine 67 which aromatize in toluene and Magtrieve™ (oxidant) and further afforded imidazoles (five examples) in 75–105 min (Scheme 20). The use of conventional heating with MnO₂ requires longer reaction times (24–48 h) to obtain good results (76–93%).

Equimolar ratio of succinic acid 70 and cyclohexane-1,2-diamine 71 were mixed together thoroughly and then subjected to MW irradiation at 850 W for 4 min to furnish the product octahydro-1H-pyrrolo[1,2-a]benzimidazol-1-one 72 in quantitative yield (Scheme 21). This one-step process for the synthesis of tricyclic heterocyclic molecules (three examples) was reported by Sondhi et al. [48].

The parent pyrrolidino[2,3,4]pyrrolidino[1,2-a]benzimidazole-2-carboxylates 78 (11 examples) have been synthesized by Meng et al. [49] utilizing a MW-assisted condensation of carbaldehyde 75 with a secondary amino ester 76 and the subsequent 1,3-dipolar cycloaddition of the S-shaped ylide 77 (Scheme 22). The reaction was carried out in xylene.

![Scheme 14. MW-assisted one-pot cascade synthesis of alkaloid-inspired polycyclic scaffold.](image1.png)

![Scheme 15. Reaction under MW irradiation to produce lophine.](image2.png)
Scheme 16. Synthesis of 2,4,5-trisubstituted imidazoles under solvent-free condition.

Scheme 17. MW-assisted reactions of 1,2-diketones for the formation of 2,4,5-trisubstituted imidazoles.

Scheme 18. MW-assisted one-pot synthesis of 2,4,5-triaryl imidazoles.

Scheme 19. Synthesis of 4,5-diaryl-2-sydnonyl-1-substituted imidazoles.

Scheme 20. MW-assisted synthesis of 2-imidazolines.
at 130 or 150°C for 20 min to afford the polycyclic pyrrolidine compounds 78 in (52–93%) yield. Azomethine ylide cycloadditions run under classical reaction conditions require longer reaction times and afford products in lower yields [49].

### 2.4. Pyrazoles

Pyrazole and its derivatives have displayed broad spectrum of pharmacological and biological activities. In particular, pyrazolo[3,4-b]pyridines are useful for treatment of a wide variety of stress-related illnesses. Well-known methods for pyrazole synthesis are Peclmann pyrazole synthesis and Knorr pyrazole synthesis [50,51].

Polshettiwar et al. [52] reported MW-assisted synthesis of pyrazole derivatives 81 (eight examples) using nano-organocatalyst in water at 140°C in 20 min in high yield (84–96%; Scheme 23).

Hatem et al. [53] reported the synthesis of 1,3,4-triaryl-5-arylpurazole-carboxamides 85 by 1,3-dipolar cycloaddition of nitrilimines 83 with 5-aryliden-2-arylimino-4-thiazolidinones 82 under solvent-free and MW-assisted conditions at 130°C for 15 min (Scheme 24).

Paul et al. [54] carried out reaction of 4-methylacetophenone 86 with ethyl trifluoroacetate 87 applying MW heating which afforded enol ketone 88 in 10 min at 160°C with high yield (95%). In contrast, the highest yielding (88%) non-MW conditions took 5 days. In the next step, 88 reacted with 4-methylphenylhydrazine 89 to deliver various 1,5-diarylpyrazoles 90 (nine examples) under MW irradiation at 160°C with 95% yield in the presence of silica-supported toluenesulfonic acid (Si-TsOH) in ethanol in 5 min. Whereas, under thermal conditions (100°C), 84 obtained in 7 h with 84% yield (Scheme 25).

Sauzem et al. [55] have synthesized 5-trifluoromethyl-4,5-dihydro-1H-pyrazoles 93 (10 examples) from one-pot cyclocondensation reaction of 4-alkoxy-1,1,1-trifluoromethyl-3-alken-2-ones 91 with the help of MW-assisted synthesis at 70°C in 4 min with high yield (82–96%; Scheme 26). Some of these compounds were effective on neurogenic pain. Conventional method entails moderate yields and a long process (ca. 24 h).

Radi et al. [56] developed multi-component MW-assisted organocatalytic domino Knoevenagel-hetero Diels-Alder reaction (DKHDA) applied for the synthesis of 2,3-dihydropyran[2,3-c]pyrazoles 98 (22 examples). When a mixture of pyrazolone 94, aldehyde 96, and ethylvinyl ether 95 was irradiated at 110°C for 30 min in the presence of the diaryl-prolinol catalyst 97 and t-BuOH as the solvent, the desired compounds 98a and 98b were obtained in 56% and 12%, respectively, and compared to the conventional heating at 80°C for 48 h for similar compounds (Scheme 27).

