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Microwave-Assisted Synthesis of Heterocyclic Scaffolds

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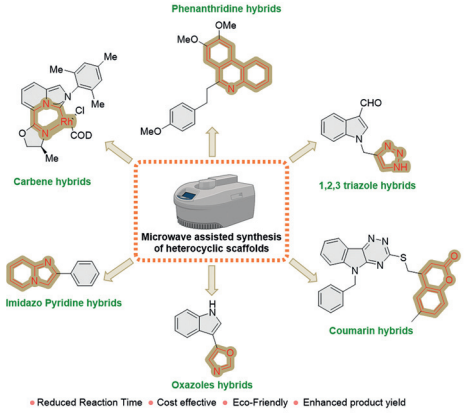

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Abstract In recent years, there has been a notable surge in the utilization of microwave energy, leading to the emergence of innovative and groundbreaking methods across various branches of chemistry, including organic synthesis, materials science, heterocyclic chemistry, and medicinal chemistry. This comprehensive literature review delves into the microwave-assisted organic synthesis of specific heterocycles, illuminating its effectiveness in producing diverse molecules with heightened efficiency and selectivity. The review highlights the significant role of microwave irradiation as a potent method for constructing a wide range of compounds. Particular emphasis is placed on the impact of the technique on synthesizing various hybrids such as 1,2,3-triazole hybrids, coumarin hybrids, imidazopyridine hybrids, phenanthridines hybrids, carbene hybrids, and oxazole hybrids. This article is valuable as it offers insights into current synthetic procedures and trends in developing innovative medications utilizing heterocyclic compounds.

Key words microwave, 1,2,3-triazole hybrids, coumarin hybrids, imidazo pyridine hybrids, phenanthridine hybrids, carbene hybrids, oxazole hybrids

1 Introduction

There is a strong push to embrace clean and renewable energy sources to combat the global warming effects induced by rising greenhouse gas concentrations.[1,2] A significant initiative in this direction is adopting sustainably produced electricity from solar and wind resources in the chemical sector. In this context, microwave (MW) technology stands out as a potential tool for enhancing industrial processes, due to its ability for quick, thorough, and targeted heating compared to traditional methods. Microwave heating shows great promise, in its adoption in the chemical industry.[3]

Ever since Gedye and Giguere introduced the use of microwaves in chemistry in 1986, Majetich has explored the impact of microwave heating on various chemical reactions in batch setups.[4,5] Over the past three decades in microwave chemistry, numerous eco-friendly methods in organic synthesis have emerged. These techniques show notable benefits over traditional heating. The inherent selective and uniform dielectric heating has contributed to energy and time conservation, facilitated the use of safer solvents or even no-solvent processes, enabled specific catalysis in fewer stages, and typically resulted in improved selectivity and yield outcomes.[6]

However, initial inaccurate temperature readings sometimes led to overestimations regarding the positive impact on reaction speeds. Despite showing rapid and effective energy transfer, MW techniques in organic synthesis were primarily restricted to the labs of a select group of specialists for quite some time. The limited data on the dielectric characteristics of materials based on temperature and frequency led to a more experience-based methodology. Concur-

rently, the focus on designing MW reactors leaned more towards its use in analytical chemistry due to the swift dispersion in sample mineralization. This absence of specialized tools often resulted in inconsistent outcomes and varied kinetics, hindering efforts to scale up for commercial use.

Even though dielectric heating demonstrated clear production advantages, industrial interest was held back by the need for safer machinery and facilities. Only the most efficient and consistent methods were chosen for further advancement.[7]

To enhance heat- and mass-transfer, a shift from batch processing to continuous processing is anticipated, a necessary step for harnessing microwave energy in industrial manufacturing. The utilization of MW in continuous-flow organic synthesis (MACOS) has been effectively explored in various organic reactions such as heterocycle synthesis and metal-catalyzed chemistry, especially in the semi-industrial production of aromatic compounds.[8] Current research on MW-facilitated synthesis has shown the potential to transition techniques from MW batch processes to either traditionally heated or MW-energized flow mode. While previous reviews and multiple publications have discussed the progress in microwave-assisted organic synthesis (MAOS) in both batch and continuous flow modes,[9–14] this overview specifically centers on recent research, highlighting the benefits and drawbacks of MW heating. This assessment particularly addresses synthetic strategies designed for process upscaling and juxtaposes various methodologies aimed at expansive synthesis. Additionally, the latest strides in stereoselective MAOS are incorporated.

This review provides a thorough and meticulously referenced analysis of microwave-assisted synthesis, offering insights into future developments. Going beyond mere theo-

Biographical Sketches

Sanjeev Kumar is a Ph.D scholar in the Medicinal Chemistry Department of the Banaras Hindu University under the supervision of Prof. Alka Agarwal. He received his undergraduate degree from Himachal Pradesh University and a post-graduation degree in chemistry from Hemvati Nandan Bahuguna Garhwal University. He passed the National Eligibility Test (NET) jointly conducted by CSIR & UGC (New Delhi, Govt of India).

Anand Maurya received his undergraduate education from the Department of Pharmacy, MJP Rohilkhand University, Bareilly, India, in 2015. Later, he completed his post-graduation from the Department of Pharmacy, Central University of Rajasthan, Ajmer, India, in 2017. He is currently pursuing his Ph.D. at the Department of Medicinal Chemistry, Banaras Hindu University under the supervision of Prof. Alka Agarwal. He has been working on various synthetic organic scaffolds and their application.

Prof. Alka Agarwal was awarded a Ph.D in 1992 from Avadh University, Medicinal Chemistry, CDRI Lucknow, UP, India. She is a recipient of the INSA Visiting Scientist Fellowship award and visited Germany. Prof. Agarwal has been working in diversified areas ranging from peptide chemistry to drug discovery. More specifically, she has been working on the synthesis of small molecules for antibacterial and antimalarial studies, X-ray crystal structure analysis of small molecules, molecular docking studies of synthesized active molecules, nanomaterials, and their applications.

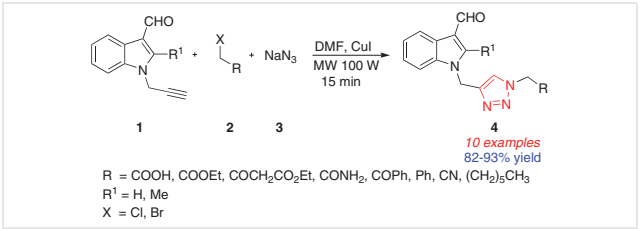
retical discourse, it furnishes practical examples and tangible advantages, rendering it an indispensable asset for scholars and practitioners engaged in synthetic chemistry.

2 Synthesis of 1,2,3-Triazole Hybrids

Triazoles consist of two carbon atoms and three nitrogen atoms arranged in a five-membered ring system. In 2002 Sharpless and Meldalin used click chemistry for the synthesis of regiospecific 1,4-disubstituted 1,2,3-triazole molecule.[15,16] The copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction has become a widely employed method for the synthesis of 1,4-disubstituted 1,2,3-triazoles, owing to its notable efficiency and selectivity. A reaction mixture of propargyl ether and azide, catalyzed by 5 mol% of sodium ascorbate and 1 mol% of copper(II) sulfate, in a 2:1 mixture of water and *tert*-butyl alcohol, a 1,4-disubstituted triazole product was obtained in a high yield of 91% stirring at room temperature for eight hours.[15]

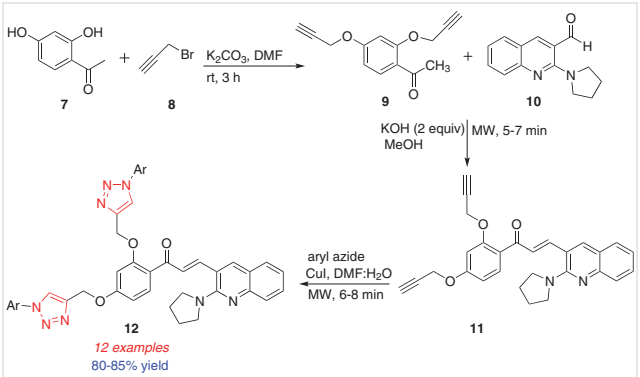
Compounds containing triazoles have garnered significant interest in the realm of drug discovery and development, attributable to their diverse pharmacological properties. Derivatives of the 1,2,3-triazole show a broad spectrum of biological activities, encompassing antimicrobial,[17] anticancer,[18] antibacterials,[19] anti-inflammatory,[20] antioxidant,[21] antimalarial,[22] apoptotic, and anticonvulsant[23,24] action.

