Reminiscing the microwave-assisted chemistry of 5- and 6-membered benzene-fused N-heterocycles

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This article is dedicated to Prof. Dr. Ahmed Kamal for his outstanding contribution to organic synthesis, bio-catalysis, and medicinal chemistry

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Abstract

The dominance of N-Heterocycles' in chemical sciences, especially in drugs and pharmacological agents, makes them fascinating to advance their sustainable chemistry. Besides, the microwave technique enables functioning at higher temperatures beyond the boiling point of the reaction medium to offer adequate chemical transformations, which tend to be hassled with the classical approach. Herein, we have discussed microwave-assisted chemical transformations of paramount N-heterocycles (five- and six-membered) from the past decade. The role of microwave technique and its benefits has been emphasized in terms of reaction time, product yields, neat and clean reaction products, chemo/regio/enantioselectivity, and mild reaction conditions to achieve efficient transformations.

Keywords: Microwave-assisted organic synthesis, N-heterocycles, indole, benzimidazole, quinoline
1. **Introduction**

Advancements in synthetic technologies through efficient and sustainable methods benefit the construction and diversification of organic frameworks.\(^1\)-\(^3\) A concern among the scientific community is to minimize toxic and hazardous reagents in chemical syntheses and find sustainable, greener approaches.\(^3\),\(^5\) The approach towards microwave chemistry with the advancement of safe instrumentations marked the beginning of an era for organic synthesis with reduced energy consumption and accelerated chemical synthesis.\(^6\)-\(^9\) The transformation of electromagnetic energy in the form of heat by organic compounds during microwave irradiation raises the system's temperature (may beyond the reaction medium) more efficiently than conventional heating (conduction and convection).\(^10\)-\(^13\) The microwave-assisted syntheses offer sustainable outputs like minimal waste/by-product formation, highly efficient heating, increased process speed, nominal use of toxic chemicals, higher purity, atom economy, solvent-free reactions with improved yields, and reduced reaction time.\(^14\),\(^15\)

Nevertheless, the application of microwave-assisted transformations in the chemical laboratory has been appraised previously. Reviews encompassing the synthesis of various heterocycles through microwave technology have been published by Kaur *et al.*, followed by a study by Frecentese *et al.* answering the importance of microwave reactions in combinatorial chemistry.\(^16\),\(^17\) Henary *et al.*, described the microwave-assisted synthesis of therapeutically active heterocycles.\(^18\) Banerjee *et al.*, published a summary of catalyst-free microwave-assisted synthesis of heterocycles.\(^19\)-\(^21\) We have recently outlined the syntheses of five-/six-membered poly-aza-heterocycles (e.g., triazole, triazine, tetrazine, triazine), as well as non-(benzo)-fused aza-heterocycles (e.g., aziridine, azetidine, pyrrole, pyridine, azepine) using microwave technologies.\(^22\)-\(^23\) Herein, we aim to collate the literature of microwave-assisted chemical transformations associated with the class of benzo-fused N-heterocycles like indole, benzimidazole, quinoline, isoquinoline, cinnoline, phthalazine, quinoxaline, quinazoline, and their analogues. This review emphasizes comparative analysis and the benefits of microwave-assisted transformations over classical heating. Eventually, such heterocycles are part of different synthetic or natural complex organic frameworks with excellent applications in various scientific domains.

Organic frameworks containing N-heterocycles are the principal component of various natural and synthetic compounds with particular applications in multiple research fields. The N-heterocycles mentioned above are abundant in natural products like tryptophan, reserpine, quinine, morphine, rutaecarpine,
vincristine, histamine, etc. The synthetic derivatives of such heterocycles possess a broad spectrum of pharmacological activities such as anticancer, antiviral, antibacterial, anti-inflammatory/analgesic, antifungal, antihypertensive, antiprotzoal, neuroprotective, antituberculosis, antihistaminic and other. These heterocycles are an integral part of top prescription drugs, e.g., indomethacin, roxindole, indalpine, ondansetron, telmisartan, albendazole, chloroquine, amodiaquine, fasudil, gefitinib, afloqualone, azelastine, hydralazine, varenicline, quinacillin, and many others. Moreover, these heterocycles have applications in pesticides, organic-electric devices, versatile building blocks, ionic-liquid, metal-ion coordination, fluorescent probes, and diagnostic agents (Figure 1). These significant and diverse applications prompted the researcher to develop a rapid and efficient protocol for various chemical transformations associated with such heterocycles.

![Figure 1](image-url)

**Figure 1.** Applications of N-heterocycles in different scientific domains and representative examples of drugs containing N-heterocyclic moiety.

### 2. Benzene-fused five-member N-heterocycles

#### 2.1. Indole

Fischer indole synthesis has given access to aromatic indoles from phenylhydrazine with aldehyde/ketone in the presence of Brönsted and Lewis acids which are unstable and hazardous. The use of SO\(_3\)H-functionalized ionic liquids was reported for synthesizing indole in an aqueous medium under microwave irradiation. This protocol uses arylhydrazine hydrochloride salts 1, (readily available and low-toxic) with various aliphatic cyclic/acyclic ketones, aromatic ketone, aliphatic aldehyde yielded indole 3, up to 96% in 15 min (Scheme 1). The use of ruthenium catalyst allowed the replacement of the carbonyls with 1° or 2° alcohols having benefits such as easy handling, low toxicity, more stability, and commercial availability. However, the heterogeneous catalyst Amberlyst-15 was also found to be useful, avoiding the use of costly metal catalysts. The use of
Microwave heating in these protocols produced the best yield in shorter time than conventional overnight heating.

Scheme 1. Microwave-assisted Fischer indole synthesis.

Peter Wipf’s research group reported the convergent synthesis of 4-substituted indoles (8) by adding an α-lithiated alkenylfuran 5 to α,β-unsaturated aldehydes followed by microwave-initiated intramolecular Diels–Alder furan (IMDAF) cycloaddition and in situ dehydrative aromatization reaction. The addition of α,β-unsaturated aldehydes to in situ generated α-lithiated alkenylfuran in anhydrous THF at -78 °C resulted in the corresponding hydroxyl homoallylic furanamines. Subsequently, the intramolecular cyclization followed by aromatization to furnish the desired product was initially conducted under conventional reflux in toluene. In the reaction, gradual decomposition of starting material was observed without detection of desired outcome up to 48 h. However, further trials under microwave heating at 180 °C for 20 min in 1,2-dichlorobenzene furnished the desired product 8 with good yields. Later, they reported the synthesis of 5-hydroxy-4-substituted indole 10 by replacing the carbonyls with substituted alkynols based on the same IMDAF approach, which helps in the aromatization of intermediate at an earlier stage with the elimination of only two molecules of water. The reaction is well tolerated with branched/cyclic aliphatic/aromatic/heteroaromatic alkynols. Sterically bulky groups promote product formation and provide better yields than aliphatic substituents (Scheme 2).
N-Aryl-β-nitroenamines 11 along with other β-electron-withdrawing substituents such as carboxyl ester (–CO₂R) or cyanide (–CN) were transformed into 3-substituted indoles 12 (nitro, cyano or ester) in the presence of palladium catalyst via intramolecular arene-alkene coupling with complete regioselectivity in microwave heating. As classic indole nitration uses harsh acidic conditions, sometimes expensive rhodium catalysts, and is limited by low functional group tolerance, lower yields, and lack of regioselectivity is often observed. In the protocol, the initial trial with conventional heating produced only about 25% yield after 48 h at 140 °C. In contrast, microwave heating reduced the reaction time to 1.5 h with product formation up to 98%. A wide variety of electron-rich, electron-deficient, or neutral α-substituted aryl enamines or aliphatic enamines were tolerated with good outcomes. In contrast, heterocyclic enamines gave lower yields due to catalyst poisoning (Scheme 3). An amide-directed intramolecular C-H amination of N-picolinoyl enamide 13 in the presence of a copper catalyst under microwave irradiation also produced 2-arylindoles 14 with good yield (Scheme 4). The mechanism involves ligand exchange of Cu(OPiv)₂ with 13 to form N,N-bidentate complex I, followed by C-H activation and subsequent reductive elimination to form II. The hydrolysis of II results in the formation of product 14.

Scheme 3. Microwave-assisted synthesis of 3-substituted indoles 12.

Scheme 4. Microwave-assisted synthesis of 2-substituted indoles 14 and its mechanism.

A one-pot three-component domino reaction of enaminones 15 was reported, resulting in multi-functionalized tetracyclic indeno-indole derivatives 17 under mild microwave reaction conditions. In the protocol, substituted cyclic enaminones were reacted with ninhydrin and aryl amines or acid anhydride, which also serves the purpose of solvent. The reaction with aryl amines in acetic anhydride follows sequential methyl migration, aromatization, and esterification steps, whereas the presence of AcOH has high syn-
diastereoselectivity. The use of microwave heating significantly improved the product yield by 87% with different N-aryl enaminoes having electron-withdrawing or releasing substituents (Scheme 5).33

Scheme 5. Microwave-assisted one-pot domino synthesis of indeno-indoles 17.