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![Scheme 21](image1.png)

Scheme 21. Synthesis of tricyclic heterocyclic molecules under MW irradiation.

![Scheme 22](image2.png)

Scheme 22. MW-assisted synthesis of polycyclic pyrrolidine.
Scheme 23. Synthesis of pyrazole derivatives using nano-organocatalyst by MW heating.

Scheme 24. Synthesis of 1,3,4-triaryl-5-N-arylpyrazole-carboxamides under MW irradiation.

Scheme 25. Synthesis of 1,5-diarylpyrazoles in the presence of silica under MW irradiation.

Scheme 26. Synthesis of 5-trifluoromethyl-4,5-dihydro-1H-pyrazoles.

Scheme 27. MW-assisted organocatalytic synthesis of 2,3-dihydropyran[2,3-c]pyrazoles.
Ju et al. [57] described the double alkylation of unprotected hydrazines 99 by alkyl dihalides 100 via cyclocondensation under MW irradiation. These reactions took place in aqueous media in the presence of a mild base with MW power of 70–100 W, at 120°C for 20 min to provide a series of pyrazoles 101 (11 examples) with high yield (60–80%) in a simple SN2-like sequential heterocyclization experimental protocol which has never been fully realized under conventional reaction conditions (Scheme 28).

2.5. Pyrazolines

Pyrazoline moieties have a wide range of applications in agricultural pesticides and luminescent and fluorescent target molecules [58]. Chemists use pyrazolines in bioactive moieties to synthesize new compounds possessing biological activities.

Manna et al. [59] have synthesized new 2-[1-(5,8-dihydro quinoxalino[2,3-b]indoloacetyl)-3-(1-benzofuran-2-yl)-4,5-dihydro-1H-pyrazol-5-yl] phenyl derivatives 104 (14 examples) using MW-assisted route with an excellent yield (84–98%) in 20–30 min (Scheme 29). In ordinary synthetic route (reflux), 28–72% yield was obtained in 8–9.5 h.

Martins et al. [60] reported the synthesis of novel 4,5-dihydro-1H-pyrazole 107 (12 examples) from cyclocondensation reaction of enones 105 with hydrazine methyl carboxylate 106 under solvent-free conditions (Scheme 30) at 50–55°C in 6 min with 70–98% yield. Conventional heating gave only moderate yields (70–79%) in 24 h.

2.6. Pyrazolones

Several heterocyclic compounds containing pyrazolone moiety were found to be useful intermediates for medical drugs. They have a wide range of approved biological and pharmaceutical activities [61]. Among other activities, pyrazolones act as appropriate precursors for the preparation of herbicides, liquid crystals, and dyes. They are traditionally synthesized by treatment of β-ketoesters with substituted hydrazines under acidic conditions at elevated temperature [62].

Pal et al. [63] have also reported the synthesis of a series of pyrazolones 110 (12 examples) from the cyclocondensation reaction of hydrazines 109 with β-ketoesters 108 under solvent-free conditions using MW heating (Scheme 31). Compared to conventional method (in refluxing MeOH for 10 h), MW-assisted reaction completes in 2–4 min in high yield (62–89%).

Mutairi et al. [62] have irradiated the mixture of hydrazine derivatives 112 and β-keto esters 111 with MW (300 W) for 1–15 min under solvent-free condition which produced pyrazolones 113 (12 examples) in moderate to good yields (40–91%; Scheme 32). 113 are also produced under conventional condition (stirring in EtOH, at room temperature [RT] for 1–5 h).
Scheme 30. Synthesis of 4,5-dihydro-1H-pyrazole under solvent-free conditions.

Scheme 31. Synthesis of pyrazolones under solvent-free conditions using MW irradiation.

Scheme 32. Synthesis of pyrazolones under microwave irradiation.

Scheme 33. Synthesis of 5-aminopyrazolones under solvent-free condition.
Deshmukh et al. [64] reported a MW-assisted process to synthesize 5-aminopyrazolone 116 under solvent-free conditions (Scheme 33) with 88% yields at 130°C in 2 min. The same conversion carried out under conventional thermal heating required 4 h and furnished the products in 80% yield [64].

2.7. Triazole

1,2,3-Triazoles are indispensable structural motifs of compounds with increasing importance in the field of pharmaceuticals, crop protection, and material sciences [65]. Conventional Huisgen’s 1,3-dipolar cycloaddition technique proved to be highly versatile in giving substituted 1,2,3-triazoles by the reaction between organic azides and substituted alkynes [66].