The distinctive structure of triazoles enables interactions with diverse biological targets, positioning them as promising candidates for the development of novel therapeutic agents. Furthermore, the presence of the triazole moiety in many existing drugs highlights its importance as a pharmacophore for enhancing bioactivity and improving drug efficacy.[25] Here, we compile the recent synthesis of 1,2,3-triazole derivatives from microwave-assisted methods. Mokariya et al. reported the synthesis of 3-formylindole-linked 1,4-disubstituted 1,2,3-triazole derivative **4** (Scheme 1) using *N*-propargyl-3-formyl indole **1**, chloroacetic acid/ester **2**, and sodium azide **3** by click reaction in 15 min. CuI was used as a catalyst, and the reaction was carried out using ultrasonic and microwave irradiation at a power of 100 W. This is an innovative and efficient method for the synthesis of compounds.[25]



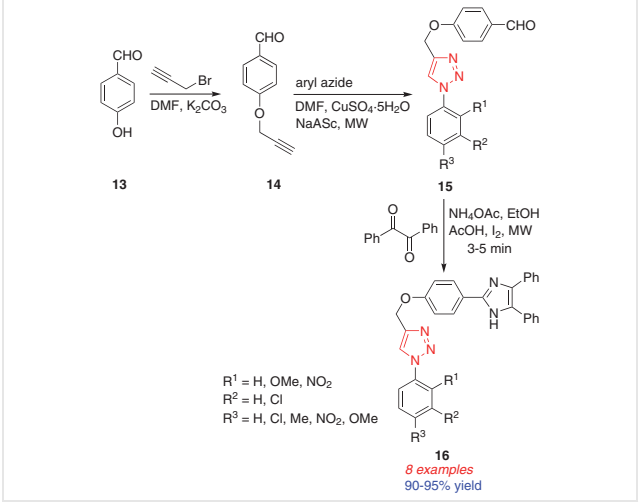
Scheme 1 Synthesis of 3-formylindole-linked 1,2,3-triazole

Pradeep et al. successfully developed a novel library of pyrrolidine-quinolinyl-bis-1,2,3-triazoles **12** (Scheme 2) by an environmentally friendly microwave irradiation technique. Propargylation, click reaction, and Claisen–Schmidt condensations were used for the synthesis, and 2,4-dihydroxy acetophenone **7** was used as the starting material, and the reaction was completed in 6–8 min with good yield (up to 85%) at a MW power of 360 W.[26]

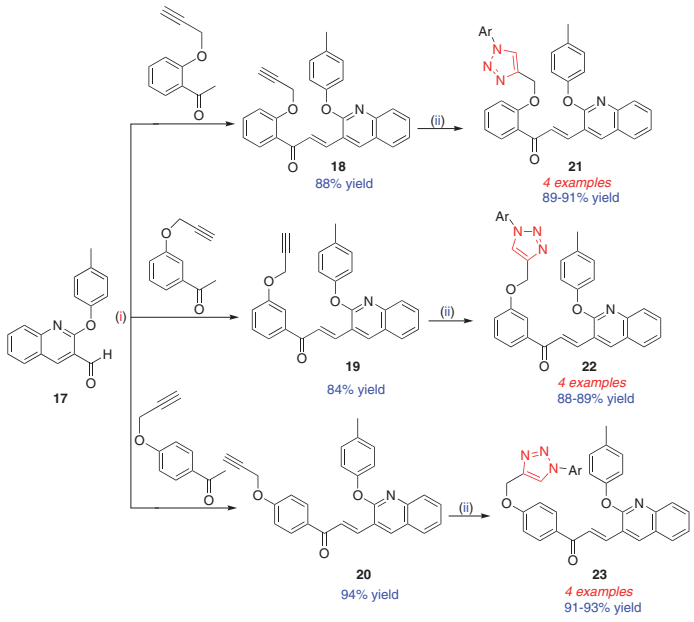


Scheme 2 Synthesis of pyrrolidine-quinolinyl-bis-1,2,3-triazoles

The microwave irradiation system was used by Subhashini et al. for the synthesis of imidazole-linked 1,2,3-triazole compounds **16** (Scheme 3). The propargylated 4-hydroxy benzaldehyde **14** was reacted with aryl azide in a click reaction, yielding the triazole ring linked 4-hydroxybenzaldehyde derivatives **15**. This process occurred in the presence of ethanol and acetic acid, under microwave irradiation, with iodine as the catalyst. The desired product was obtained in excellent yield (up to 95%).[27]



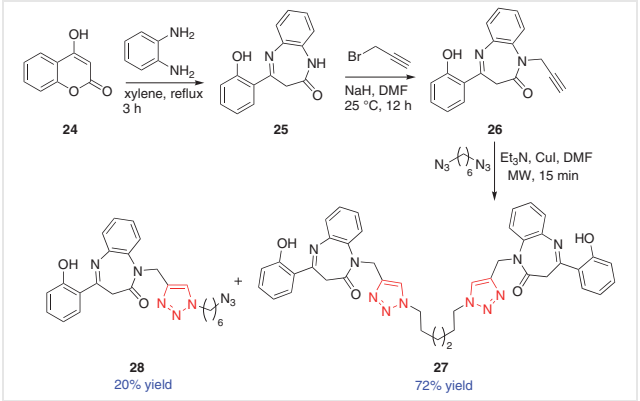
Scheme 3 Synthesis of imidazole-linked 1,2,3-triazoles



Scheme 4 Synthesis of *p*-tolyloxyquinoline-triazole hybrid

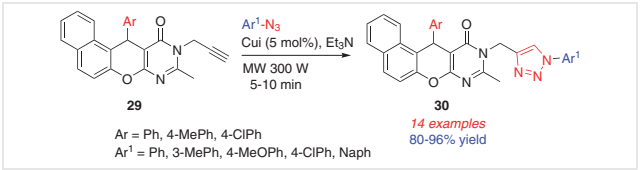
The microwave-assisted technique was used by Vishnuvardhan et al. for the synthesis of 2-(*p*-tolyloxy)quinoline-triazole hybrids **21**–**23** from 2-(*p*-tolyloxy)quinoline-3-carbaldehyde **17** and hydroxylacetophenes with CuI as a catalyst.[28] This method is convenient and efficient, providing good yields of the desired compounds (Scheme 4). In another synthesis, Zouhour et al. synthesized novel compounds, *N*-bis-1,2,3-triazole-linked 1,5-benzodiazepine-2-ones (BZD) **27** and **28** (Scheme 5) under microwave irradiation through Cu(I)-catalyzed dual 1,3-dipolar alkyne–azide coupling reaction in significant yields. 4-Hydroxycoumarin **24** and *ortho*-phenylenediamine were used as starting materials to get 4-(2-hydroxyphenyl)-3*H*-1,5-benzodiazepin-2-one **25**, the propargylation of which in anhydrous dimethylformamide (DMF) catalyzed by sodium hydride (NaH) at room temperature yielded the dipolarophile product **26**.[29]

According to Cherif et al., a novel set of hybrid regioisomeric molecules denoted as N-linked 1,2,3-triazole **30**, incorporating a pyranopyrimidinone moiety, were synthesized utilizing microwave irradiation in the presence of copper(I) catalyst (Scheme 6).[30] Dharavath et al. used a highly efficient and eco-friendly approach for the synthesis of 1,4-disubstituted 1,2,3-triazole-linked coumarins hybrids **35** (Scheme 7). The reaction was achieved through a click reaction involving several substituted aryl azides, and terminal alkynes **34**, in the presence of CuI as a catalyst. The synthetic approach yielded better results under microwave irradiation and was easier to access than the conventional heating methods.[31]