Microwave-assisted regioselective synthesis of 2-aryl-3-functionalized indole derivatives 21 was reported via a three-component domino reaction between anilines, arylglyoxal monohydrates, and cyclic 1,3-dicarbonyl compounds. The protocol uses green solvent and mild reaction conditions; produced good results with electron-rich or electron-deficient anilines as well as arylglyoxals in short reaction times (Scheme 6). Apart from the superior tolerance achieved over both electron-withdrawing and electron-donating substituents, substitution at ortho-position of aniline resulted in steric hinderance, thus reducing the reaction outcome.34

A catalyst-free multi-component bicyclization from arylglyoxals, cyclic enaminoes, and amino acids resulted in diastereo-enriched oxazolo-indoles 23 under microwave irradiation with high yields and high diastereoselectivity. This environment-friendly approach (only water as a by-product) was compatible with electron-rich, neutral, and electron-deficient substituents; notably, a single diastereomer was obtained with β-alanine as substrate (Scheme 7). Increment in the length between carboxylic group and amine in the amino acid favored the higher diastereoselectivity and electron donating groups in the enaminoe favored the reaction compared to enaminoes substituted with electron-donating groups.35
Microwave-assisted cascade strategy was applied for synthesizing quinolone fused indoles 26 starting from 2-(phenylethynyl)anilines and aryl isothiocyanates in the presence of a silver catalyst. Due to the failure of conventional heating to produce good yields with various catalysts, solvents, and temperatures for 24 h, the author shifted to microwave heating, where a significant yield improvement of 81% was observed in a short reaction time (only 30 min). The protocol has good substrate scope with substituted anilines and aryl isothiocyanates. In an expedition to synthesize N-aryl sulphonyl indoles as α/γ/δ PPAR triple activators, including clinical candidate lanifibranor from 2-iodo-nitrobenzene (27), the central indole framework was prepared through a microwave-assisted reaction. Out of five steps, intramolecular cyclization was performed under microwave irradiation in the presence of a copper catalyst resulting in a good yield of N-sulfonyamide indole derivatives 29, which upon further ester hydrolysis, led to the desired compounds. Similarly, another silver/copper-catalyzed selective anti-Michael hydroamination of β-(2-aminophenyl)-α,β-ynones 30 furnishing 2-acylindoles 31 was reported under microwave irradiation. The extensive screening for suitable catalysts, solvents, and temperatures showed that these reactions produced inappreciable yields (32%) along with the remaining 60% starting material in conventional heating for 16 h at 100 °C. The application of microwave heating in this conversion produced a good yield (up to 92%) with complete conversion in 15 – 20 min under the same catalytic system. In the protocol, a wide range of substrates produced satisfactory yields except for thienyl and cyclohexyl substitutions (Scheme 8).

Narayana et al., (2018) reported the regioselective synthesis of chiral-enriched tetrahydrohexanone-fused indoles via nitro-reductive cyclization of Ullmann products 33 (a chiral-rich synthon) under microwave irradiation. The Ullmann products were synthesized under microwave heating, producing a good yield within 20 min. Further, the reductive cyclization was optimized with a molybdenum-based catalyst under microwave conditions for 15 - 20 min, resulting in tetrahydrohexanones 34 with satisfactory outcomes. In contrast, this transformation required about 12 h in classical reflux. The strategy was applied in synthesizing the precursor for indoloquinoline alkaloid cryptosanguinilentine (37), possessing antimicrobial and cytotoxic activity (Scheme 9). The various substitutions over the phenyl group did not affect the reaction significantly and halogen/keto moieties in the substrates did not underwent any change during the conversion. Moreover, in our laboratory, we have developed an intramolecular azido-reductive cyclization method by employing TPP or NiB in HCl–MeOH (1M) using microwave irradiation for the synthesis of naturally occurring rutanecarpine (39) and their derivatives (Scheme 9).
Scheme 8. Microwave-assisted synthesis of indoles from 2-ethynylanilines.

Scheme 9. Microwave-assisted synthesis of hexanone-fused indoles, cryptosanguinilentine, and rutaecarpine.
Similarly, an environmentally benign synthesis of bioactive indole derivatives 41 from respective urethanes was reported in the presence of a base. The reactions use mild conditions with a significantly improved yield up to 92% under microwave compared to the conventional result of 62%. The oxidative cyclization of 2-substituted-α-(trifluoromethyl) styrenes 42 in the presence of ceric ammonium nitrate (CAN) under microwave irradiation produced the corresponding 3-(trifluoromethyl) indoles 43. The transformation furnished good yields with desired products in a short reaction time of 3 min under microwave while about 24 h is taken in conventional reflux (Scheme 10). A variety of substitutions on the phenyl ring were tolerated in the protocol along with different N-H protections such as mesyl and tosyl groups.

![Scheme 10. Synthesis of 2-acylindoles, indole-2-carboxylates and 3-(trifluoromethyl)indoles.](image)

In pursuit of further diversification, various chemical functionalization of indoles under the microwave technique was reported. Diselenide 44 was reacted under microwave conditions with N-1 or C-2/5/6 substituted indoles 45 resulting in combretastatin A-4 analogues of 3-(3,4,5-trimethoxyphenylselenyl)-1H-indoles 46. The microwave-assisted synthesis of 3-selenyl indole was reported with the best results obtained in 30 min with the isolated yield up to 84% as they already reported conventional protocol by Fang et.al., involved long reaction time of around 36 to 48 h and with the same condition use of other substrate produced only 47% of the desired product after 48 h reflux. The reaction was reproduced with different C-2 alkyl or aryl or C-5/6 electron-withdrawing or donating substituents over indoles; although C-5-NH₂ has not produced satisfactory results (Scheme 11).

![Scheme 11. Microwave-assisted synthesis of 3-(trimethoxyphenylselenyl)-1H-indoles (CA-4 analogues).](image)

The structural analogues of ervatamine-silicine alkaloids having cycloheptaindole scaffold were synthesized starting from substituted 2-bromobenzaldehyde 47 in three steps. The final Heck coupling was performed with microwave irradiation in which N-boc protected-bromoindole was used in the presence of palladium catalyst with base producing satisfactory yields of products 49 in 10 min, although unprotected free N-H had lower yields. A direct approach for synthesizing tetracyclic fused carbazoles by tricyclization of N-
propargylanilines 50 bearing conjugated diynes was reported via cascade reaction through allenylindole intermediate 51a and rearrangement of N-propargyl group followed by intramolecular nucleophilic addition and subsequent hydroalkenylation. The electron donating substituents (5-OMe) hindered the product formation, attributed to the decreased stability of the product due to high electron density or due to competitive nucleophilic attacks. The report shows that reaction performed under conventional heating could not produce desired results even after a longer reaction time. In contrast, microwave heating produced good results with 100% atom economy from various diversified substrates having yields up to 86%. Further, the compound formed in the conventional method 51b, has been reacted under microwave heating which furnished the titled compounds 52; indicating that the conventional method was unable to cross the energy barrier for the transformation and justified the importance of microwave technology (Scheme 12).46

Scheme 12. Microwave-assisted synthesis of benzocycloheptaindoles (a) and tetracyclic fused carbazoles (b).

Microwave-accelerated one-pot tandem synthesis of unsymmetrical urea was reported via Curtius rearrangement from (hetero)aromatic acids and aryl amines in the presence of diphenylphosphorylazide (DPPA). This method enabled highly rapid (1 - 5 min) construction of an array of unsymmetrical urea with excellent yields and applicable to the gram-scale synthesis of key biologically active congeners. In the same course of reactions, 5-chloro indole-2-carboxylic acid with aniline furnished an acceptable yield of indole containing urea 55 just in 1 min under microwave condition (Scheme 13).47

Scheme 13. Microwave-accelerated synthesis of unsymmetrical urea 55.
1-Alkoxypyrazino-indoles 58, were synthesized from the corresponding N-[(propargyl)indol-2-carbonitriles 56 with primary/secondary alcohol or thiols in the presence of a base under microwave condition via domino process; proceeds through an alkyne-allene rearrangement followed by nucleophilic cyclization. The reaction optimization shows about 50% yield under conventional heating at 80 °C in DMSO for 18 h; the yield reached 80% when the reaction was refluxed in DBU for 18 h without using any other solvent. Moreover, reaction time dropped down to 30 min by using microwave heating at 150 °C with comparable yields. This protocol offers substrate scope with a phenyl ring of indole as well as over alkyne moiety, although the allenyl intermediates were observed when 2,2,2-trifluoroethanol or t-butanol was used (Scheme 14).48 The use of secondary alcohols such as isopropanol and cyclohexanol did not yield the desired products.

Scheme 14. Microwave-assisted base-promoted synthesis of 1-alkoxypyrazino-indoles.

A one-pot metal-free atom-economic three-component cascade condensation of N1-boc-3-amino indole 59, benzyl isocyanide and various aldehydes resulted in pyridobiindole 61 by microwave-assisted reaction in an acidic medium. The work aimed to synthesize pyrrolo-indoles via Schiff base formation and subsequent cyclization under thermal conditions. However, the result was knocked out as an expanded pyridobiindole ring demonstrating decent anticancer activity. The reaction produced the best results with microwave heating (100 °C, 10 min) in an acidic medium for various aliphatic or aromatic aldehydes with electron-donating/withdrawing substituents (Scheme 15).49

Scheme 15. Microwave-assisted one-pot metal-free synthesis of pyridobiindoles.

Michael’s addition of 2-aryl-indole 62 with various chalcones substituted with electron-withdrawing/donating groups using ZrCl4 as Lewis acid catalyst resulted in cytotoxic agents such as 1,3-diaryl-3-(2-(phenyl-1H-indol-3-yl)propan-1-ones 64. The reaction was performed under microwave heating in neat conditions and notably improved yield up to 91% with exclusive single product formation observed just in 40
min compared to 73% yield after 8 h reflux in acetonitrile (Scheme 16).\textsuperscript{50} Moreover, exclusive product formation was observed in all the substrates and electron-withdrawing substituents on the chalcones favored the reaction.

Indoles bearing 2-nitroethyl and polar azole moiety were synthesized by conjugate Michael addition of 1,3-dicarbonyl compounds to 3-(2-nitrovinyl)-1H-indoles 65 followed by cyclo-condensation with hydrazine or hydroxyl amine to generates pyrazole (68a) or isoxazole (68b) ring respectively. The Michael addition reaction has been performed at room temperature and under microwave heating, and the latter technique gave better results, especially with C-2 bulky substituted indoles, which produced unsatisfactory results at ambient temperature. Similarly, the next cyclization step with hydrazine or hydroxyl amine under microwave heating had excellent results, completed in 1 h while in the ambient condition needed 14 h (Scheme 17).\textsuperscript{51}

![Scheme 16. Microwave-assisted synthesis of 1,3-diaryl-3-(2-phenyl-1H-indol-3-yl) propan-1-one.](image)

![Scheme 17. Microwave-assisted synthesis of indoles bearing 2-nitroethyl and polar azole moiety.](image)

Microwave-assisted protocols have been utilized in our endeavor to synthesize various heterocycles of potential biological interest.\textsuperscript{52,53} Pyrrolidine fused bis-spirooxindoles were constructed from the reaction of 3-alkenyloxindoles with \textit{in situ} generated azomethine ylide via [3+2] cycloaddition. The catalyst-free one-pot reaction of alkenyloxindoles 69, α-amino acids 70, and isatin 71 efficiently yielded the products 72 under microwave irradiation at 100 °C for 15–20 min. The reaction kinetics was effectively improved under microwave irradiation without using any additive or catalyst and enabled high yields (66–95%) in short reaction time with broader substrates scope (Scheme 18).\textsuperscript{52}
Scheme 18. Microwave-assisted synthesis of pyrrolidine fused bis-spirooxindoles.