Tsai et al. [67] have synthesized 4,5-disubstituted-2H-1,2,3-triazoles 119 (14 examples) via cycloaddition reactions of azides 118 with terminal alkynes 117 following the MW procedure (75 W) in DMSO at 130°C in 4–90 min with 60–99% yields (Scheme 34). In contrast, the conventional method to get 113 requires 6–10 days.

Yang et al. [68] have described a convenient and efficient one-pot synthesis of C-carbamoyl-1,2,3-triazoles 123 (14 examples) under MW irradiation with 72–93% yield (Scheme 35), whereas, conventional method requires long reaction time and needs purification of the intermediates.

Meng et al. [69] have reported regioselective MW-assisted synthesis of N1-substituted 3-amino-1,2,4-triazoles 126 (10 examples) in 34–70% yields (Scheme 36).

Ball et al. [70] developed a rapid synthesis of unprecedented [1,3]oxazololo[3,2-b][1,2,4]triazoles 131 (eight examples) using MW irradiation by tandem alkylation/cyclization reaction of 3-bromo-1,2,4-triazoles 127 and z-haloketones 128, via intermediate enolate 130 at 100°C in 10–20 min in the presence of a base with 30–81% yields (Scheme 37).

Synthesis of a triazole-linked 3–5 thymidine dimer 133 was reported by Lucas et al. [71] making use of 1,3-dipolar cycloaddition under MW irradiation in 1–3 min with 62–84% yield at 80°C (Scheme 38). MW-assisted route is faster than the conventional method, which requires heating at 80°C for 5 h to achieve the desired product.

2.8. Pyridine

Pyridines have a wide range of applications in medicinal chemistry. Pyridine derivatives have been used as herbicides and for enrichment of cereals. Some bifunctional pyridines are used as nonlinear optical materials, electrical materials, chelating agents in metal–ligand chemistry, and as fluorescent liquid crystals [72]. Despite the numerous synthetic methodologies available in the literature [72], novel methods for pyridines synthesis are still in demand.

Heating enaminones 134 with excess of ammonium acetate (as an ionic liquid), at 110°C for 20 min or irradiating under MW for 1 min at 105°C (400 W), yielded the pyridines 137 (five examples). This work was reported by Khadijah et al. [73] (Scheme 39).
Yield obtained following the MW procedure is higher (65–77%) than the heating method (50–62%).

A one-pot effective Körnke condensation reaction was carried out by Tu et al. [74] in an aqueous medium using MW irradiation (6–10 min) and ammonium acetate for the synthesis of substituted pyridines 139 (18 examples) at 130°C with 90–96% yield (Scheme 40). Heating in oil bath requires much more time (2.5–4 h) with 76–84% yield.

A facile solvent- and catalyst-free method for the synthesis of a series of new hydroxylated 2,4,6-trisubstituted pyridines 142 (15 examples) was
obtained in high yield (83%) under MW irradiation (400 W) at 120°C for 30 min via a three-component condensation of 4-hydroxybenzaldehyde 140, acetophenone 141, and NH₄OAc (Scheme 41). This work was reported by Yin and his co-workers [75].

But, treatment of hydroxyl-substituted aryl ketone (4-acetylphenol) 143 (five examples) with benzaldehyde 51 under the same conditions afforded bis-hydroxyl compound 144 in 82% yields (Scheme 42).

Yan et al. [76] described a modified Krohnke procedure of annulated pyridine derivatives 148 (10 examples) in one-pot reactions of N-phenacylpyridinium bromide 145 with aromatic aldehydes 147 and cyclic ketones 146 in the presence of ammonium acetate and acetic acid under MW irradiation in 2–4 min with 70–80% yield (Scheme 43).

Compounds were produced in 84% yields by heating a mixture of five reaction components at 90°C for 3 h.

The chemoselective synthesis of thiazolo[3,2-α]pyridine derivatives 152 and 153 was achieved by Shi et al. [77] in water via MW-assisted three-component reactions of malononitrile 149, aromatic aldehydes 150, and 2-mercaptoacetic acid 151 with molar ratios of 2:1:1.5 and 2:2:2:1, respectively (Scheme 44). 130 was obtained at 90°C with 80–89% yield in 6–9 min and 131 was produced at 100°C with 82–89% yield in 6–7 min.

A highly efficient, MW-assisted, regioselective one-pot three component synthesis of trisubstituted pyridines 158 (eight examples) and 7,7-dimethyl-2-aryl-5,6,7,8-tetrahydroquinoline-5-ones 156 (five examples) from enaminones 154 in the presence of potassium dodecatungstocobaltate trihydrate, K₄CoW₁₂O₄₀·3H₂O (as a reusable heterogeneous catalyst) within 3–6 min with an excellent yield (up to 98%) under solvent-free conditions was reported by Kantevari et al. [78] (Scheme 45).