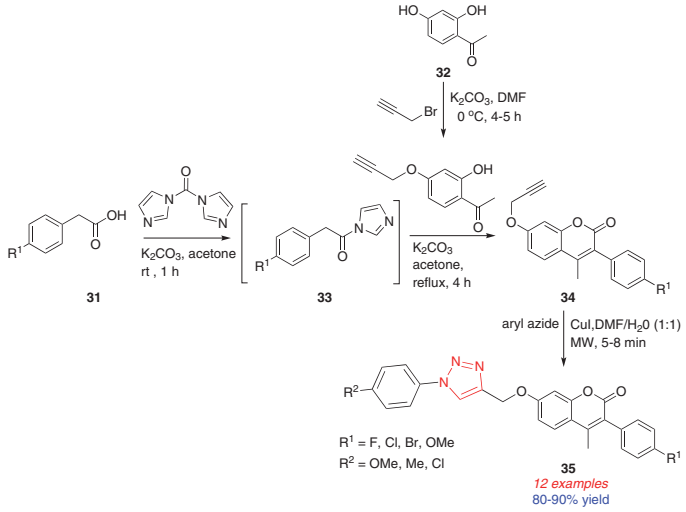


Scheme 5 Synthesis of *N*-bis-1,2,3-triazole-linked 1,5-benzodiazepin-2-ones

Aarjane et al developed an easy and eco-friendly regiospecific 1,3-dipolar cycloaddition reaction between aromatic azides and 10-(prop-2-yn-1-yl)acridone derivatives **37** using CuI as a catalyst for the synthesis of novel 1,2,3-

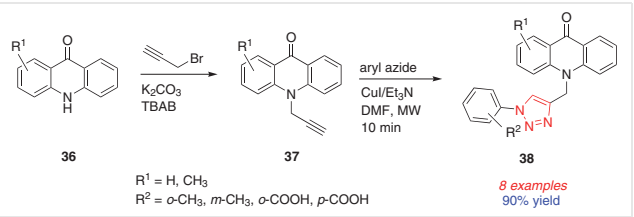


Scheme 6 Synthesis of N-linked 1,2,3-triazole



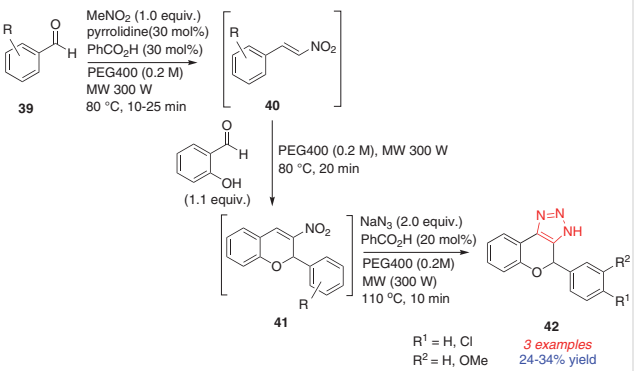
Scheme 7 Synthesis of 1,4-disubstituted 1,2,3-triazole

triazole compounds **38** (Scheme 8). Both traditional and microwave-assisted techniques were used for the synthesis of compounds and under microwave heating the product was obtained in excellent yields in 10 min.[32]

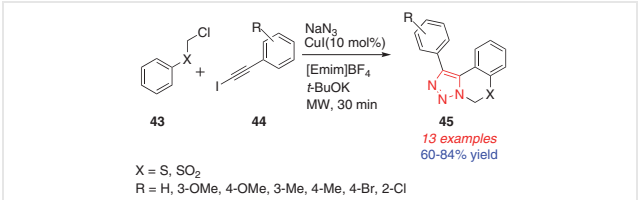


Scheme 8 Synthesis of 1,2,3-triazole compounds

Alves et al. reported the synthesis of the 4-aryl-1,4-dihydrochromene-triazoles **42** (Scheme 9) in an environmentally friendly 'one-pot' method without the need for metals, with PEG400 as the solvent. Starting with easily accessible



Scheme 9 Synthesis of 4-aryl-1,4-dihydrochromene-triazoles



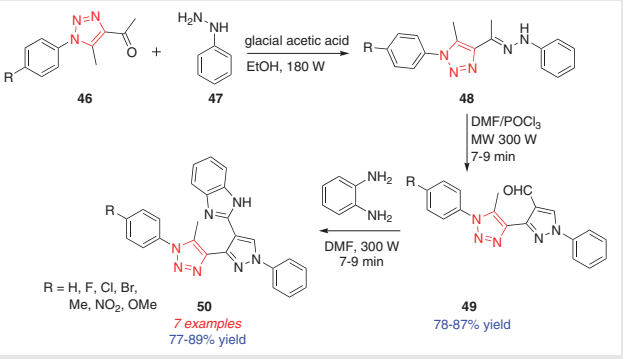
Scheme 10 Synthesis of 1,2,3-triazoles

building blocks, triazole derivatives were produced using microwave irradiation in 10 min with yields of 24–34%.[33]

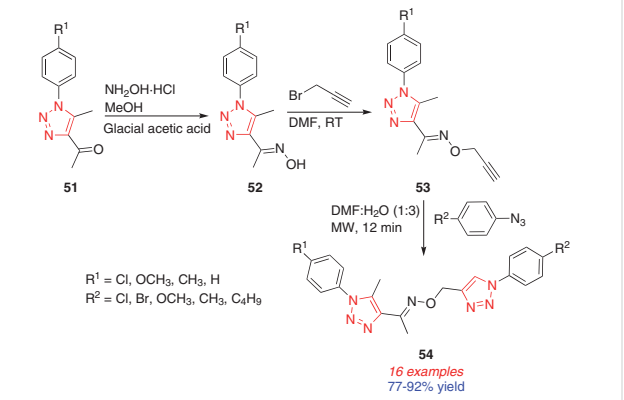
Sucharitha et al. described microwave-assisted, effectively one-pot, three-component reaction sequences that involve Cu(I)-catalyzed 1,3-dipolar cycloaddition reactions to give 1,2,3-triazoles **45** (Scheme 10) in the presence of ionic liquid [Emim]BF_4. This method provides benefits including short reaction times (30 min), simple workup procedures, and excellent yields (up to 84%).[34] Further, Ashok et al. synthesized a novel series of 3-(5-methyl-1-aryl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehydes **49** and their benzimidazole derivatives **50** (Scheme 11) using both conventional and microwave irradiation methods. The reactions resulted in excellent yields (up to 89%) within a short duration of 7–9 min under microwave irradiation.[35]

In another work, Ashok et al. used a click reaction between alkynes and organic azides for the synthesis of several novel 1,2,3-triazole derivatives **54** (Scheme 12). CuI was used as the catalyst to achieve higher yields (up to 92%) under microwave irradiation in a shorter time (12 min).[36]

Znati et al. reported a novel series of cytotoxic 1,2,3-triazole-linked flavonol hybrids **57** (Scheme 13), using CuAAC under microwave irradiation and classical methods. This cycloaddition process was conducted in a regiospecific



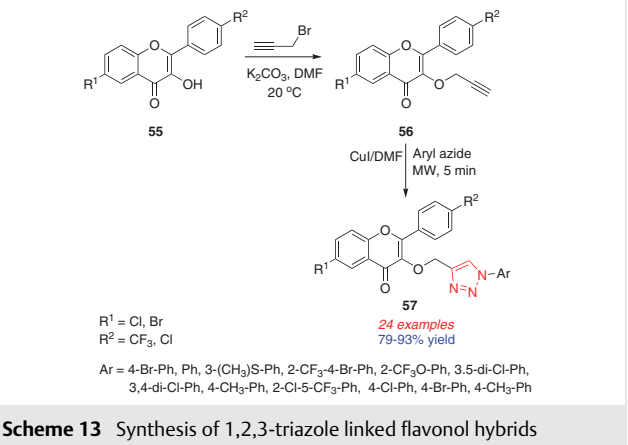
Scheme 11 Synthesis of 1,2,3-triazole analogues



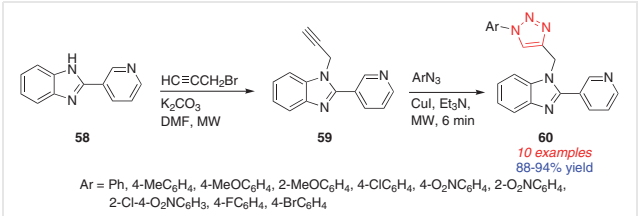
Scheme 12 Novel 1,2,3-triazole derivatives

manner under microwave irradiation, yielding pure compounds with affordable yields (up to 93%) in a comparatively short amount of time (5 min), making it an especially appealing technique.[37]