Another regioselective Friedel–Crafts arylation of 3-hydroxy-3-phenylethynyl oxindoles 73 with different electron-rich nucleophiles was established to construct a new C-C bond. The reaction of 3-hydroxy-3-(arylethynyl)oxindole with nucleophiles such as phenols, sulphonamides, anisole, benzofuran, and benzothiophene employing BF$_3$\cdot$\text{OEt}_2$ under microwave was performed. The reaction furnished high yields of densely substituted 3-substituted-3-propargyloxindoles 76a (up to 89%) in 5 - 10 min at 60 °C (Scheme 19).

Scheme 19. Microwave-assisted regioselective Friedel–Crafts arylation and new C-C bond formation.

2.2. Benzimidazole

Kahveci et al., (2017) provided a comprehensive review of the microwave-assisted synthesis of benzimidazole and its derivatives from 1994 – 2016. In this section, we aimed to discuss reports hereafter for the synthesis and functionalization of benzimidazoles. Ortho-phenylenediamine 77 (OPDA) with aldehydes is the most common precursor; 2-(bis-indolyl)methyl benzimidazoles 78a were prepared by solvent and catalyst-free green protocol in neat conditions. The reaction of OPDA with bis-indolymethane-based aryl aldehydes under microwave irradiation afforded benzimidazoles with yields ranging between 86-94% within 3-5 min. DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) has been efficiently used as an oxidant in similar reaction for chemoselective one-pot synthesis of 2-arylbenzimidazoles 78c from OPDA with substituted benzaldehydes.
under microwave heating, where electron-withdrawing group substituted aldehydes were more favourable.\textsuperscript{56} OPDA 77 and methyl 4-formylbenzoate also reacted in the presence of Na\textsubscript{2}S\textsubscript{2}O\textsubscript{4} in DMF under microwave for 5–10 min furnished imidazoles 78b. Product 78b was engaged in a series of transformations to afford the compounds with anticanidal, cytotoxic/anticancer, intestinal antiseptic, antimicrobial, COX inhibition, and antifungal profiles (Scheme 20).\textsuperscript{57} The OPDA has also been replaced with 2-hydroxy/mercapto-anilines 79 in the presence of EDC·HCl to synthesize 2-ethylaminobenzimidazole 80 under microwave for 15 min (Scheme 21). Electron-donating substituents on the OPDA achieved higher yields compared to electron-withdrawing substituents as a resultant effect on the basicity of OPDA.\textsuperscript{58}

![Scheme 20](image)

**Scheme 20.** Microwave-assisted synthesis of 2-(bis-indolyl)methyl benzimidazoles.

![Scheme 21](image)

**Scheme 21.** Synthesis 2-aminoethylbenzimidazoles using EDC·HCl with OPDA or its analogues.

Many pharmacologically active agents were synthesized in a very efficient manner with the help of microwave-assisted chemistry. Pyrazole-aldehydes 81 on reaction with OPDA, produced anti-proliferative benzimidazole derivatives 82 tethered with triazole and pyrazole under microwave irradiation. The conventional synthesis of these compounds needed about 8–10 h producing 60–65% yields, whereas the application of microwave took about 15–25 min to complete protocol (2-steps) with improved outcomes up to 89% (Scheme 22).\textsuperscript{59} Antimicrobial agents like methyl 1-(4-fluorophenyl)benzimidazole-5-carboxylates 85, were prepared from 2-(\(p\)-fluorophenyl)amino-aniline 84 (instead of OPDA) upon reaction with various alkyl/aryl/heteroaryl aldehydes under solvent and catalyst-free microwave heating. The results were compared with mechanochemical (grinding) and conventional process; grinding yielded only 10–56% of products, the traditional process improved yields to 60–90\% in 12–18 h, whereas microwave reaction afforded excellent yields ranging from 85 to 97\% in 5–8 min (Scheme 23).\textsuperscript{60}
Scheme 22. Synthesis of triazole and pyrazole tethered benzimidazole derivatives.

\[
\begin{align*}
\text{Ph-NH-NH}_2 + \text{Ar-Co-Me} & \rightarrow \text{Ar} = \begin{array}{c}
\text{R} \\
\text{H} \text{F} \text{ClBrMe} \text{OME}_{\text{NO}_{2}}
\end{array} \\
& \begin{array}{c}
\text{Ph} \\
\text{Ar}
\end{array}
\end{align*}
\]

(i) EtOH, H^+, MW, 180W, 5 - 6 min.  
(ii) POCl_3, DMF, MW, 300W, 6 - 10 min.

Better yields and reduced reaction time, in compare to classical heating

Scheme 23. Synthesis of 2-substituted methyl 1-(4-fluorophenyl)benzimidazole-5-carboxylates.

The one-pot two-step reaction of OPDA precursor/analogue o-nitrochlorobenzene 86 with substituted (hetero)aryl amines under microwave resulted in 2-aryl benzimidazole-N-oxides 87. The isolation of these coordination compounds (with push-pull electron donor/acceptor group) was a significant challenge during conventional heating (yield 20–30%), whereas 40 min microwave heating yielded product in pure form with >75% yield (Scheme 24).\(^1\) The presence of string electron withdrawing groups in the substrate facilitate the cyclization through deprotonation of amine group in the intermediate.

\[
\begin{align*}
\text{HO}_2\text{C} & \rightarrow \text{MeOH}, H^+, MW, 80^\circ C, 10 \text{ min.} \\
\text{NO}_2 & \rightarrow \text{MeOH}, \text{H}_2\text{O}, rt, 10 \text{ min.} \\
\end{align*}
\]

Ar = 4-F-C_6H_4; alkyl = nBu, nHept; aryl = Ph; 4-F/Cl/Br/IOH/NO_2/CF_3/Me/OME/NH_2/NMe_2/SMc-C_6H_4; 3,4-(OH)_2-C_6H_5; 2,3,4-(OH)_3-C_6H_5; /\text{naphthyl}; /\alpha-(E)-prop-1-en-1-y-Phe; 2-OH-4,6-(OME)_2-C_6H_5; furen-2-yl, thiophen-2-yl, 6-chloroquinolin-2-yl

Scheme 24. Microwave-assisted synthesis of 2-arylbenzimidazole-N-oxides.

In another three-step protocol, o-nitro-p-trifluoromethylchlorobenzene 88 with various amines under microwave transformed to OPDA analogues followed by NO_2-reduction to 89, and used for the synthesis of 1,2-dialkyl-5-trifluoromethylbenzimidazoles 90. Initially, only 48% yield was observed under conventional reflux, whereas a remarkable yield improvement to 93% was observed with microwave heating at 120 °C. Further, cyclization with aliphatic ortho-esters (instead of aliphatic acids - prone to decomposition) was optimized under solvent and catalyst-free microwave heating at 150–190 °C with >95% overall yields. These substrates are helpful in synthesizing miconazole/fluconazole analogues (Scheme 25).\(^2\) Microwave-assisted reductive cyclization of 5-piperazino/morpholino-2-nitroaniline 92 (constructed from 5-chloro-2-nitroaniline) with aldehydes afforded piperazine/morpholine containing 2-arylbenzimidazoles 93. The S_NAr and cyclization
both steps took 15 min each under microwave heating; whereas conventional heating at the same temperature required 24 h and 6 h, respectively, for two steps (Scheme 26).63

*use of aliphatic acids in place of aliphatic ester for cyclization, didn’t afforded satisfactory results due to decomposition at high temperature

Scheme 25. Microwave-assisted synthesis of 1,2-dialkyl-5-trifluoromethylbenzimidazoles.


ortho-Haloanilines with cheap, non-toxic aqueous ammonia (as nitrogen source) and different aldehydes resulted in 2-alkyl/aryl substituted benzimidazoles 97 under solvent-free microwave heating at 100 °C with appreciable yields up to 95% within 15 min. Aldehydes containing electron-donating substituent enhanced the formation of N-phenylformimine, a key intermediate of reaction. Moreover, this protocol has been useful for the efficient synthesis of anthelmintic albendazole and mebendazole (Scheme 27).64 The reaction of o-fluoroarylformamidines 100 with alkyl/benzyl amines (primary amine) by microwave irradiation furnished N1-alkyl-2-unsubstituted benzimidazoles 101 without using any catalysts. Although in this protocol, aryl/heteroaryl amines were not producing the desired results or satisfactory yields, various aliphatic, benzyl, and hydroxyl substituted amines (strong nucleophiles) were well tolerated. Moreover, electron-withdrawing solid groups over o-fluoroarylformamidines favoured the regioselective results in a short time (Scheme 28).65

Scheme 27. Microwave-assisted Ni-catalyzed synthesis of benzimidazoles.
Scheme 28. Microwave-assisted metal-free synthesis of \(N^1\)-alkyl-2-unsubstituted benzimidazoles.

Polymer bound \(N^1\)-substituted OPDA 102 with 4-fluoro-3-nitrobenzoic acid produced \(N^2\)-amide coupled intermediate 104 in 15 min; followed by acid-catalyzed intramolecular cyclization under microwave afforded good yields of polymer immobilized \(N^1\)-substituted 2-(4-fluoro-3-nitrophenyl)benzimidazoles 105 at 100 °C for 15 min. Further, this aryl fluoride was subjected to \(S_nAr\) with pyrrole-2-carboxylate in presence of base under microwave heating for 10 min offering efficient access to 106; whereas conventional protocol required about 18 h due to less reactivity of fluorides towards aromatic nucleophilic substitutions (Scheme 29).

Scheme 29. Synthesis of polymer immobilized \(N^1\)-substituted 2-(4-fluoro-3-nitrophenyl)benzimidazoles.