2.9. Quinoline

Quinoline derivatives occur in various natural products, especially in alkaloids and are often used for the design of many synthetic compounds with diverse pharmacological properties [79]. A number of methods of quinoline synthesis viz. Skraup, Doebner-von Miller, Friedlander, Pfitzinger, Conrad-Limpach, Combes have been known since the late 1800s [80].

Muscia et al. [81] synthesized a series of substituted quinolines 161 (10 examples) in good yields (50–89%) via the Friedländer reaction by the reaction of 2-aminoacetophenone 159 or benzophenones with a variety of ketones 160 and keto esters and a catalytic amount of hydrochloric acid within a time period of 1.5–12 min following the MW procedure (Scheme 46). Conventional synthesis requires prolong heating (6 h) at 100°C.

Balamurugan et al. [82] also have reported regioselective 2,9-diaryl-2,3-dihydrothieno[3,2-b]quinolines 164 (18 examples) via the Friedländer reaction (Scheme 47). A mixture of 5-aryldihydro-3(2H)-thiophenone 163, 2-aminoaryl ketone 162, and trifluoroacetic acid was irradiated in an MW oven at 100°C (40 W) for 30 min. This reaction proceeded more rapidly and afforded better yields (60–98%) than the thermal reaction at 100°C (60–85% yields in 2–3 h).

Scheme 40. Synthesis of substituted pyridines by Krohnke reaction using MW irradiation.

Scheme 41. MW-assisted synthesis of 4-(2,6-diphenylpyridin-4-yl)phenol under solvent- and catalyst-free conditions.
Scheme 42. MW-assisted synthesis of bis-hydroxyl compound under solvent- and catalyst-free conditions.

Scheme 3. MW-assisted synthesis of annulated pyridines.

Scheme 44. Synthesis of thiazolo[3,2-a]pyridine derivatives under MW irradiation.

Scheme 45. Regioselective one-pot three component synthesis of trisubstituted pyridines and 7,7-dimethyl-2-aryl-5,6,7,8-tetrahydroquinoline-5-ones under solvent-free MW irradiation conditions.

Scheme 46. Synthesis of substituted quinolines via the Friedländer reaction catalyzed by hydrochloric acid.
Fluorine-containing spiro[piperidine-4,4-pyrano[3,2-c]quinolines] 168 (14 examples) were synthesized by Dandia et al. [83] through a rapid one-pot multicomponent reaction under MW irradiation (Scheme 48) with an excellent yield (80–96%) and short reaction time (3–10 min), whereas conventional heating needs 5–12 h to get 68–76% yield.

Mali et al. [84] has recently developed a one-pot water-mediated synthetic route to produce quinoline derivatives 171 (eight examples) using both thermal and MW energy resources (Scheme 49). MW-assisted route offers high yields (87–93%), short reaction times (1.5–2.5 h) compared to conventional heating which affords 85–91% yield within 7–10 h.

Tu et al. [85] synthesized N-substituted furo[3,4-b]quinoline derivatives 175 (28 examples) via a three-component reaction of an aldehyde 172, an enaminoic acid 174, and tetrionic acid 173 in glacial acetic acid without any catalyst (Scheme 50). Following the MW procedure at 100°C, the reaction time was strikingly shortened to 5–9 min from 3 to 5 h required under traditional heating conditions, and the yields were increased to 90–98% from 37% to 56%.

2,3-Dihydro-1H-pyrrolo[3,2-c]quinoline 179 (13 examples) core from substituted 2-unsubstituted thieno[2,3-d]pyrimidines 190 (14 examples) was synthesized by Phoujdar et al. [90] through the chlorination of the corresponding 2-unsubstituted thieno[2,3-d]-pyrimidin-4-ones 187, followed by the nucleophilic displacement of the 4-Cl group of 188, with a variety of anilines 189. Compared to conventional method in refluxing iso-propanol that completes in 5–9 h with 59–85% yield, the entire four-step MW-assisted reactions require 2 h in high yield (Scheme 54).

2.10. Pyrimidine

Pyrimidine derivatives serve both as biomimetic and reactive pharmacophores due to their diverse medicinal properties. The importance of partially hydrogenated pyrimidine derivatives in medicinal chemistry is widely known [88]. Most popular method for pyrimidine synthesis is Biginelli reaction [89]. In order to improve the yields obtained in the described classic conditions for the synthesis of pyrimidines, much effort has been made.