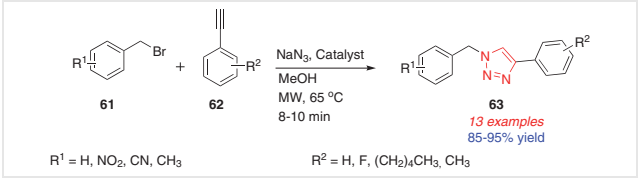
Vishnuvardhan et al. used microwave irradiation to develop a range of new 1,2,3-triazole-tethered 2-pyridinyl benzimidazole derivatives **60** from 2-(pyridine-3-yl)benzimidazole (Scheme 14). The microwave-assisted approach delivered excellent yields (up to 94 %) in 5 minutes and is easy to use.[38] Saikia et al. prepared a series of 1,4-disubstituted 1,2,3-triazole derivatives **63** using ionic liquid supported Cu(II) catalyst in methanol solvent under microwave irradiation (Scheme 15) in excellent yield (up to 95%) in 8–10 min.[39]



Scheme 13 Synthesis of 1,2,3-triazole linked flavonol hybrids

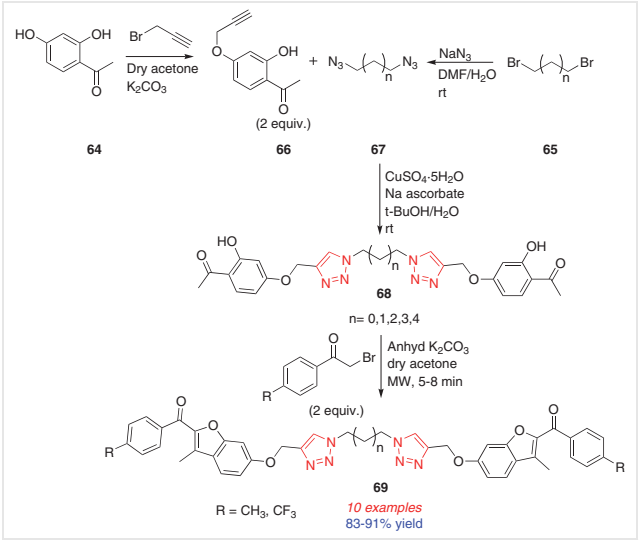


Scheme 14 Synthesis of 1,2,3-triazole-tethered benzimidazole derivatives



Scheme 15 Synthesis of 1,4-disubstituted 1,2,3-triazoles

Vani et al. reported the synthesis of dimers of 1,2,3-triazole benzofuran bearing alkyl spacer derivatives **69** using microwave-assisted and conventional techniques. The microwave technique is more convenient and produces excellent yields (up to 91%) in 5–8 min (Scheme 16).[40]



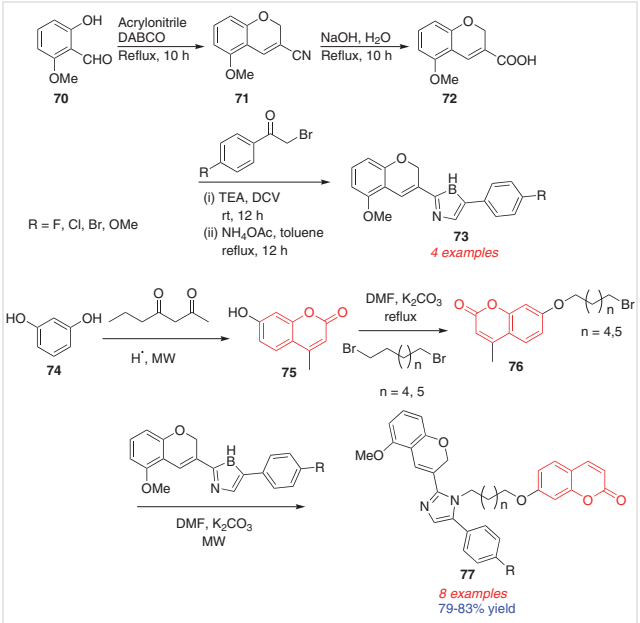
Scheme 16 Synthesis of 1,2,3-triazole-benzofuran

3 Coumarin Hybrids

Coumarins (2*H*-1-benzopyran-2-one) are chemically classified as lactones and also referred to as 1,2-benzopyrone. The Pechmann, Knoevenagel, Wittig, Perkin, Kostanecki–Robinson, and Reformatsky reactions can be used for the synthesis of coumarins.[41]

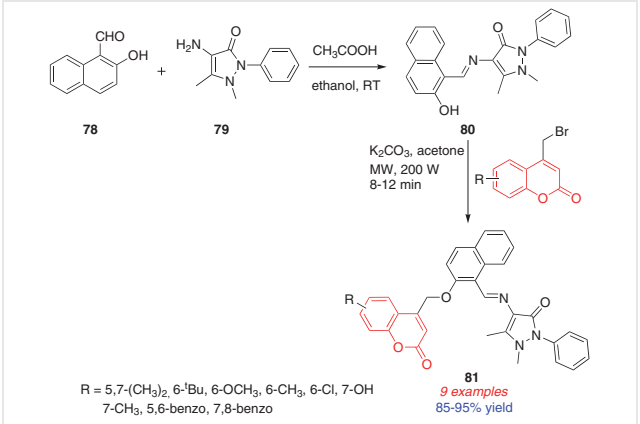
The coumarin nucleus, featuring an α,β-unsaturated lactone motif, is prevalent in various natural products and bioactive pharmaceutical compounds and, being recognized as a highly privileged structure, it holds significant biological relevance. It has been reported that coumarins and hydroxyl coumarins, having at least one hydroxyl functional group, exhibit activity by donating electrons and hydrogen to free radicals.[42] Coumarin derivatives demonstrate diverse biological activities, encompassing anticancer,[42] anti-HIV,[43] antimicrobial,[44] antituberculosis,[45] anti-influenza,[46] anti-Alzheimer,[47] and antiviral[48] action.

Ashok et al. synthesized new imidazole-coumarin analogues **77** (Scheme 17) using a conventional heating MW irradiation method. The process was initiated by treating substituted salicylaldehyde **70** with acrylonitrile and 1,4-diazabicyclo[2.2.2]octane (DABCO) catalyst via the Baylis–Hillman reaction, yielding chromene-3-nitrile **71**. Subsequent hydrolysis of **71** produced chromene-3-carboxylic acid **72**. Compound **72** reacted with substituted acyl bromides in the presence of TEA, then upon refluxing with NH_4OAc in toluene, 2-(substituted-2*H*-chromen-3-yl)-5-aryl-1*H*-imidazoles **73** was formed. Resorcinol **74**, when combined with ethyl acetoacetate and concentrated sulfuric acid, underwent MW irradiation to produce 7-hydroxy-4 methylcoumarin **75**. The latter, upon treatment with terminal dibromo alkane and refluxing over anhydrous potassium carbonate, generated bromo alkylated compounds **76**. Subsequent reaction with intermediate products **73** in DMF yielded the targeted compounds **77**.[49]



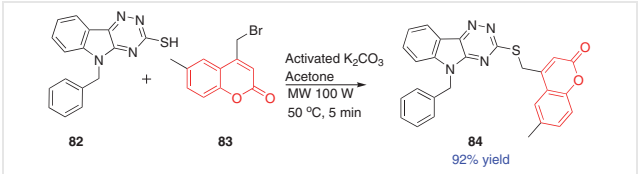
Scheme 17 Synthesis of 2-(2*H*-chromen-3-yl)-5-phenyl-1*H*-imidazole based coumarin derivatives

Chavan et al. prepared a series of (*E*)-1,5-dimethyl-4-((2-((substituted-2-oxo-2*H*-chromen-4-yl)methoxy) naphthalene-1-yl)methylene-amino)-2-phenyl-1,2-dihydropyrazol-3-one derivatives **81** containing Schiff base structures (Scheme 18) with excellent yields (up to 95%) in 8–12 min under microwave irradiation. The microwave-assisted method was 30-45 times faster than the traditional method.[50]