The various chemical modifications of benzimidazole were efficiently accessed under microwave conditions to produce the most desirable molecules. The first report of base-catalyzed one-pot multicomponent Povarov reaction of 2-aminobenzimidazole with aldehydes and electron-deficient dienophiles (alkynes) afforded a library of dihydropyrimido-benzimidazole 110 with an unusual 1,3-sigmatropic rearrangement under microwave heating for 10 min. Moreover, the 1,3-sigmatropic rearrangement was not observed with ketones, disubstituted alkylnes, and with the rigid configuration of Povarov product like in the case of 2,3-dihydrofuran as dienophiles. The reaction was also tried with conventional reflux or excessive heating in a sealed tube took a longer reaction time of 24 h (Scheme 30).

C. M. Sun and their group explored various reactions of 2-aminobenzimidazole and similar analogues for cycloaddition reactions under microwave heating. The regioselective condensation of soluble polymer-supported 2-aminobenzimidazoles 111 with \(\alpha\)-bromoketones followed by subsequent intramolecular cyclization promoted by microwave heating afforded imidazobenzimidazoles 112a at 150 °C for 15 min. The methodology was well-tolerated among aliphatic and aromatic ketones with an exception for heteroaromatic aldehydes. In contrast to prolonged conventional Ugi reaction for synthesizing the desired product, microwave-assisted protocol quickly afforded a high yield of guanidine implanted heterocyclic library. Similarly, a one-pot three-component reaction of 111 with aryl aldehydes and isocyanides afforded the same
kind of heterocycles 112b with good yields. In this protocol, it was observed that initial imine formation with aldehyde and cycloaddition with isocyanides were promoted by microwave heating. Also, all the three reactants irrespective of their stereo-electronic nature resulted the products in good yields. In contrast, a sealed tube reaction at a similar temperature for 12 h produced lower yields (Scheme 31).69 Aza-pentacyclic benzimidazo-pyrrolo-isoquinolones 115 were prepared in the two-step, three components coupling of ionic liquid supported 2-cyanomethylbenzimidazoles with methyl 2-formyl benzoate followed by cycloaddition with isocyanides promoted under microwave conditions. In this protocol, the synergy of ionic liquid (IL) with microwave heating was observed, where microwave activated both steps (Knoevenagel followed by cycloaddition). The cycloaddition under conventional sealed tube heating (180 °C, 12 h) has a significantly reduced yield; whereas microwave heating resulted in a better yield in a shorter time and at a lower temperature (150 °C, 15 min) (Scheme 31).70

Scheme 30. Microwave-assisted base-mediated Povarov reaction of 2-aminobenzimidazole.

Scheme 31. Microwave-promoted synthesis of imidazobenzimidazoles and benzimidazo-pyrrolo-isoquinolines.

N-Difluoro methylated benzimidazoles and imidazoles 117, were synthesized directly using inexpensive, commercially available TMS-CF₃ (Ruppert-Prakash reagent) under microwave conditions in relatively shorter
reaction time. Moreover, this protocol also works with conventional heating but requires a longer time (3-8 h). The earlier report used chlorodifluoromethane (ozone-depleting) or TMSCF₂Br (commercially not available) under strongly acidic conditions (conventional approaches). Benzimidazoles and imidazoles with electron-withdrawing/donating substituents showed similar reactivity (Scheme 32). Further, this protocol was extended for the difluoromethylation of theophylline and 8-(1H-benzimidazol-2-yl)quinoline as amyloid β-peptide inhibitor.

Telmisartan is a widely prescribed antihypertensive drug containing two benzimidazole moieties. A new convergent synthetic route was developed with some key steps under the microwave, significantly improving yield and reducing total reaction time. The previous approach was limited in terms of low overall yield (about 21%) and harsh reaction conditions (high temperature and acidic medium), which impacted yield and purity. The new protocol combines two functionalized benzimidazoles (121 and 124) by a high-yielding Suzuki reaction catalyzed by a homogeneous palladium source or graphene-supported palladium nanoparticles. This protocol produced high yields of commercial drug telmisartan (Scheme 33).

Another significant result for the influence of microwave was observed in one-pot metal-free C-N bond formation/cleavage in the synthesis of benzimidazoquinazolines 126 from N-(2-benzimidazolyl)-o-aminobenzamides and ortho-halogenated aldehydes under basic medium. The conventional protocol uses transition-metal catalysis with expensive ligands and additives. This metal-free microwave-promoted method furnished the designed product in 5-15 min at 130 °C with appreciable yields up to 77%; whereas conventional heating to the same temperature for 16–18 h produced only 36% yield (Scheme 34).

We have published gratifying results from the Knoevenagel condensation between N-substituted thiazolidine-2,5-dione 128 and 2-substituted benzimidazole-5-carboxaldehyde 130 under the microwave. The reaction furnished the corresponding benzimidazole-thiazolidinedione derivatives 131 as potential anticancer scaffolds. The comparative results from conventional and microwave protocols; showed better yields up to
95% in 5–10 min for microwave-assisted synthesis. The conventional protocol has significantly lower products of all the analogues (up to 79%) in 6–12 h (Scheme 35).  

Scheme 34. Microwave-accelerated one-pot metal free synthesis of benzimidazoquinazolines.

Scheme 35. Microwave-assisted synthesis of benzimidazole-thiazolidinediones as anticancer scaffolds.

A pleasant explanation of condition-based scaffold divergence for condensing 2-cyanomethyl benzimidazole 132 with α-bromoketone was accomplished, where regioselective C- vs. N-alkylation was observed under conventional and microwave conditions, respectively. Owning to the fact, two non-equivalent nucleophilic centers (C- or N- of 132) react selectively under conventional and microwave heating affording 2-amino-5-aryl furan-3-yl-benzimidazoles 134a or 3-cyano-4-aryl-pyrrolo-benzimidazoles 134b as a result of intramolecular cyclization of corresponding C- or N- alkylated intermediates respectively (Scheme 36).  

Cho and co-workers explored the condensation of 2-aminobenzimidazoles with β-bromo-α,β-unsaturated aldehydes under microwave-assisted transition-metal free basic medium furnishing polycyclic benzimidazo-pyrimidines 137. The protocol used organic (TEA) or inorganic (K₂CO₃) bases in DMF with various aliphatic, alicyclic, and aromatic aldehydes and furnished the corresponding N-fused benzimidazoles (Scheme 37).  

Cyclic β-bromo-α,β-unsaturated aldehydes produced better yields (72–82%) compared to benzo-fused β-bromo-α,β-unsaturated aldehydes (61% in 2 hours). Other reactions reported with benzimidazole include Knoevenagel condensation, and microwave-enhanced Suzuki-Miyaura coupling with improved functional group tolerability.
Scheme 36. Conventional or microwave condition-based regioselectivity in 2-cyanomethyl benzimidazole.

Scheme 37. Microwave-assisted synthesis of pyrimidine/quinazoline fused benzimidazoles.

3. Benzene-fused six-membered N-heterocycles

3.1. Quinoline and isoquinoline
The sustainable synthesis of quinoline heterocycle using microwave was suitably collected in early 2019;\textsuperscript{83} new synthetic approaches that appeared afterward are discussed in this section. The one-pot reaction of 2-nitrobenzaldehyde and indole was reported as a new variant of Friedlander synthesis for constructing 3-(o-aminoaryl)quinoline 140. This robust reaction involved the reduction of 2-nitrobenzaldehyde in the presence of SnCl\textsubscript{2}, which provides an acidic medium to the reaction and leads to the formation of products 140 (Scheme 38).\textsuperscript{84}

Scheme 38. Microwave-assisted one-pot synthesis of 3-(o-aminoaryl)quinoline.
Microwave-assisted metal-free synthesis of C-4 arylated quinolines 142 using multicomponent Povarov reaction with (+) camphor sulphonic acid (CSA) catalyst was reported. The reaction involved [4+2] cycloaddition of in situ generated imine with alkynes without any observation of Troger’s base formation, which was inhibited by CSA. The earlier reported synthesis of 4-arylated quinoline involved longer heating with metal catalysts, thus the microwave-assisted reactions are energy efficient which were completed within 20 min without any metal catalyst.85 Similarly, metal-free synthesis of 2,4-diarylquinolines 145 from 2-aminobenzophenones and β-ketosulphones was also reported. This microwave-assisted Friedlander reaction was catalyzed by p-TsOH·H₂O and had good atom economy with improved product yields (Scheme 39).86 The four-component metal-free microwave-assisted reaction between arylaldehydes, dimedone, malononitrile, and ammonium acetate in the presence of a recyclable homogenous catalytic amount of N-methylpyridinium tosylate (ionic liquid) furnished appreciable yields of titled products. This protocol has been featured with operational simplicity, short reaction time (3–8 min), excellent product yields, and high energy efficiency (Scheme 40).87

![Scheme 39. Microwave-assisted metal-free synthesis of 4-arylquinolines.](image)

![Scheme 40. Microwave-assisted metal-free synthesis of 4-aryl hexahydroquinoline.](image)

Apart from these recent synthetic reports, several reactions and applications regarding quinoline derivatives have been explored under microwave conditions, including nucleophilic substitution reactions,88-90 multicomponent reactions,91-94 C-H functionalization95,96 and others.97,98 Regioselective nucleophilic substitution reaction of 2,4-dichloro-3-nitroquinoline 148 with different aryl/alkyl amines was explored. The reaction yielded only traces of products in conventional heating, whereas 10-15% of the product was obtained in neat microwave heating. Further, using water as a solvent with microwave heating led to the temperature-dependent regioselective formation of products 149a and 149b. Moreover, with organic polar/nonpolar solvents, regioselectivity was not observed. The regioselectivity of the reaction was attributed to the solvent-assisted electron delocalization towards nitrogen and increased electrophilicity at C-4 position of the quinoline. The water can also stabilize the Meisenheimer complex via ‘ambiphilic dual activation’, which is less likely to happen at C-2 position of the quinoline (Scheme 41).90
Scheme 4.1. Regioselective nucleophilic substitution of 2,4-dichloro-3-nitroquinoline.