Various 2-unsubstituted 4-(substituted)anilinothieno[2,3-d]pyrimidines 190 (14 examples) were synthesized by Phoujdar et al. [90] through the chlorination of the corresponding 2-unsubstituted-thieno[2,3-d]-pyrimidin-4-ones 187, followed by the nucleophilic displacement of the 4-Cl group of 188, with a variety of anilines 189. Compared to conventional method in refluxing iso-propanol that completes in 5–9 h with 59–85% yield, the entire four-step MW-assisted reactions require 2 h in high yield (Scheme 54).
Scheme 49. Synthesis of quinoline derivatives by MW heating.

\[
\begin{align*}
R^1 & = H, \text{OMe, Me, } R^2 = H, \text{Et, } R^3 = H, \text{Ph} \\
\end{align*}
\]

Scheme 50. Synthesis of \(N\)-substituted furo[3,4-\(b\)]quinoline derivatives.

\[
\begin{align*}
R & = 4-\text{OMe-Ph, 4-Br-Ph, 3-NO}_2\text{-Ph, Thiophen-2-yl, 4-Cl-Ph, 4-OMe-Ph, 3-NO}_2\text{-Ph, n-Bu, } R^1 = H, \text{Me, } R^2 = \text{Ph, Me, Cyclopropyl, CH}_3\text{COOH, 4-OMe-Ph} \\
\end{align*}
\]

Scheme 51. Synthesis of 2,3-dihydro-1\(H\)-pyrrolo[3,2-\(c\)]quinoline by MW heating.

\[
\begin{align*}
R^1 & = H, \text{F, } R^2 = H, \text{CF}_3, R^3 = H, \text{Cl, CF}_3, \text{CO}_2\text{Me, } R^4 = H \\
\end{align*}
\]

Scheme 52. Reaction of 4,7-dichloroquinoline with aromatic amines under micro-mode irradiation for the formation of 4-aminophenyl-7-chloroquinoline.

Scheme 53. Reaction of 2-chlorobenzothiazole with various amines under MW heating to produce 2-aminophenylbenzothiazoles.
Novel chromeno[2,3-b] pyrimidine derivatives \(194\) (11 examples) were obtained by Rai et al. \[91\]. MW irradiation of intermediate \(193\) with different amines in acetic acid gave \(194\) within 5 min in reasonably good yields (64–75%; Scheme 55). All these compounds were screened for their antimicrobial activity. 2,4,6-Triarylpyrimidines \(197\) were synthesized by Bagley et al. \[92\] by MW-assisted tandem oxidation/heterocyclocondensation using BaMnO\(_4\) (Scheme 56) at 145°C in 45 min. In contrast, traditional method under conductive heating by cyclocondensation of \(195\) and \(196\) at reflux in EtOH in the presence of NaOH, moisture, and air for 10 h produces \(197\) in 0–40% yield. Shaaban \[93\] has synthesized 6-thienoyl-7-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyrimidine \(201\) in 91% yields (and 6-thienoyl-7-(trifluoromethyl) benzimidazo[1,2-a]pyrimidine \(202\) in 83% yields) by MW irradiation of 4,4,4-trifluoro-1-(thien-2-yl)butane-1,3-dione \(198\), 3-amino-1,2,4-triazole \(199\) (or 2-amino-benzimidazole \(200\)), and triethylorthoformate at 100°C for 5 min (Scheme 57). Most of the thermal syntheses of such compounds consume a lot of time and/or lack of high selectivity \[93\].

6-(2-Hydroxybenzoyl)-5-methyl-7-phenylpyrazolo[1,5-a]pyrimidines \(205\) (eight examples) have been synthesized directly by the solvent-free reaction between 5-amino-1H-pyrazoles \(203\) and 3-benzoyl-2-methyl-4H-chromen-4-one \(204\) using MW-assisted route in 2 min in 88–93% yield (Scheme 58). This work was reported by Quiroga et al. \[94\]. Conventional heating at 180°C for 20 min gives the product in 70–76% yield.

Aminopyrimidines \(208\) and \(210\) were made by reaction of \(206\) with guanidine \(207\) and thiourea \(209\), respectively (Scheme 59). Urea \(30\) and thiourea \(209\) were also used to obtain a wide variety of pyrazolyl-substituted pyrimidines \(212\) and \(213\) (Scheme 60). These reactions were reported by Hoz et al. \[95\]. All reactions were performed under MW irradiation, and reaction times were in the range of 20–60 min. These conditions gave good yields of \(208\) and \(210\) (38–56%) and \(212\) and \(213\) (58–70%).

Daniels et al. \[96\] synthesized a series of functionalized pyrazolo[3,4-d]pyrimidines \(219\) (seven examples) on MW irradiation (Scheme 61). The last reaction step that required >48 h at reflux and provided 40–65% yield under conventional method has been optimized to 20 min with 74–91% yields on MW heating.