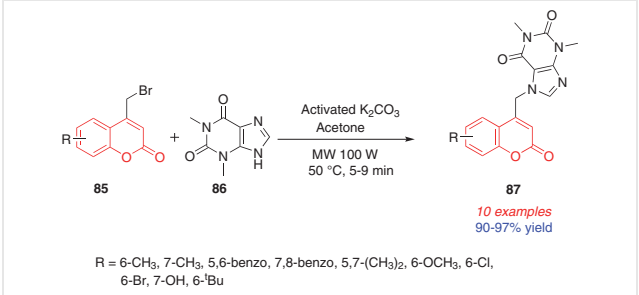


Scheme 18 Synthesis of coumarin derivatives

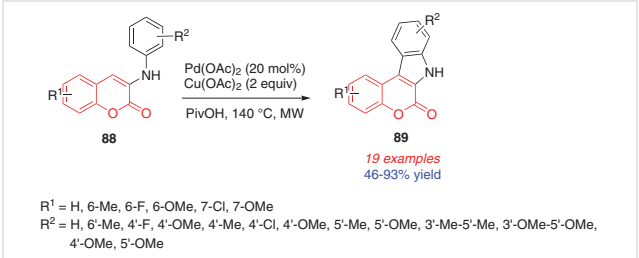
Mangasuli et al. synthesized a novel triazinoindole-coumarin hybrid **84** under the microwave-irradiation method in 5 min, which is more convenient than the conventional method (4 h) (Scheme 19).[51] Furthermore, Mangasuli et al. reported an easy and convenient microwave-assisted method for the preparation of coumarin-purine hybrids **87** (Scheme 20). The microwave-assisted method provides an outstanding yield (up to 97 %) within 5–9 min.[52] Gu et al. synthesized a variety of indolo[2,3-*c*]coumarins **89** (Scheme 21) in high yields (up to 93%) through the palladium-catalyzed base-free intramolecular cross-dehydrogenative coupling of quinolinones and 3-amino coumarins under microwave irradiation.[53]



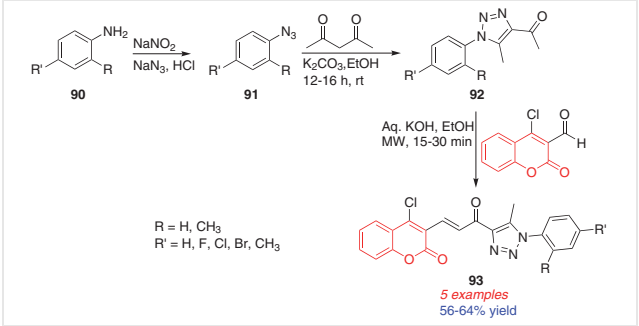
Scheme 19 Synthesis of triazinoindole-coumarin hybrid



Scheme 20 Synthesis of coumarin-purine hybrids

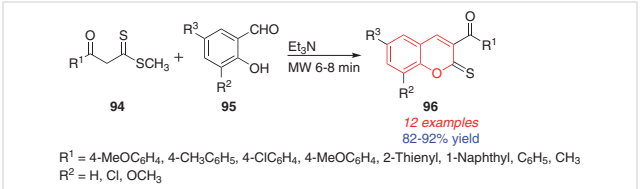


Scheme 21 Synthesis of indolo[2,3-*c*]coumarin derivatives

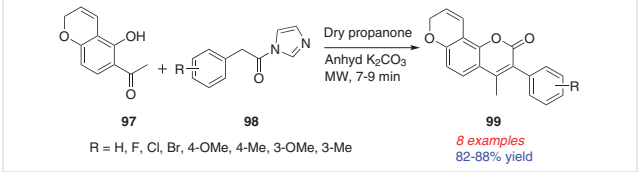


Scheme 22 Synthesis of α,β-unsaturated carbonyl linked coumarin-triazole hybrids

Vagish et al. prepared a range of α,β-unsaturated carbonyl-linked coumarin-triazole hybrids **93** (Scheme 22) using substituted aromatic primary amines **90** as a starting material under microwave radiation at low temperatures and shorter periods. They prepared the target compounds by both MW irradiation as well as traditional reflux techniques and found that microwave-assisted synthesis required a shorter reaction time than traditional heating.[54] Bhaskaran et al. synthesized 2*H*-chromene-2-thiones **96** (Scheme 23) in excellent yield (up to 92%) using β-oxodithiocarboxylates **94** and salicylaldehydes **95** as a starting material under microwave irradiation.[55] Dharavath et al. synthesized several novel 4-methyl-3-arylpyrano[2,3-*f*]chromen-2(8*H*)-one derivatives **99** (Scheme 24) in an effective and eco-friendly method. This work represents an effective approach for the synthesis of compounds using



Scheme 23 Synthesis of 2*H*-chromene-2-thione derivatives



Scheme 24 Synthesis of 4-methyl-3-arylpyrano[2,3-*f*]chromen-2(8*H*)-one derivatives

microwave irradiation in comparison to traditional heating techniques. The microwave irradiation approach produced encouraging yields (up to 88%) within 7–9 min.[56]

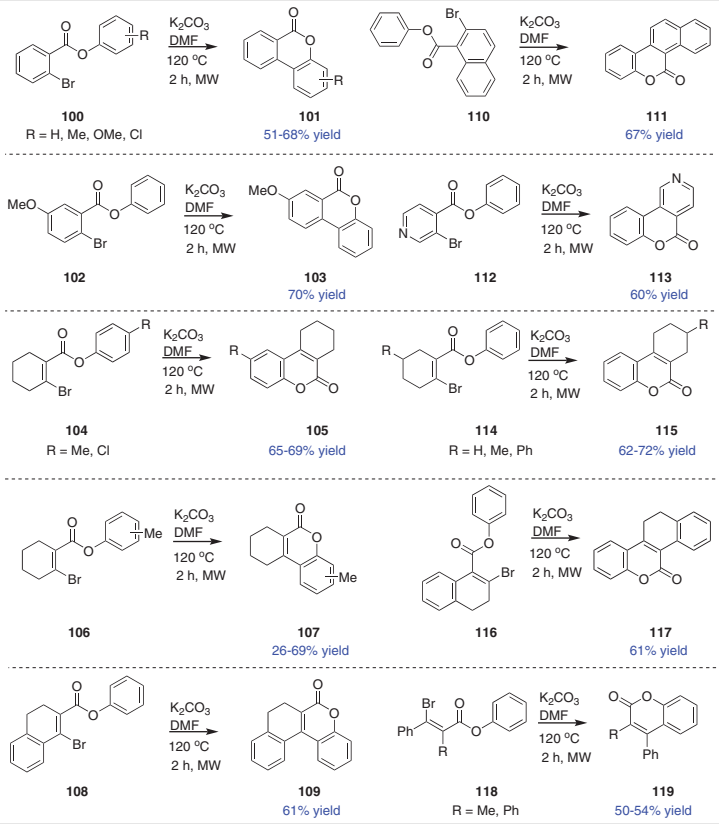
6*H*-Benzo[*c*]chromen-6-ones **100–119** and their tetrahydro analogues (Scheme 25) were synthesized by Dao et al. This method involves the cyclization of aryl 2-bromobenzoates, aryl 2-bromocyclohex-1-enecarboxylates, and K_2CO_3 in DMF under microwave irradiation.[57]

4 Imidazo Pyridine Hybrids

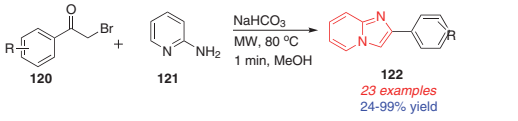
One significant class of fused nitrogen-bridged heterocyclic compounds is imidazo[1,2-*a*]pyridines. Many physiologically active substances, including natural products, contain the imidazo[1,2-*a*]pyridine scaffold. There are several methods for the synthesis of this moiety but the most commonly used method involves the condensation of α-halocarbonyls and 2-aminopyridine.[58] These classes of compounds exhibit numerous medicinal properties, such as antimicrobial,[58] anti-inflammatory,[59] antioxidant,[60] and fungicide[61] action, and they are also used as biomarkers and fluorescence sensors.[62,63]

Rodríguez et al. successfully synthesized imidazo[1,2-*a*]-pyridine derivatives **122** (Scheme 26) under microwave radiation in excellent yields ranging from 24 to 99% within 15 min. The advantage of the microwave irradiation method is that the yield of the product is high and the reaction requires less time.[64]