The catalyst-free one-pot multicomponent reaction of 4-hydroxy-2-quinolone 150 (1,3-dicarbonyl precursor) with malononitrile and arylglyoxal furnished fused pyranoquinolines derivatives 151. The reaction was assisted by microwave heating at 110 °C in ethanol producing good yields of 72-92%. The protocol featured catalyst-free, atom-efficient, use of greener solvent, short reaction time, easy purification, and applicability to a wide range of substrates, including naphthoquinones, coumarins, and pyrans.91 Similarly, the one-pot, three-component condensation of 8-hydroxyquinolines 152 with aryl/heteroaryl aldehydes and malononitrile also furnished pyranoquinolines 153 under microwave irradiation just in 2 min (Scheme 4.2).92


The one-pot multicomponent reaction of quinoline-2-carboxaldehyde 154 with substituted phenylacetylenes and secondary amines furnished the pyrrolo[1,2-a]quinolines 155. The reaction performed in the presence of copper nanoparticles as a heterogeneous catalyst under microwave conditions in a recyclable green solvent like ethylene glycol at 100 °C for 30 min produced the desired products with only water as by-product.93 Another multicomponent reaction of 2-chloroquinoline-3-carboxaldehyde 156 with acetophenone and piperidine under solvent-free microwave condition furnished quinoline-chalcone derivative 157 via a cascade of aldol condensation and nucleophilic substitution (Scheme 4.3).94 Michael’s addition of 2-methylquinoline with β-nitro-styrene furnished the product 159 via water-mediated catalyst-free benzylic C-H functionalization. Interestingly, among the solvents screened, water gave
the best result without any catalyst under microwave irradiation (no effect was detected with iodine as a catalyst in organic solvents). The developed protocol is advantageous in using green solvents, energy efficient, easy work-up and isolation. The reactions were tolerated with 8-nitroquinoline and various nitrostyrene-bearing electron-releasing/withdrawing groups in which electron-releasing groups offered better yields. Microwave-assisted solvent-free Rh-catalysed C(sp<sup>3</sup>)-H activation of 8-methylquinoline was reported with phenyl isocyanates providing the corresponding C-C coupled products 161, in 10 min with appreciable yields and purity (Scheme 44).96

![Scheme 43. Reactions of quinolines forming pyrroloquinolines or quinoline-chalcones.](image)

Scheme 43. Reactions of quinolines forming pyrroloquinolines or quinoline-chalcones.

![Scheme 44. C-H functionalization of quinoline derivatives under microwave conditions.](image)

Scheme 44. C-H functionalization of quinoline derivatives under microwave conditions.

Quinoline N-oxide with aryl diazonium salts in a catalyst-free regioselective reaction under microwave irradiation furnished two products, namely 3-hydroxyquinolines 163a and 2-anilinoquinolines 163b, in which acetonitrile (solvent) act as single nitrogen source forming two new C-N bonds. The conventional approaches required copper/silver catalysts or diethyl hydrogen phosphonate with prolonged reaction time (>20 h) at elevated temperatures using arylisothiocyanates or arylamines as nitrogen sources. The microwave heating at 120 °C enabled the reaction without any metal catalysts, which upon further acid hydrolysis, led to the formation of 2-anilinoquinolines 163b within 15 min up to 65% yield. Interestingly, when the reaction was performed with C-2 substituted quinoline N-oxide, the product was 1,3-oxygen shifted C-2 substituted 3-hydroxyquinolines 163a (Scheme 45).98
Scheme 45. Regioselective synthesis of 2-anilinoquinolines and 3-hydroxyquinolines.

We also synthesized hexahydroquinolin-5-one fused with phenanthrene 165 in a one-pot single-step conversion of phenanthrene-9-amine 164, arylaldehydes, and 1,3-dicarbonyl compounds. The microwave-assisted catalyst-free protocol offered broad substrate scope with high product yields (89 – 95%) within 20 min at 150 °C (Scheme 46). The prepared series displayed significant in vitro cytotoxicity profiles in sub-micromolar concentration against various cancer cells and were safer to normal cell line.99

Scheme 46. Microwave-assisted synthesis of hexahydroquinolin-5-one fused with phenanthrene.

Isoquinoline is equally important, being a structural isomer of quinoline.100 Isoquinoline is a core part of several drugs such as dimethisoquin, quinapril, debrisoquine, sequinavir, papavarine etc.101-103 It has also been used as an organic catalyst in several reactions alone or along with metal catalysts as a ligand.104 Past decade witnessed several reports on microwave-assisted synthesis of isoquinolines and their derivatives. The basic reaction course involved C-C coupling between 2-halobenzaldehydes with alkynes in generating 2-alkynyl benzaldehydes, which upon reaction with different nitrogen sources, converted to imines, followed by annulation to furnish 3-substituted isoquinolines. The reaction of 2-bromobenzaldehydes 166 with various alkynes under palladium catalyst and copper additive (Sonogashira coupling) resulted in the corresponding alkynyl aldehyde 167, which upon treatment with ammonia (nitrogen source) under microwave heating for 30 min at 130 °C furnished isoquinolines 168 with moderate yields over two steps.105 The reaction produced the same results in three component single-step reaction with slightly prolonged heating under microwave irradiation.106 The propargylated ketone derivatives 169 have been implemented with good results (in place of aldehyde) by replacing the catalytic system with silver triflate.107 The key steps in these reactions were imination of the carbonyl group, replacement of ammonia with ammonium acetate under palladium catalysis without any additive, improved the product yields up to 80% from <60% (in the case of ammonia). Thus, it indicates better efficiency of ammonium acetate as a nitrogen source and for imination.108 2-Propargyl benzaldehydes 170 were employed with ammonium acetate, and good yields of isoquinoline derivatives 168 were observed.109 t-Butyl amine was used to have a more effective nitrogen source. Interestingly, the reaction furnished anticipated quinolines 168 within 4 min under microwave conditions only with economical copper-
catalyst and avoided the uses of expensive palladium catalysts. Pleasingly, 2-chloro arylaldehydes also gave isoquinoline in good yields when used in place of 2-bromobenzaldehydes. It was also found that the use of benzamidine 171 (as nitrogen source) furnished the product without any metal catalyst in 5 min using microwave heating. All the results together indicate the imination efficiency of different nitrogen sources as ammonia < ammonium acetate < tert-butyl amine < benzamidine, which was followed by intramolecular cyclo-annulation obtained isoquinoline with appreciable yields in a short reaction time (Scheme 47).

Vinyl isocyanides 172 were efficiently used in the synthesis of isoquinolines; hydroxyl-containing isoquinolines 173 were prepared by the reaction of vinyl isocyanides with alcohols under metal-free microwave conditions via radical cyclization. Radical insertion/cyclization of vinyl isocyanides with C(sp³)-H bond adjacent to a heteroatom in the presence of iron catalyst was also reported to generate isoquinoline 174. Isooxazoline-functionalized isoquinolines 175 were prepared via radical cascade cyclization of vinyl isocyanides with α,β-unsaturated ketoximes using n-Bu4NI (TBAI) catalyst under microwave condition (Scheme 48). These microwave-assisted reactions have been advantageous in terms of high yields, short reaction time, eco-friendly, broad substrate scope, good functional group tolerance, and the use of cheaper metal-catalyst or free of catalysts.

Dibenzoylhydrazine (ketazine, 176) was used for annulation with internal alkynes in the presence of ruthenium catalyst and resulted in isoquinoline derivatives 177 via C-H/N-N activation under microwave condition for 10 min. The protocol fulfills the need for sustainability in terms of green chemistry principles and applies to gram-scale synthesis. Another ruthenium-catalyzed reaction of aryl ketones/α,β-unsaturated ketones 178, alkynes, and ammonium acetate resulted in the isoquinoline or substituted pyridines 179. The three-component reaction preceded via C–H activation → N-annulation sequence under microwave resulted in appreciable yields of isoquinolines in 10 min (Scheme 49). We have accomplished an efficient microwave-assisted protocol for the direct oxidative coupling of acetophenones with secondary amines such as

![Scheme 47. Synthesis of isoquinolines via aldehydes – alkynyl coupling followed by cyclization.](image-url)
tetrahydroisoquinolines, tetrahydro-β-carbolines, and alkylamines to afford α-ketoamides 180. The protocol was optimized with the use of Cu(I) complex as a catalyst in water under microwave conditions producing high yields (72–92%) at 60 °C for 10 min compared to lower yields at conventional heating for 12 h (Scheme 50).

Scheme 48. Synthesis of isoquinolines from vinyl isocyanide via radical insertion/cyclization.

Scheme 49. Microwave-assisted C-H/N-N activation for synthesis of isoquinoline.

Scheme 50. Microwave-assisted oxidative coupling of ketones with secondary amines, including isoquinoline.
3.2. Cinnoline and Phthalazine

A microwave-assisted domino strategy was implemented with benzofuran derivatives to access cinnoline-4-carboxamides efficiently. The microwave-promoted reaction between arylglyoxals, isocyanides, and cyclic 1,3-dicarbonyl compounds resulted in high yields of multi-functionalized 6,7-dihydrobenzofuran-4-ones 181 (EtOH, 60 °C, 25 min; 71–92%). The regioselective ring-opening of 181 in the presence of hydrazine hydrate under the same reaction condition afforded the corresponding hexahydrocinnoline-4-carboxamides 182 with good yields of 70–83% (Scheme 51).117

![Scheme 51. Synthesis of cinnoline-4-carboxamides 182, from benzofuran derivatives.](image)

Unsymmetrical benzo[c]cinnolines have been synthesized from 2,2'-dinitro-1,1'-biphenyls by a domino partial nitro group reduction followed by intramolecular diazo bond formation.118 A short, metal-free, green and efficient approach using 4-methyl-pyridazine-3-carboxylate 183 with nitro-olefins was presented to synthesize poly-functionalized cinnolines 184. The controlled microwave heating at 100 °C for 20 min in the presence of piperidine afforded high yields (86–93%) of expected cinnoline derivatives without detecting possible phthalazine formation (Scheme 52).119 This synthetic strategy was implemented for reaction inside natural Lycopodium clavatum sporopollenin (LCS) microcapsules for the first time and synthesized cinnoline-loaded microcapsules along with pure cinnoline and were evaluated for antibacterial potential against gram-positive and gram-negative bacteria.120 Alternatively, these molecules have also been constructed with aryl aldehyde and nitromethane instead of nitroolefins under similar microwave-assisted reaction conditions.121

![Scheme 52. Synthesis of poly-functionalized cinnolines from 4-methyl-pyridazine-3-carboxylate.](image)

Tandem one-pot annulation (aldol-condensation followed by Michael-type addition) of 3-oxo-2-arylhydrazonopropanals 185 with aceto-acetanilide in the presence of mild base gave access to 2-arylcinnolin-6-one derivatives 186. The initial screening of the reaction condition revealed ethanol with triethylamine as the best combination offering the highest yields. The reaction was performed under different heating modes: conventional reflux, ultrasound waves, and microwave heating. The conventional reflux was inefficient with
low yield and long reaction time (45–75%; 2–4 h), whereas the application of ultrasound improved the reaction efficiency to an extent (50–82%; 40–80 min). The application of microwave heating enhanced the reaction rate and furnished the highest yields (60–90%) within 3–10 min (Scheme 5). In addition, some cinnoline has also been reported to be used in the Stille-coupling under microwave condition.