Arya et al. \[97\] synthesized fluorinated spiro[indole-3,2-pyrido[1,2-a]thiazolo[5,4-e]pyrimidines] \(222\) (four examples) and spiro[indole-3,2-thiazolo[4,5-d]pyrimidines] \(223\) (four examples) under MWs in the presence of montmorillonite KSF (Mont. KSF). Micheal addition of 2-aminopyridine \(221\) and arylidenes derivatives \(220\) yielded \(222\) in the presence of Mont. KSF in 85–91% yield in 5–6 min. Reaction of arylidenes derivatives \(220\) with thiourea \(209\) afforded \(223\) in 85–90% yield in 3–5 min (Scheme 62).

### 2.11. Pyrimidinones

There is a continuous widespread interest in the synthesis of pyrimidinones because of the diverse
biological properties associated with this system [98,99]. Synthetic procedures are generally based on the modifications of the century-old Biginelli’s reaction [89], involving an acid catalyzed three-component condensation of a 1,3-dicarbonyl compound, aldehyde, and urea. Shingare et al. [100] synthesized various pyrimido [4,5-\(d\)]pyrimidine-2,4,7-triones (16 examples) by multicomponent reaction of aldehyde (225), urea (30), thiourea (209), barbituric acid (224), and alumina (Al\(_2\)O\(_3\)) on MW irradiation (600 W) within a time of 25–40 sec (Scheme 63). Traditional procedures
typically involved longer reaction time and less yield [100].

An efficient, simple MW-assisted synthesis of 3,4-
dihydropyrimidinones 230 (14 examples) in excellent yields was obtained in the presence of water without additional solvent/acid catalyst in 2 min with 88–98% yield. This reaction has been reported by Singhal et al. [101] as shown in Scheme 64. The same reaction was also been executed under conventional heating which was found to be much slower (gets completed in 45–75 min).

Mojtahedi et al. [102] reported the preparation of pyrimidinones 232 (four examples) and thiopyrimidinones 233 (three examples) in solvent-free and MW-assisted conditions (Scheme 65) with good yields (53–81%) in 2–6 min. Conventional method, in refluxing ethanol (containing metallic sodium), completes within 6–7 h with 4–78% yields.

Khunt et al. [103] developed a solvent-free MW-assisted process for the preparation of tetrahydropyrimidinones 236 and tetrahydrothiopyrimidinones 237 employing equimolar amounts of neat 1,3-dicarbonyl compounds 234, different aromatic aldehydes 235 and urea 30 (or thiourea 209; Scheme 66). The reaction mixture was irradiated at 110–120°C with
MW for 1.5–6.5 min with 78–85% yield (15 examples). In contrast, conventional thermal heating method involving THF (as solvent) and InCl₃ (as catalyst) furnishes the products in hours.

Dihydropyrimidinones 240 and 241 (15 examples) were synthesized by aqueous Biginelli protocol using polystyrenesulfonic acid (PSSA) as a catalyst under MW irradiation [104] at 80°C for 20 min with an excellent yield of 86–92% (Scheme 67). This reaction proceeds without using any phase-transfer catalyst (PTC). Conventional heating condition (oil bath) requires 5–6 h for completion.

2.12. Quinazoline

Quinazoline and its derivatives are a class of heteroaromatic compounds that have drawn much attention because of their biological and pharmaceutical activities [105].

Rad-Moghadam et al. [106] synthesized various quinazolines 244 (five examples) under both MW irradiation and conventional heating conditions from a mixture of 2-aminobenzonitrile 242, orthoester 243, and ammonium acetate under solvent-free conditions (Scheme 68). MW method offers products in high yields (82–89%), in 5–7 min, whereas conventional method occurs in oil bath at 120°C, in 30–80 min with 83–92% yield.

2-(Aminoaryl)alkanone O-phenyl oximes 245 and carbonyl compounds 246 in toluene solution with emimPF₆ as ionic liquid were irradiated with MWs (Scheme 69) at 160°C for 30 min to afford dihydroquinazolines 247 (five examples) in high yields (72–94%). This reaction was reported by Portela-Cubillo and his coworkers [107]. When 0.3 equivalents of ZnCl₂ is included in the mixture, quinazolines 248 (eight examples) are obtained instead. With the exception of the CuCl₂ catalyzed reaction of
aldehydes with anthranilamide, methods of forming the quinazoline ring either require multi-step preparations of special reagents/reactants or give moderate yields [107]. An effective route to the formation of benzimidazo[2,1-b]quinolin-12(5H)-ones 251 (11 examples) from o-aryl isothiocyanate esters 249 and o-phenylenediamines 250 has been reported by Carpenter et al. [108] in 91–98% overall yield via tandem DIC-mediated benzimidazole cyclization and MW-assisted benzimidazoquinazolinone cyclization with barium hydroxide (Scheme 70). Common approaches to 251
require ~200°C and give low yields or sometimes together with byproduct.