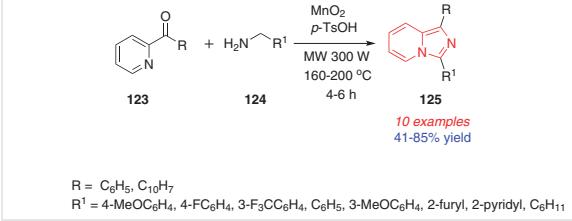
Herr et al. provided a rapid, highly effective, microwave-assisted method for the synthesis of imidazo[1,5-*a*]pyridine derivatives **125** (Scheme 27) using ketones **123** and amines **124** as starting material and activated MnO_2 as oxidant, under solvent-free conditions. The reaction exhibited vast scope and tolerated a variety of functional groups; however, the yields were very low in the case of aliphatic amines.[65]



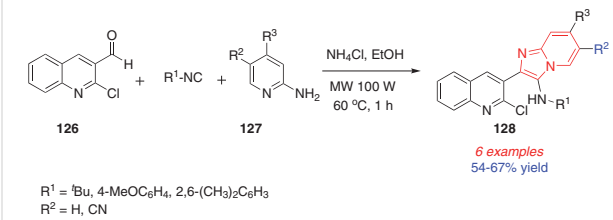
Scheme 25 Synthesis of 6*H*-benzo[*c*]chromen-6-ones and their 7,8,9,10-tetrahydro analogues



Scheme 26 Synthesis of imidazo[1,2-*a*]pyridine derivatives



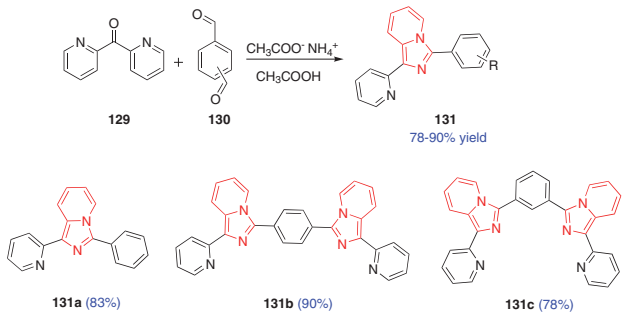
Scheme 27 Synthesis of imidazo[1,5-*a*]pyridine derivatives



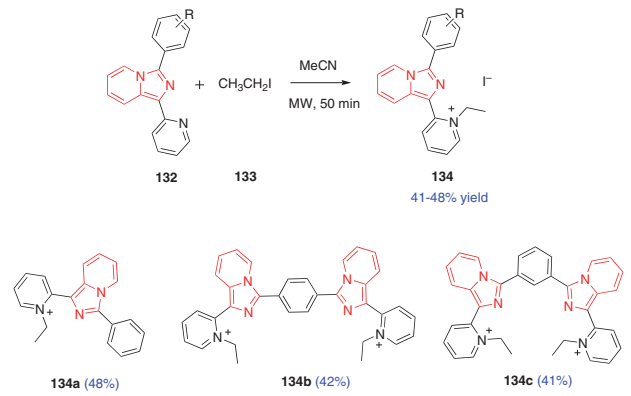
Scheme 28 Synthesis of Imidazo[1,2-*a*]pyridine linked quinolones

Ramírez-López et al. produced a set of six fused bis-heterocycles **128** through microwave irradiation, where imidazo[1,2-*a*]pyridine was bound to a quinolone moiety (Scheme 28).[66] Cavinato and colleagues synthesized a range of pyridylimidazo[1,5-*a*]pyridine derivatives **131a–c** (Scheme 29) and the corresponding pyridinium salts **134a–c** (Scheme 30). Their optical properties were used to assess the quantization that affected the optical characteristics of the polymeric matrix in the solution.[67]

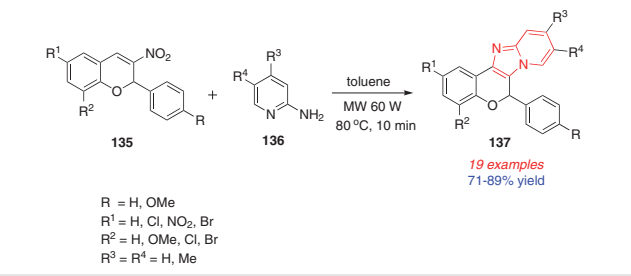
Mishra et al. synthesized 6*H*-chromeno[4′,3′:4,5]imidazo[1,2-*a*]pyridine derivatives **137** (Scheme 31) under microwave irradiation in an effective one-pot Michael addition–cyclization reaction. This procedure has several notable advantages, including rapid reaction times, ease of operation, and tolerance to a broad range of functional groups.[68] Kusy et al. generated mild, rapid, and, metal-free microwave-assisted synthesis of 3-formyl imidazo[1,2-*a*]-pyridines **140** (Scheme 32). This approach is a convenient alternative to existing methods for several reasons; namely, (1) it utilizes readily available starting compounds, (2) it uses an environmentally friendly solvent mixture, specifically ethanol and water in a 1:1 ratio, and (3) it is compatible with a substituted 2-aminopyridine moiety **138**.[69]



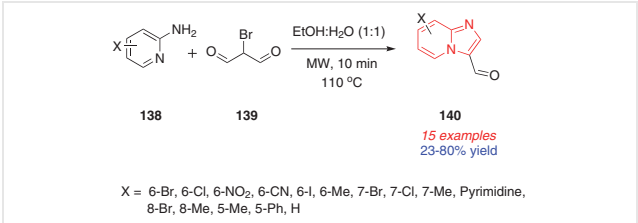
Scheme 29 Synthesis of pyridylimidazo[1,5-*a*]pyridine derivatives



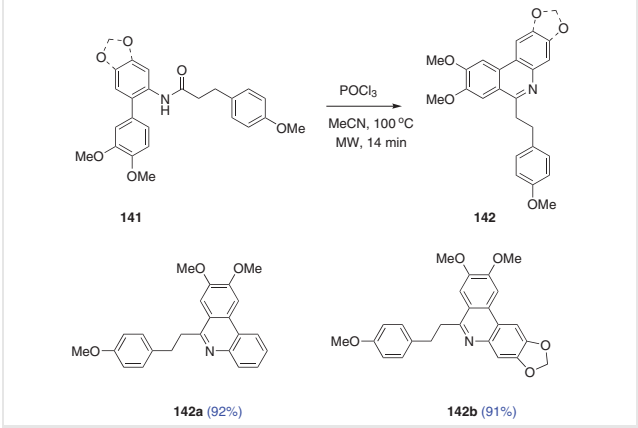
Scheme 30 Synthesis of pyridylimidazo[1,5-*a*]pyridinium salts



Scheme 31 Synthesis of 6*H*-chromeno[4′,3′:4,5]imidazo[1,2-*a*]pyridine derivatives



Scheme 32 Synthesis of 3-formyl imidazo[1,2-*a*]pyridines



Scheme 33 Synthesis of 6-phenethylphenanthridine derivatives

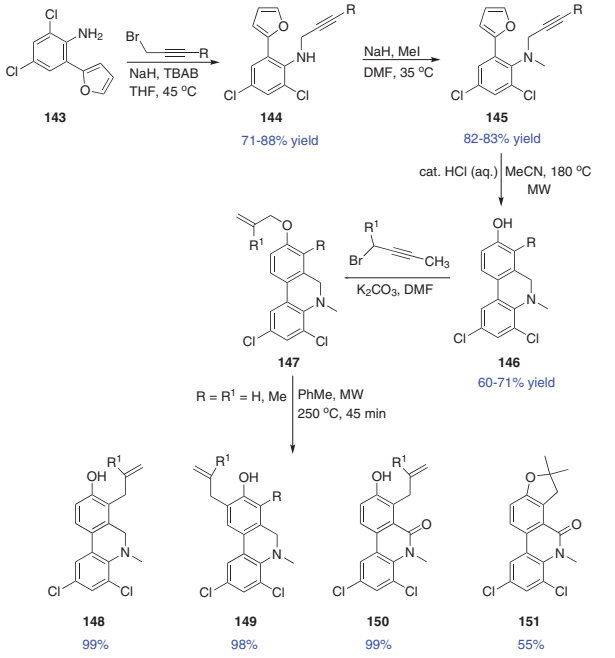
5 Phenanthridine Hybrids

Phenanthridines are polycyclic aromatic compounds containing a tricyclic structure composed of two benzene rings fused in a linear arrangement with a nitrogen atom. Due to the vast range of biological actions and uses such as anticancer agents,[70] anti-infectives,[71] antivitiligo compounds as well as PET tracers,[72,73] the phenanthridine nucleus has captured the interest of the scientific community, especially organic and medicinal chemists. The naturally occurring phenanthridine analogues possess potent anti-cancer properties. This discovery has motivated the development and utilization of synthetic techniques to produce these compounds in the laboratory.[74]