Scheme 53. One-pot annulation of 3-oxo-2-arylhydrazonopropanals with acetoacetanilide.

In an attempted reaction of 4,7-dichlorobenzalphthalides 187 with methylhydrazine, a new scaffold pyrazolo[3,4,5-d,e]phthalazine 188 was confirmed under classical reflux (via a phthalazinone intermediate); even with an equimolar amount of substrates (1:1) and mild heating. The reaction cannot be stopped at phthalazinone intermediate stage under reflux. Interestingly, this transformation has been controlled by microwave heating, where exclusively phthalazinone products 189 were obtained even with an excess of hydrazine. Although some hydrazine derivatives led to the formation of other heterocyclic isooindolinone 190 as a significant or exclusive product. Alternatively, dihydrophthalazine-1,4-dione(s) 191 can be prepared by direct reaction of phthalic anhydride with a variety of substituted hydrazines/amines under microwave heating for a short reaction time (<5 min) at 160–170 °C. Although with electron-deficient hydrazine, the reaction ended with isoindol-1,3-diones 192, which were subjected to ring expansion in a subsequent step towards preparing phthalazine derivatives (Scheme 54). However, there is no report for the conversion of 190 to 189; unlike 192 to 191.

Scheme 54. Microwave-controlled synthesis of phthalazines (pyrazolo-phthalazine with classical heating).
Regioselective isocyanide insertion was observed in the synthesis of phthalazines in the presence of a Pd(0) catalyst. The reaction of ortho-(pseudo) halobenzoate 193 with hydrazine and isocyanide under microwave heating for 5 min progressed by isocyanide insertion to the ortho-halogen-carbon bond followed by amine attachment and lactomization to 4-aminophthalazin-1(2H)-ones 194 with the high yield up to 99%. Another palladium-catalyzed reaction of ortho-bromobenzaldehyde with arylhydrazines yielded N-arylphthalazinone 195. In the reaction, Mo(CO)₆ was employed (avoided use of toxic carbon monoxide), which furnished appreciable yields up to 75% with microwave heating at 140 °C for 60 min (Scheme 55).

Scheme 55. Microwave-assisted synthesis of phthalazines from ortho-halo-benzoate/benzaldehyde and hydrazine.

A catalyst-free synthesis of pyrazolo/indazolo[1,2-b]phthalazine-diones 196 under controlled-microwave irradiation was achieved in a benign reaction media. The one-pot MCR reaction of phthalic anhydride, hydrazine hydrate, arylaldehyde, and active methylene reagents (malononitrile, ethylcyanoacetate, cyclic diones etc.) in glycerol under microwave heating at 60 °C for 15–20 min, furnished the high yields of phthalalizinones 196a,b respectively, with nitriles or diketones (Scheme 56). The reaction under conventional heating up to 4 h produced poor yields of 60% only.

Scheme 56. Synthesis of pyrazolo/indazolo[1,2-b]phthalazine-diones.

Microwave-assisted Suzuki-coupling of 1-arylamino-4-chlorophthalazine 198 gave access to 1-arylamino-4-(hetero)arylphthalazines 199; capable of reducing the production of PGE₂. Similarly, Suzuki-coupling employed with boron-difluoride complex of N-pyridyl-1-amoio-4-chlorophthalazine 201 with phenylboronic acid under microwave heating; furnished the corresponding high blue fluorescent boron difluoride complexes 202 (Scheme 57).
4-Benzyl-phthalazin-1-one derivatives 203 were subjected to \(N^2\)-alkylation (amidic–NH) in a biphasic reaction media using phase-transfer catalyst cetrimide via a microwave-promoted reaction which yielded up to 92% of \(N^3\)-alkylated 4-benzyl-phthalazin-1-one derivatives 204 within 30 min at a temperature below 50 °C. The reaction attempted under classical heating at 50 °C for 14 h, resulted in much lower yields.\(^{131}\) Microwave-assisted S-glycosylation of 4-arylphthalazine-2-thione 205 with par-acetylated ribose furnished phthalazine based S-glycosides 206; having antiviral and antimicrobial potential (Scheme 58).\(^{132}\)

**Scheme 57.** Suzuki-coupling of 1-arylamino-4-chlorophthalazine under MWI.

The \([3+2]\) cycloaddition reaction of \(N^2\)-alkylated phthalazine 207 with methyl propionate or dimethyl acetylene dicarboxylate offered access to fluorescent building blocks pyrrolophthalazines 208. Excellent yields were observed under microwave heating for 10 min (94% and 91%); while conventional approaches have compromised the yields with incomplete aromatization leading to non-aromatic side product (Scheme 59).\(^{133}\)

**Scheme 58.** Microwave-assisted \(N^2\)-alkylation and S-glycosylation of 4-aryl-phthalazin-1-one.

**Scheme 59.** Synthesis of pyrrolophthalazines – a fluorescent building block.
3.3. Quinazoline

The rapid solvent-free reaction of ortho-aminobenzonitrile 209 with arylnitriles under microwave irradiation (in a domestic oven) produced 2-substituted 4-aminquinazolines 210 in high yields (up to 93%) in the presence of potassium tertiary butoxide. Another three-step conversion of anilides 211 to 2,4-disubstituted quinazolines 213 was reported via cascade of photochemical Fries-rearrangement to ortho-aminocarbonylbenzene followed by reaction with acyl chloride to an amide derivatives 212. These amides were efficiently cyclized to quinazolines 213 using ammonium formate (as nitrogen source) under neat microwave-heating for 4–20 min (Scheme 60).

\[
\text{Scheme 60. Microwave-enhanced solvent-free synthesis of quinazolines.}
\]

ortho-Halobenzoic acids 214 with amidines efficiently produced 4-quinazolinone 215 in the presence of FeCl₃ under microwave conditions in aqueous media via C-N coupling followed by intramolecular cyclization. Although the reactions proceeded smoothly in dimethyl formamide (DMF) and Fe₂(acac)₃ with almost similar yields, the use of water and readily available cost-effective FeCl₃ catalyst with L-proline is considerably better due to the green and economic aspects of the method. This reaction produces good yield with electron-rich substrates and even non-active amidines like guanidines. Similarly, N-(2-cyanophenyl)acetamide 216a (obtained form 2-aminobenzonitrile) in mild oxidative condition using UHP (Urea Hydrogen Peroxide) under aqueous microwave condition furnished 2-chloromethyl-4-quinazolinone 217a in 90 min (30 h in conventional heating, have poor yields). Alternatively, the one-pot reactions of N-acyl-2-aminobenzamides 216b (from 2-aminobenzamides) in water under microwave heating have also been furnished quinazolinone 217b with yields up to 87% (Scheme 61).
Apart from 2-aminobenzamide, its precursor, 2-nitrobenzamide 218 has been used to synthesize 4-quinazolinone 219 via a cascade of palladium-catalyzed hydrogen transfer followed by condensation and was promoted by microwave-irradiation at 150 °C for <10 min. This method was also used for the synthesis of benzimidazoles and 1,4-benzodiazepines by replacing o-nitrobenzamides with respective substrates (Scheme 62).138

A solvent and catalyst-free one-pot microwave-promoted strategy was developed to synthesize 4-aryl-dihydro-quinazolines. The reaction of 2-aminobenzophenones with different aldehydes and urea (as nitrogen source) furnished excellent yields of dihydroquinolines 220a with little traces of aromatic counterpart 220b, after microwave irradiation for 4 min at 130 °C. This clean and simple protocol has wide substrate scope for benzophenone derivatives and aldehydes; ammonium acetate has also been used effectively as a nitrogen source producing high yields 80–90%. These syntheses under the classical approach in acetic acid required continuous reflux for 10 h.139 Another one-pot Lewis acid-mediated activation of aliphatic/aromatic nitriles with amino-benzophenone efficiently produced 4-aryl quinazolines 220b via in situ amidine generation under solvent-free microwave conditions. The reaction produced high yields ranging from 72–81% under microwave heating at 100 °C for 10 min in the presence of TMSOTf. The protocol was equally effective with anthranilic acid; afforded good yields of 4-quinazolinones 220c (Scheme 63).140
Tetrahydroquinazoline 221 has been prepared from a three-component one-pot reaction of guanidine carbonate, aldehydes, and cyclic ketones using an acidic ionic liquid catalyst under solvent-free microwave conditions. Although the reaction was also attempted with ultra-sounds using an excess of ionic liquid (as solvent and catalyst), the solvent-free microwave condition was proved more efficient in terms of chemical yields and reaction time (Scheme 64).^{141}

![Scheme 63. Microwave-assisted solvent-free synthesis of 4-aryl quinazolines from benzophenones.](image)

Scheme 64. Microwave-assisted solvent-free IL-catalysed synthesis of tetrahydroquinazoline.