2.13. Miscellaneous

Fused 1,3-oxazin-6-ones constitute an interesting class of pharmacologically active compounds because they have shown a multitude of biological activities [109]. A MW-assisted solid-phase synthesis of heteroannulated 1,3-oxazin-6-ones 260 has been developed by Che et al. [109] (Scheme 71). Overall reaction time has been dramatically shortened when compared to the conventional procedures.

Sondhi et al. [48] recently reported the new products 2-(2-aminophenyl)isoquinoline-1,3(2H,4H)-dione 263 (three examples) and 11H-benzimidazo [1,2-b]isoquinoline-11-one 264 (three examples) from the reaction between 2-(carboxymethyl)benzoic acid 261 and diamines 71 (or 262) under MW irradiation that gets completed within 5–6 min in 99% yield (Scheme 72).

In the similar way, the same group [48] has investigated the condensation reaction of phthalic acid 265 and diamines 71 (or 262) under MW irradiation that gives another set of tetracyclic heterocyclic compound 266 (three examples), in good yields (95–98%) in 4–5 min (Scheme 73).

Pyrazolo[3,4-b]pyridin-6-ones have been shown to be inhibitors of cyclin-dependent protein kinase-2 (cdk-2), cyclin-dependent protein kinase-5 (cdk-5), and phosphatidylinositol 3-kinase (PI3-K) [110]. Thus, these compounds have potential in the treatment of bipolar disorder, diabetes, dementia, Alzheimer’s disease, schizophrenia, depression, and cancer [110]. Rodrigues-Santos et al. [111] have reported the synthesis of pyrazolo[3,4-b]pyridin-6-ones 270 (12 examples) both by the conventional method and by MW irradiation (Scheme 74). 270 were obtained in moderate to good yields (50–85%) using the conventional methanol reflux method in 4–24 h. Using this MW method, 270 were produced in moderate yield (50–65%), which is low compared to the conventional methodology, but is 12–96 times faster than conventional method.

Regio- and chemoselective synthesis of 1,4,6,7,8,9-hexahydro-1H-pyrazolo[3,4-b]quinolin-5-ones 274 (eight examples) and 5a-hydroxy-4,5,5a,6,7,8-hexahydropyrazolo[4,3-c]quinolinizin-9-ones 275 (nine examples) starting from 5-amino-3-phenylpyrazole 271, cyclic 1,3-dicarbonyl compounds 273, and
aromatic aldehydes 272 under MW irradiation is described by the Chebanov et al. [112]. Whereas in most cases, the three-component coupling in ethanol under reflux conditions provides mixtures of both possible regioisomers pyrazoloquinolinones and pyrazoloquinazolinones in varying ratios (Scheme 75).

Pyrazoloquinazolinones 279 (eight examples) were also produced (with 54–70% yield) by the same group [112] when the three-component condensation was executed in the presence of trimethylsilylchloride (Me3SiCl) as reaction mediator at higher temperature (170 °C) for 30 min (Scheme 76). Reaction involving the condensation of these three reactants in refluxing ethanol at ~80°C is rather unpredictable [112].

A new heterocycle tetracyclic pyrimido[4,5-c]carbazole 282 was prepared by Debray et al. [113] in three
steps from 3-aminocarbazole 280 (Scheme 77). A mixture of 281 and montmorillonite K-10 (K-10) clay was irradiated in an MW oven at 80°C for 1 h to furnish 282 in 77% yield. In classical methods, the Friedel-Craft type cyclization of 281 catalyzed by Me3SiCl in dimethylformamide (DMF) works well; however, the efficiency of the work-up is very sensitive to the nature of the R group, and sometimes produce lower yields.

Nucleosides play important roles in various biological processes. Kinase inhibitors, C6-cycloamine-substituted purines and their analogs 285 (42 examples) were synthesized by Qu et al. [114] via a mild aqueous MW protocol that afforded the desired compounds at 100°C in 8 min in higher purity and yield (73–94%), making this methodology suitable for rapid drug discovery (Scheme 78). Traditional routes often involve long reaction time (15% yield after 24 h), toxic-solvent, and labor-intensive operation [114].