By using a Pictet–Hubert microwave-assisted process, Villamizar et al. reported an effective technique for the synthesis of 6-phenethylphenanthridine derivatives **142a**,**b** (Scheme 33). This technique is a unique, high-yielding, clean, and easy microwave-assisted method.[74]

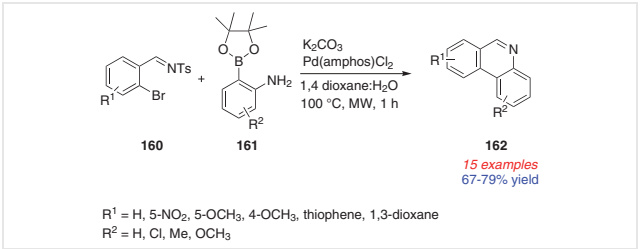
The regioselective C-7 functionalization of phenanthridines using Claisen rearrangements of 8-allyloxyphenanthridines under microwave irradiation was reported by Lepsøe et al. They introduced various functional groups at the C-7 position of phenanthridine derivatives **148**–**151** (Scheme 34). If the 7-position is substituted, rearrangement occurs at the C-9 position and the reaction proceeds slowly through the sequential microwave-assisted intramolecular Friedel–Crafts alkylation and direct C–H arylation.[75] Villamizar et al. reported a quick, effective, and unique microwave synthesis of novel pyrido[3,2,1-*de*]phenanthridin-6-ones **154** (Scheme 35).[76]

The total synthesis of (+)-asiaticumine and its enantiomer **159a**,**b** (Scheme 36) involved several key steps. After the microwave-assisted electrocyclization, Nishiyama et al. employed the Sharpless asymmetric dihydroxylation to introduce the chiral centers. These findings represent a significant advancement in the field of asymmetric synthesis and pave the way for further exploration of the biological activ-

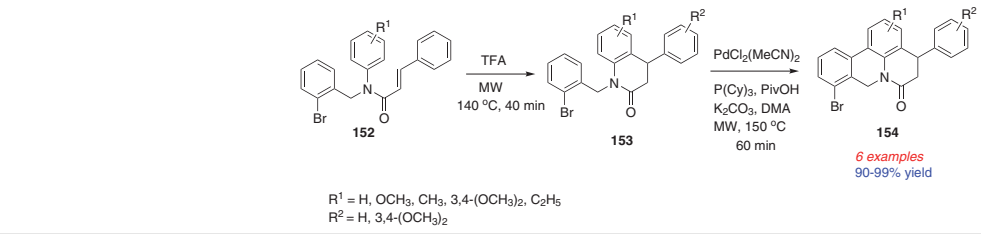


Scheme 34 Synthesis of 8-allyloxyphenanthridine derivatives

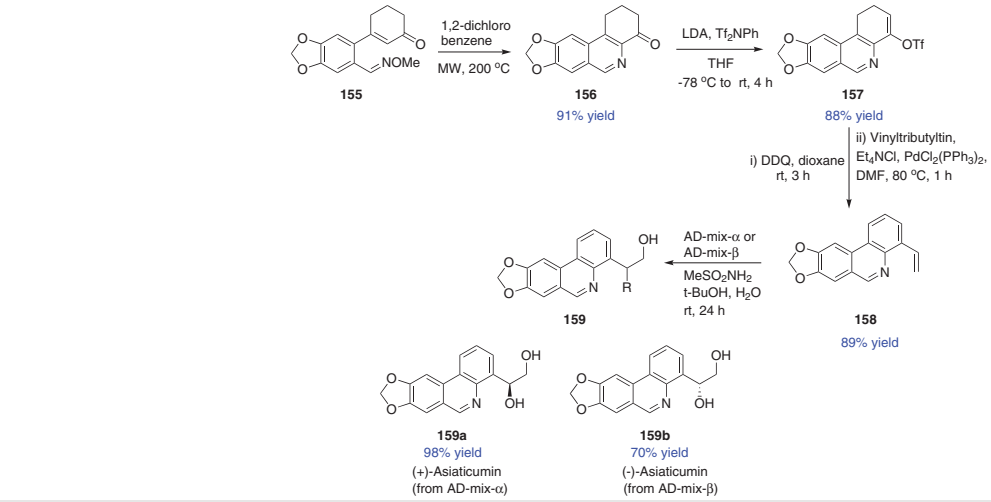
ities of this natural product.[77] Further, the Suzuki cross-coupling reaction is a widely used method for the synthesis of carbon–carbon bonds. Dende et al. demonstrated the successful application of Suzuki cross-coupling reaction in the synthesis of phenanthridine derivatives **162** (Scheme 37) using suitably substituted aromatic *o*-bromo *N*-tosylhydrazones **160** and 2′-aminobenzeneboronic acid **161** under microwave irradiation. The presence of Pd(amphos)Cl_2 catalyst enables the efficient formation of these derivatives.[78]



Scheme 37 Synthesis of phenanthridine derivatives



Scheme 35 Synthesis of pyrido[3,2,1-*de*]phenanthridin-6-one hybrids

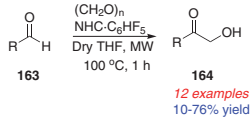


Scheme 36 Synthesis of (+)-asiaticumine and its enantiomer

6 Carbene Hybrids

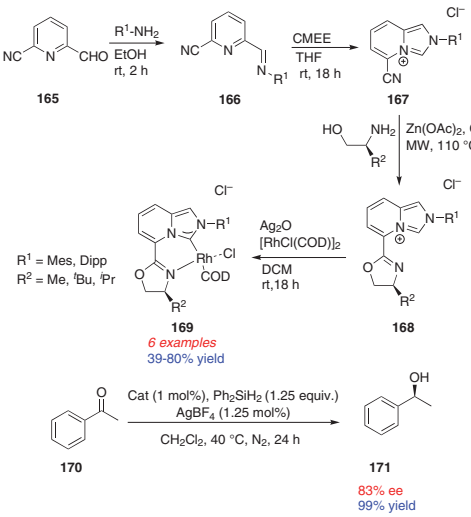
In the past two decades, *N*-heterocyclic carbenes (NHCs) have become a focal point of extensive research as ligands for transition-metal complexes. The first stable Fisher carbene complex was reported by Ernst Otto Fischer in the late 1960s. These ligands skyrocketed after the isolation and characterization of free carbenes by Smith et al.[79] Due to their ability to interact with aldehydes, to generate corresponding reactive intermediates, N-heterocyclic carbenes (NHCs) are widely acknowledged as highly valuable and versatile tools applicable in a diverse array of organocatalytic reactions. This versatility has spurred increased research on NHCs in recent years. Among the most prevalent NHC-catalyzed reactions is the formation of a Breslow intermediate, achieved by the reaction of an aldehyde with the NHC catalyst. This reaction involves umpolung chemistry, which is the polarity reversal of the substrate to form a new C–C bond. The Breslow intermediate is utilized in various reactions such as Stetter reactions, hydroacylations, and benzoin condensations. Additionally, NHC-catalyzed reactions can give rise to other reactive intermediates such as homoenolates for condensation reactions, such as Michael additions, and enolates for aldol reactions.[80]

Papadaki et al. reported microwave-assisted hydroxymethylation **164** of numerous aliphatic and aromatic aldehydes **163** (Scheme 38) catalyzed by pentafluorobenzene-based NHCs. The carbenic centers were well protected by the inclusion of the C_6HF_5-group, which also made it possible for the active carbene to be released under microwave or normal heating conditions.[80] A new range of N-heterocyclic carbene ligands **169** (Scheme 39) has been synthesized by Varenikov et al.[81] the synthesis was based on an imidazo[1,5-*a*]pyridine-3-ylidine backbone, which is fused to a chiral oxazoline adjunct. Installing the oxazoline functionality using a microwave-assisted condensation of a cyano-azolium salt **167** with various 2-amino alcohols is a crucial step in the synthesis of these ligands. The enantioselective hydrosilylation of structurally different ketones **170** can be efficiently catalyzed by the chiral bidentate NHC oxazoline ligands, which formed stable complexes with rhodium(I).[81] The rhodium(II) catalyst, featuring ligands R^1 (Dipp) and R^2 (^{i}Pr), exhibited remarkable efficacy under the initial reaction conditions, yielding the highest enantioselectivity (83% ee).