The chemical reactions of quinazolines include microwave-assisted synthesis of 2/4-arylaminoquinazolines 223a,b by substituting 2/4-chloroquinazoline with aromatic amine to furnish biologically relevant molecules. Before that, 2-chloroquinazoline 222a was prepared by chlorinating quinazolines-2,4-dione with phosphorous oxychloride, followed by selective dehalogenation with activated zinc and aqueous ammonia. Similarly, 4-chloroquinazoline 222b was prepared from 2-aminobenzonitrile by condensation with formic acid followed by chlorination. Further, both 2- or 4-chloroquinazoline were subjected to nucleophilic substitution with arylamines under microwave at 150 °C for 15 min.^{142} A well-known C-N bond forming reaction, Buchwald-Hartwig cross-coupling uses palladium catalysts; as an alternate, DMAP-catalysed amination with microwave condition was reported. The reaction of 4-chloroquinazoline 222c with different aryl/heteroaryl amines under microwave irradiation furnished considerable yields of 223c up to 98% with a broad scope of anilines and other heterocyclic amines (Scheme 65).^{143}
Scheme 65. Microwave-assisted alternative Buchwald-Hartwig reaction for the synthesis of 2-/4-arylaminourazoles.

A simple and efficient cyclization of 2-(2-aminophenyl)quinazoline-4-amine 224 with various aryl aldehydes furnished tetracyclic dihydroquinazolines 225. The microwave-assisted protocol produced high yields up to 96% within 5 min; while 2–4 h continuous reflux was required for comparable yields in the classical approach. 2-(Chloromethyl)-4-quinazolinone 226 subjected to amidic -NH methylation under microwave condition at 60 °C for 30 min followed by nucleophilic substitutions with arylsulfonyl chloride or nitroalkyl anions furnishing the corresponding sulfones 227a or 2-ethylenic derivatives 227b, respectively (Scheme 66).

Scheme 66. Synthesis of tetracyclic dihydroquinazolins and 2-substituted 4-quinazolinone.
3.4. Quinoxaline

The most often adapted synthetic strategy is double condensation of 1,2-dicarbonyls with 1,2-diaminoaromatic compound. A neat reaction of N,N-diphenacylaniline with o-phenylenediamine (OPDA) in the presence of p-TSA produced unexpected 2-arylquinoxaline (228) (presumably proceeded by tandem carbonyl addition → eliminative cyclization → air oxidation sequence) under microwave irradiation for 10 min in open vessel domestic microwave oven. A efficient solvent and catalyst-free green protocol used for the reaction of various substituted OPDA with phenyl/furyl substituted 1,2-dicarboxyls under microwave afforded the corresponding quinoxalines (229) up to 98% in 2-6 min. The replacement of 1,2-dicarbonyls with α-hydroxylimino ketones (easily prepared from corresponding α-CH₂-ketones) under neat microwave heating offered high yields (up to 96%) of respective quinoxalines (230) in 6–10 min. Another replacement of dicarbonyl with a cost-effective α-hydroxy ketone (2-hydroxy acetophenone derivatives); in the presence of silica-gel afforded good yields of quinoxalines (231) under solvent-free microwave heating for <20 min. However, this reaction under conventional reflux or with various organic solvents offered poor conversion (yields <10%). A fast multicomponent approach for the reaction of acetophenone derivatives in the presence of oxidants (AgI, iodine, and succinamide) was optimized towards synthesizing 2-arylquinoxalines (232). The protocol used green reaction media ethanol:water or PEG400:water with microwave heating, in which in situ generated α-iodoacetophenone condensed with OPDA; resulted in a high yield of anticipated aryloxiquinoxalines (232) within 5–10 min. Bis-(α-bromoketone) i.e., acetophenone derivatives, were employed under microwave heating to prepare quinoxalines (233). Although the protocol attempted with various solvents, bases, and heating modes proceeded towards product formation. Still, the best yields of up to 90% were obtained in ethanol and piperidine under microwave heating for 10 min. The reaction of a simple p-OH derivative of acetophenone did not afford any expected product, whereas when 2,3-diaminopyridine was employed, two regio-isomers were observed. An efficient solvent-free protocol for synthesizing quinoxalines from sterically/bulky glyoxalate was optimized under microwave with the use of a Mont-K-10 catalyst. The Hinsberg hetero-cyclization of imidazo-pyridyl based α-ketoesters under conventional reflux did not proceed even after 48 h. Concurrently, the reaction with microwave activation resulted in effective transformation to the corresponding imidazo-pyridylquinoxalin-2-ones (234) with appreciable yields. A fascinating copper-catalyzed one-pot A³-coupling of OPDA with ethylglyoxalate and terminal alkyne was optimized towards the synthesis of furoquinoxalines (235). The protocol has broad substrate scope for the reaction of various substituted OPDA and terminal alkynes in toluene under microwave heating at 110 °C for 10 min; affording high yields up to 93% (Scheme 67).
Scheme 67. Synthesis of quinoxalines by condensation of 1,2-dicarboxyls with 1,2-diaminoaryls.

The reaction of indane-1,2,3-trione with OPDA using a Mont-K-10 catalyst under solvent-free microwave irradiation for 5 min generated good yields of indenoquinoxalines 236, which has been further treated with indole derivative to produce bis-indole-containing indeno[1,2-b]quinoxalines 237. Similarly, the reaction of OPDA and isatin in glacial acetic acid under microwave heating at 75 °C produced indolo[2,3-b]quinoxalines 238 in high yields up to 90% within 3–5 min. The quinoxaline 238 was further functionalized with oxadiazoles by sequential reaction with ethyl-2-chloroacetate, hydrazine, and carboxylic acids. A solvent-dependent microwave-assisted approach for the chemoselective synthesis of 3-benzylquinoxalin-2-ones 239 was reported. The reaction of OPDA with 4-arylidene-2-phenyloxazol-5-ones under microwave heating at 120 °C, resulted in different products depending upon the choice of solvent made; ethylene glycol with a catalytic amount of TFA afforded high yields of 239 up to 90% in 10–20 min (Scheme 68). Moreover, the reaction in acetic acid or DMSO, respectively, resulted in benzimidazole and β-amino dipeptides.
Scheme 68. Synthesis of quinoxalines by condensation of OPDs with different di-keto or its analogues.

The reaction of OPDA with N-methyl-4-hydroxy-5-oxo-pyrroles 240 in acetic acid furnished quinoxalines 241. The reaction under conventional heating produced a mixture of 2,4-dihydro-pyrrolo-quinoxalines 241a and aromatized pyrrolo-quinoxalines 241b. In contrast, an attempt for the sole aromatized product could not be achieved even by extending the reaction time or by means of an oxidizing reagent (decomposition of starting material was observed). Later, the reaction with microwave heating exclusively produced 241a after 3 min at 40 °C or exclusive aromatized products were afforded at 180 °C for 10 min (Scheme 69).156

Scheme 69. Temperature-controlled microwave-assisted synthesis of pyrrolo-quinoxalines.

PEG-400 has been found as a catalyst for the reaction of 1,2-diamines with dicarbonyls in synthesizing quinoxalines. A protocol was optimized with microwave heating for 4–6 min at 120 °C afforded yields up to 96% for various aliphatic/aryl/hetero-aryl diamines with a catalytic amount of PEG-400 (Scheme 70).157

Scheme 70. Microwave-assisted synthesis of quinoxalines catalyzed by PEG-400.

Isocyanide-based chemistry of coupling reactions was used for the preparation of quinoxalin-2-one. Ugi adduct (4C-MCR – isocyanide, aldehyde, amine, and acid) was effectively used to construct the quinoxalines.
The adduct 244 of indole-2-carboxaldehyde(s), 2-iodoanilines, isocyanides, and carboxylic acid derivatives were exclusively transformed into 5,6-dihydroindolo[1,2-a]quinoxalines 245 using a copper catalyst, through microwave-accelerated chemoselective C-N and C-C bond formation during intramolecular cyclization.158 Another intramolecular cyclization of Ugi adduct 246 from N1-boc-phenylenediamines, bromoacetic acid, arylaldehydes, and isocyanides in the presence of a mild base under microwave heating at 80 °C for 10 min afforded quinoxaline derivatives 247 in substantial yields after Boc-deprotection (Scheme 71). Moreover, the protocol has access to benzimidazopyrazinone derivatives when the reaction is performed in reverse order i.e., Boc-deprotection followed by intramolecular cyclization.159

Scheme 71. Microwave-assisted intramolecular cyclization of Ugi-adducts to quinoxalines.

In the above-discussed intramolecular cyclizations, the generation of diamide intermediate/Ugi-adduct (particularly with the use of amino acids - in place of carboxylic acids) had a challenging issue. A stepwise synthetic strategy under microwave was implemented to address the diamide generation. PEG-bonded anilines and aldehydes were irradiated with microwave for 10 min at 110 °C followed by the addition of N-protected amino acids and isocyanides with further heating for 20 min at the same temperature, which resulted in crucial diamide intermediates 249. The synthesis of Ugi adducts 249 under conventional reflux required 5–10 h with poor yields of <50%. Further, amine deprotection followed by selective intramolecular cyclization resulted in tetrahydroquinoxalin-2-ones in the presence of a base, which was cleaved from PEG followed by air oxidation to dihydroquinoxaline-2-one 250 (Scheme 72).161

Scheme 72. Microwave-promoted stepwise synthesis of diamide intermediate to quinoxaline.
The one-pot two-component coupling of boc-protected 2-aminobenzonitrile with glyoxylic acids under microwave irradiation produced intermediate $N$-formylamide. The boc-deprotection (10% TFA-DCE) followed by intramolecular cyclization under microwave heating to 100 °C for 10–15 min afforded significant yields of quinoxalin-2-ones 251 (Scheme 73). This protocol also offered access to $N^1$-acylbenzimidazoles with the application of carboxylic acids in place of glyoxylic acids.\(^{161}\)

The benzofuroxan derivatives 252 with 2-cyanoacetophenone gave quinoxaline-1,4-di-$N$-oxide 253. The protocol aimed for a comparative study of conventional and microwave-assisted synthesis with different strategies to prepare the designed compounds, but the presence of hydrazone or aldehyde group in starting material did not afford any product. In contrast, with the alkyl group, poor yields were observed. Finally, the reaction of 252 with 2-cyanoacetophenone afforded satisfactory results in 30 min under microwave, whereas it took 96 h by conventional approach (Scheme 74). Further, it was modified as 2-($N$-acylhydrazone) derivatives with anti-tubercular potential.\(^{162}\)

Scheme 73. Two-component coupling of 2-($N$-boc-amino)phenylisocyanide with glyoxylic acids.