Pyrazole nucleus in fusion with benzopyrans confers pharmacological properties [115]. Benzopyran-4,3-c[pyrazoles 289 (seven examples) were synthesized by heterocondensation reaction between in situ-generated 3-arylidene-2,4-chromanediones 287 and N-substituted hydrazine 288 moieties under MW irradiation conditions in 2–4.5 min (Scheme 79). This high yielding (75–85%) protocol was reported by Kidwai et al. [115]. Under conventional method, second stage requires 5–8 h to obtain 45–78% yield.

Spiro-amino acids incorporated into bioactive peptides are useful for both restricting the flexibility
of the peptide and providing information on the topographical requirements of peptide receptors. An efficient method for the synthesis of spiro-2,5-diketopiperazines (spiro-DKPs) (four examples) was developed by Jam and his co-workers [116] by cyclization of Boc-protected dipeptides containing spiro-amino acids using MW heating in water in the presence of O-(7-Azabenzotriazol-1-yl)-N,N,N'-tetramethyluronium hexafluorophosphate (HATU) at 160°C in 10 min with 80–86% (Scheme 80). Older methods used for peptide bond formation are inefficient with sterically congested amino acid residues like spiro-amino acids, offer low yield and need excess of reagents to complete the reaction [116].

Das and his co-workers [117] reported a simple and general solventless reaction for the synthesis of 9-substituted acridines (11 examples), by a modification of classical Bernthsen reaction (Scheme 81), using p-TSA as the catalyst using MW irradiation method. This paves the way for an environmentally benign condition without compromising viability and speed. The reaction time has been dramatically reduced to 4 min with 80% yield at 450 W than the conventional method (75% yields in 20 h).

Tu et al. [74] have developed a first facile and clean Körncke reaction for the synthesis of 4-aryl-2,2:6,2-terpyridines (11 examples) in water under both MW irradiation or conventional heating conditions at 130°C (Scheme 82). The use of MW irradiation at 200 W significantly reduces the reaction time to 16 min from 240 min required under conventional synthesis and improves the reaction yields 82–93% from 71% to 81%.

Triazines and tetrazoles are important class of nitrogen heterocycles that form an integral part of therapeutically interesting compounds which display diverse biological activities. Shie et al. [118] reported a method for the direct conversion of aldehydes to triazines (five examples, 69–83% yields) and tetrazoles (five examples, 70–83% yields) with high optical purity via cycloadditions of intermediate nitriles with dicyandiamide and sodium azide under MW irradiation (Scheme 83). Formation of triazines and tetrazoles requires refluxing (e.g., ~100°C) for a prolonged period (12–48 h) in traditional methods.

The benzoxazole moiety is an important pharmacophore due to the biological activity (melatonin receptor agonist and cyclooxygenase inhibitory, anticancer antimycobacterial, elastase inhibitory, etc.) displayed by 2-substituted benzoxazoles [119]. Chakraborti et al. [119,120] described an efficient new methodology for the synthesis of 2-substituted benzoxazoles (16 examples)/benzothiazoles (18 examples) from carboxylic acids by direct condensation with 2-aminothiophenol/2-aminophenol following the MW procedure in absence of any metal catalyst and under solvent-free conditions (Scheme 84). Reaction of 2-aminophenol with various carboxylic acids under MW irradiation in a domestic MW oven using micro-mode operation and full power for 20 min provided good yields (up to 90%). In contrast, the conventional methodologies suffer from harsh reaction condition (refluxing at higher temperature ~200°C for days/hours).
Scheme 80. Synthesis of spiro-2,5-diketopiperazines by MW protocol.

Scheme 81. Synthesis of a 9-substituted acridines using the catalyst under MW radiation.

Scheme 82. Synthesis of 4\(^{-}\)aryl-2,2\(^{-}\)-terpyridines in aqueous media.

Scheme 83. Synthesis of triazines and tetrazoles using MW heating.
Investigation [119] by this group reveals that in the case of dicarboxylic acids 310, the reaction proceeds via the formation of the corresponding anhydride and affords predominant formation of the mono-benzoxazole 311 (Scheme 85).

4. Conclusion

The development of more environment-friendly methodologies is certainly a very current topic. Synthetic organic reactions performed under MW irradiation are gaining popularity, because this technique offers simple, clean, fast, efficient and economic for the synthesis of a large number of organic compounds including N-containing heterocycles. This technique enables a number of reactions to be completed under mild reaction condition, in shorter reaction times, and with higher yields that either do not occur under conventional heating or occur at much higher temperatures. We herein describe the current developments in the synthesis of N-containing heterocyclic compounds using MW heating. We believe that in the coming future many more MW-assisted reactions could be done on industrial scales thereby increasing the overall efficiency of the processes. The future for the application of MW technology looks bright because of its efficiency and its potential to contribute to clean products.

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