R = C_3H_7, C_6H_{13}, 2-phenylethane, cyclohexane, *p*-methoxybenzene, *p*-fluorobenzene, C_4H_9, C_9H_{19}, C_6H_5, methylbenzoate, *p*-chlorobenzene, $N(Boc)_2CHCOOMe$, $N(Boc)_2CH(Boc)$

Scheme 38 Synthesis and hydroxymethylation of various aliphatic and aromatic aldehydes



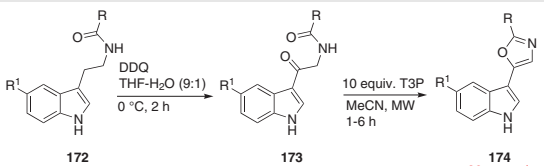
Scheme 39 Synthesis of *N*-heterocyclic carbene ligands

7 Oxazole Hybrids

Oxazole hybrids are unsaturated five-membered rings with an oxygen and a nitrogen atom at positions 1 and 3. Oxazoles and their derivatives indeed play a significant role in medicinal chemistry.[82] Oxazole is the parent compound for a vast class of heterocyclic aromatic compounds and has been studied for its promising biological and pharmacological activities such as antimicrobial,[82] antitubercular,[83] antihyperglycemic,[84] and antifungal properties.[85] Oxazole has emerged as a lead molecule in medicinal chemistry and a potential candidate for drug development.

The commercially available non-steroidal anti-inflammatory medication oxaprozin (4,5-diphenyl-2-oxazolepropionic acid) is a significant member of this family. Oxazoles have also been used in polymer science,[86] as fluorescent dyes,[87] and as intermediates in organic transformations. Many simple and complex oxazole alkaloids have been identified from a diversity of natural sources; i.e., microorganisms, marine invertebrates, and plants belonging to the *Rutaceae* and *Gramineae* families.[88]

The synthesis of 2-substituted 5-(3-indolyl)oxazoles **174** (Scheme 40) has been developed under microwave ir-



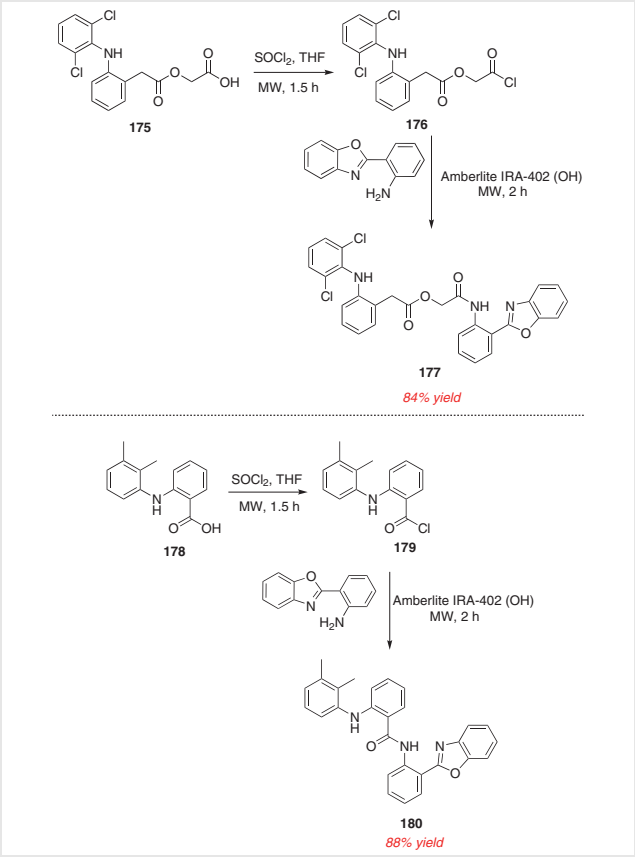
R = Me, Bn, Bu, ^{t}Bu, hexyl, $CH_3(CH_2)_{13}CH_2$, ^{t}Bu, CF_3, Ph, 3-ClC_6H_4, 4-FC_6H_4, naphthalen-1-yl, Et, Pr, ^{i}Pr, pentyl, octyl, cyclopropyl, 4-methoxybenzyl, CF_3CF_2, 2-FC_6H_4, 3-$F_3CC_6H_4$, 3-$OMeC_6H_4$, thiophen-2-yl

R^1 = H, Cl, OMe

Scheme 40 Synthesis of 2-substituted 5-(3-indolyl)oxazoles

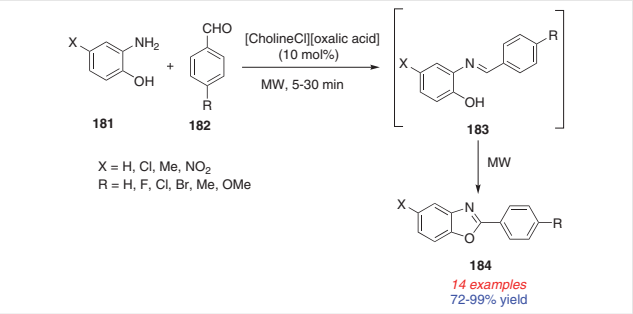
radiation, by Szabó and co-workers.[88] This process was aided by propyl phosphonic anhydride (T3P) and involved cyclization of *N*-acyl-β-oxotryptamines **173** under microwave irradiation, the reactions occurred smoothly in acetonitrile and gave the purified products in good yields (up to 100%).[88]

Using amber lite-IRA-402 (OH) ion exchange resin as a base catalyst, Angajala et al. reported an effective microwave-assisted synthesis of 2-substituted benzoxazole derivatives **177** and **180** (Scheme 41) from anti-inflammatory drugs aceclofenac **175** and mefenamic acid **178**, respectively.[89]



Scheme 41 Synthesis of 2-substituted benzoxazole derivatives

Pham et al. reported rapid and simple Choline (oxalic acid) catalyzed microwave-assisted synthesis of benzooxazoles **184** (Scheme 42). This technique involved the use of deep eutectic solvent (DES) as a catalyst in the environmentally safe cyclization of 2-aminophenols **181** and benzaldehydes **182** to produce benzoxazoles under microwave irradiation. Benefits of the method include the removal of costly and hazardous reagents, moderate reaction conditions, higher yields (up to 99%), a wide range of substrate compatibility, and a recyclable catalyst.[90]



Scheme 42 Synthesis of benzooxazoles derivatives

8 Conclusion

The discussions presented herein highlight the significant efficacy of microwave-assisted organic synthesis as a highly efficient method for conducting a diverse array of chemical reactions within a short reaction time, with good product yields, and high selectivity. This study focuses on compiling recent advancements in microwave irradiation techniques, specifically emphasizing the synthesis of various heterocyclic moieties, including 1,2,3-triazole hybrids, coumarin hybrids, imidazopyridine hybrids, phenanthridine hybrids, carbene hybrids, and oxazole hybrids.

In summary, microwave-assisted synthesis has emerged as a revolutionary catalyst in organic synthesis, offering accelerated reactions, improved yields, and energy efficiency, making it an essential instrument for scientists. As we delve further into its mechanisms and innovative uses, microwave-assisted synthesis is poised to influence the future direction of chemistry significantly. The data provided highlights numerous instances of successful microwave-assisted synthesis applications, demonstrating increased yields, reduced reaction times, and enhanced selectivity. These examples underscore the versatility and effectiveness of microwave irradiation in various synthetic processes.

Conflict of Interest

The authors declare no conflict of interest.

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