Scheme 74. Synthesis of quinoxaline 1,4-di-$N$-oxide from benzofuroxan derivatives.

Microwave-assisted reactions were also found beneficial in the synthesis of different functionalized quinoxalines such as triazolo-quinoxalines,\(^{163}\) or imidazo/pyrazolo[1,5-$a$]quinoxalin-2-amines,\(^{164,165}\) avoiding harsh conventional reaction condition or metal catalyst. These compounds found their utility as anti-inflammatory agents by inhibiting IKK1, IKK2 or selective TLR7 antagonists.

Conclusions

In summary, the syntheses and reactions of nitrogen-containing 5- and 6-membered benzene-fused heterocycles by employing microwave-assisted technology from the past decade have been discussed. It was appealing to find that microwaves have played a significant role in the sustainable construction and chemical modification of various heterocycles. The use of microwave technique in a chemical laboratory benefits the chemist in a way or other. There is example where the improvement in the yields was not observed but the reaction produced completely new class of product which not even traced in conventional heating. Indeed, the occurrence of chemical reactions in a domestic oven and rapid acceleration; indicates the catalytic role of microwaves. Moreover, the advancement in technology and the development of special instruments to
perform a reaction under high pressure in closed vessels bring many opportunities to use the temperature beyond the boiling point of the reaction medium. Indeed, the use of microwave irradiation benefits reduced side products, chemo/regioselectivity concerns, and avoiding the use of several harsh/toxic/hazardous reagents or catalysts. The future of microwave technology in chemical laboratories thrives by developing surplus protocols for various chemical transformations. In our wisdom, large-scale industrial synthesis is still an obscure area for microwave techniques, and microwave-assisted flow chemistry can open a novel state-of-the-art. Developing special instruments/hyphenated techniques to apply microwaves for bulk synthesis is very much needed.

**List of Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>MW/μW</td>
<td>Microwave (heating)</td>
</tr>
<tr>
<td>MWI</td>
<td>Microwave irradiation</td>
</tr>
<tr>
<td>IMDAF</td>
<td>Intramolecular diels–alder furan</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TEA</td>
<td>Triethylamine</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>EWG</td>
<td>Electron withdrawing group</td>
</tr>
<tr>
<td>EDG</td>
<td>Electron donating group</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>PPAR</td>
<td>Peroxisome proliferator-activated receptor</td>
</tr>
<tr>
<td>TPP</td>
<td>Triphenylphosphine</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulphoxide</td>
</tr>
<tr>
<td>DCE</td>
<td>Dichloroethane</td>
</tr>
<tr>
<td>DMA</td>
<td>Dimethylacetamide</td>
</tr>
<tr>
<td>CAN</td>
<td>Ceric ammonium nitrate</td>
</tr>
<tr>
<td>DABCO</td>
<td>1,4-Diazabicyclo[2,2,2]octane</td>
</tr>
<tr>
<td>BTMAB</td>
<td>Benzyldimethylammonium bromide</td>
</tr>
<tr>
<td>DPPA</td>
<td>Diphenylphosphorylazide</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5,4,0]undec-7-ene</td>
</tr>
<tr>
<td>OPDA</td>
<td>Ortho-phenylenediamine</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-Dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DCC</td>
<td>Dicyclohexyl carbodiimide</td>
</tr>
<tr>
<td>TBAI</td>
<td>Tetra-n-butylammonium iodide</td>
</tr>
<tr>
<td>TEAF</td>
<td>Tetra-n-butylammonium fluoride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(Dimethylamino)pyridine</td>
</tr>
<tr>
<td>NBS</td>
<td>N-Bromo succinimide</td>
</tr>
<tr>
<td>CSA</td>
<td>Camphor sulphonic acid</td>
</tr>
<tr>
<td>TFE</td>
<td>2,2,2-Trifluoroethanol</td>
</tr>
<tr>
<td>TBPB</td>
<td>Tertiary butyl peroxybenzoate</td>
</tr>
<tr>
<td>UHP</td>
<td>Urea hydrogen peroxide</td>
</tr>
<tr>
<td>MCR</td>
<td>Multicomponent reaction</td>
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References

https://doi.org/10.1002/qsar.200420039.
https://doi.org/10.1039/D0RA01378A
https://doi.org/10.2174/221333560701200422091717.
https://doi.org/10.1089/Sustain.2020.00014-X.
https://doi.org/10.2174/221333560802211028163413.
https://doi.org/10.1039/C8OB01746D.
https://doi.org/10.1002/ejoc.202001472.
https://doi.org/10.3390/molecules25081909.
https://doi.org/10.1039/D0RA09198G.
https://doi.org/10.1021/ol3030956.
https://doi.org/10.3390/app9235168.
https://doi.org/10.1039/B816989F.
https://doi.org/10.1021/jo3022605.
https://doi.org/10.1021/ol303314X.
https://doi.org/10.1021/acs.joc.7b01667.
https://doi.org/10.1021/ol3023038.
https://doi.org/10.1021/acscombsci.7b00126.
https://doi.org/10.1021/acs.joc.7b00129.
https://doi.org/10.1021/acs.joc.6b02912.
https://doi.org/10.1021/acs.jmedchem.7b01285.

https://doi.org/10.1021/acs.joc.8b00508.

https://doi.org/10.1021/acs.orglett.8b01656.


https://doi.org/10.1002/ajoc.201900061.


https://doi.org/10.1016/j.ejmech.2014.11.024.

45. Goswami, P.; Borah, A. J.; Phukan, P. J. Org. Chem. 2015, 80, 438–446.  
https://doi.org/10.1021/jo502443a.

https://doi.org/10.1021/acs.orglett.5b03254.

https://doi.org/10.1021/acs.joc.6b02521.

https://doi.org/10.1021/acs.joc.8b01279.

https://doi.org/10.1021/acs.orglett.8b03245.

https://doi.org/10.1002/slct.201900088.


https://doi.org/10.1002/slct.201802847.

https://doi.org/10.1002/slct.202001660.

https://doi.org/10.2174/2213335603666160517154048.
https://doi.org/10.24820/ark.5550190.p009.971.


https://doi.org/10.3390/molecules22040507.


https://doi.org/10.1007/s10044-016-1763-z.

https://doi.org/10.3390/molecules24203639.

https://doi.org/10.1002/slct.201700623.


https://doi.org/10.1016/j.tetlet.2019.03.028.

https://doi.org/10.1021/acscombsci.5b00010.


https://doi.org/10.1021/acscomb sci.1300075.

https://doi.org/10.1021/acscomb sci.1300049.

https://doi.org/10.1016/s0040-4039(01)99204-4.


https://doi.org/10.1021/ol403007j.
   https://doi.org/10.1021/jo5025333.
   https://doi.org/10.1021/jo5007398.
   https://doi.org/10.1021/acssuschemeng.5b01669.
   https://doi.org/10.1016/j.ejmech.2017.06.035.
   https://doi.org/10.1021/acscsombsci.7b00052.
   https://doi.org/10.1021/acsomega.8b02755.
   https://doi.org/10.24820/ark.5550190.p011.121.
   https://doi.org/10.1016/j.ejmech.2018.11.026.
   https://doi.org/10.1016/j.tetlet.2019.03.047.
   https://doi.org/10.1002/ejoc.201900325.
   https://doi.org/10.1039/c9ob02445j.
   https://doi.org/10.1021/ol034072h.
   https://doi.org/10.1021/jo9008386.
   https://doi.org/10.1016/j.bioorg.2014.11.004.
   https://doi.org/10.1039/c5ra25536h.


   https://doi.org/10.1039/c8ob01229f.
   https://doi.org/10.1002/ejoc.201900366.
   https://doi.org/10.1002/chem.201302699.
   https://doi.org/10.1039/c6gc00557h.
   https://doi.org/10.1021/co500097.
   https://doi.org/10.1002/slct.201701993.
   https://doi.org/10.1039/c8ra04195d.
   https://doi.org/10.1039/c8ra06494f.
   https://doi.org/10.1016/j.ejps.2015.12.017.
   https://doi.org/10.1016/j.tetlet.2013.05.006.
   https://doi.org/10.1002/jhet.3659.
129. Medda, F.; Sells, E.; Chang, H. H.; Dietrich, J.; Chappeta, S.; Smith, B.; Gokhale, V.; Meuillet, E. J.; Hulme, 
130. Vuong, T. M. H.; Weimerskirch-Aubatin, J.; Lohier, J. F.; Bar, N.; Boudin, S.; Labbé, C.; Gourvilleau, F.; 
   https://doi.org/10.1039/c6nj00726k.
https://doi.org/10.1002/jhet.2316.
https://doi.org/10.3390/molecules24203760.
https://doi.org/10.1016/s0040-4099(00)00090-3.
https://doi.org/10.1021/ol062540s.
https://doi.org/10.1039/b916124b.
https://doi.org/10.1039/b816723k.
https://doi.org/10.1039/c4ra15765f.
https://doi.org/10.1039/c0gc00838a.
https://doi.org/10.1002/ejoc.201701585.
https://doi.org/10.1016/j.molliq.2014.09.018.
https://doi.org/10.1016/j.bmc.2010.11.059.
https://doi.org/10.1016/j.tet.2014.09.024.
https://doi.org/10.1039/c5ra19785f.
https://doi.org/10.1002/jhet.73.
https://doi.org/10.1080/00397910902838862.
https://doi.org/10.1016/j.tetlet.2013.11.100.
https://doi.org/10.24820/ark.5550190.p011.031.
https://doi.org/10.1021/ol502072k.


https://doi.org/10.1002/jhet.2272.

https://doi.org/10.1021/acscombsci.5b00053.

https://doi.org/10.1016/j.tetlet.2014.01.106.

https://doi.org/10.1080/00397911.2010.496134.

https://doi.org/10.1002/ejoc.201300667.

https://doi.org/10.1007/s11030-018-9855-y.

https://doi.org/10.1021/acscambsci.5b00053.


https://doi.org/10.1002/jhet.2830.

https://doi.org/10.1016/j.tetlet.2014.02.080.


https://doi.org/10.1021/acs.jmedchem.9b00411.
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