New Developments in Nitrogen-Containing Multicomponent Reaction Techniques

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Aslihan Ayvaz, Ahmet Demirbas,
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Cambridge
Scholars
Publishing

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This book first published 2024

Cambridge Scholars Publishing

Lady Stephenson Library, Newcastle upon Tyne, NE6 2PA, UK

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

ISBN (10): 1-0364-0621-0
ISBN (13): 978-1-0364-0621-9

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PREFACE

"Why do these topics matter?"

All lives revolve around organic chemistry and everything done regarding organic compounds closely affects life, whether it is all understood or not. When organic chemistry is understood, it is realized how life itself would be unfeasible without it, how the quality of life depends upon it, and how organic chemistry affects life from every direction.

However, with time, concerns about the environmental impact due to the growth of human society have become omnipresent; sustainability has increased gradually and reached alarming levels in every field of human activity nowadays. The chemical industry plays a prior role in the progress of humanity. However, it has increased pressure on chemists to improve the sustainability of their methods since it is thought that one of the major causes of environmental pollution is the chemical industry. Hence, this concern has directed the chemists to canalize their methods into green strategies.

In this respect, the expression "Green Chemistry" has been defined as designing chemical products and methods via the way to remove or at least the minimized use of unsafe materials. New eco-friendly approaches, including multicomponent reaction techniques, unconventional energy sources, solvent-free media, etc. have become an integral part of the production of privileged structures, drug-like compounds, and improving industrial processes. In fact, the primary aim is to prevent waste formation in the first place, rather than the end-of-pipe remediation approach, which contains elimination of waste after production. At the same time, it has been a reliable focus for chemists to achieve the desired conversion with minimum waste to create alternative and environmentally benign reaction conditions by eliminating the use of hazardous solvents as much as possible. The toxic and volatile nature of solvents, which are frequently used in laboratories, has an undesirable impact on environmental pollution. Therefore, the elimination of the employment of these solvents is crucial. In recent years, solvent-free methodologies, or reactions including water or ionic liquids as reaction solvents, have gained interest.

Another green approach aiming to overcome environmental pollution is one-pot multicomponent reaction techniques, at the same time, which are cost- and time-effective, atom economic and clean procedures. Multicomponent reactions (MCR) are one-pot operations in which at least three or more components generate a single product incorporating most or even all the starting materials. Therefore, the design and development of MCRs affording varied heterocyclic scaffolds with the desired substitution patterns, functionalities, and diversity have attracted great interest.

The enormous interest in such one-pot Multicomponent reactions has directed chemists to combine these approaches into eco-friendly methodologies such as combinatorial methods, solid-phase synthesis, and alternative energy sources, etc. These strategies provide chances for higher efficiency and convenience and improve regioselectivity.

Nowadays, when the energy crisis affects our lives and living expenses, energy consumption in reactions that last for hours or even days in classical methods constitutes one of the important environmental and economic problems. To minimize or eliminate this energy consumption, the chemists have directed their attention to using alternative energy sources, such as ultrasonication, microwave irradiation, mechanochemical synthesis, photocatalytic reactions, etc. These methods enabled the procedures with shortened reaction times giving selective and high-yield products.

On the other hand, the term "combinatorial chemistry" refers to the general techniques allowing the simultaneous synthesis of many molecules with structural differences. This new technique, which has become one of the methods reducing time and cost in generating efficient and competitive new drugs or drug candidates, is defined as the producing a series of analog series under the same conditions, with the same methods in the same container. Thanks to the developments in this technique, today hundreds of molecules can be synthesized simultaneously. Combinatorial chemistry has become a separate branch of medicinal chemistry and an integral part of the notion of sustainability as well. In the context of combinatorial chemistry, high throughput screening studies submit the possibility of in vitro screening of drug candidates in sub-microgram quantities in 1536-3456 well titer plates. This ultra-high throughput screening approaches make it possible to screen 100.000 compounds in one day, supplying time and material savings.

Nitrogen-containing heterocyclic compounds frequently take part in the privileged structures named pharmacophores. The prerogative role of such compounds is the ability to act as bond donors/acceptors influencing the medicinal scaffolds and their goal interaction.

However, accessing them generally suffer from particular problems, such as a lack of generality, multistep reaction sequences, starting from acyclic precursors, etc. Thus, the successful synthetic strategies yielding heterocyclic scaffolds have remained limited. Therefore, developing new, effective, and environmentally benign methodologies for the focused libraries of such compounds is of great importance

This book makes it possible to access newly developed strategies, which are favored by green-chemistry principles affording nitrogen-containing heterocyclic products, most of which display at least one biological activity of advanced students, graduates, and researchers from both academia and industry.

In this research-oriented book, chemical structures have been illustrated in depth with clearly drawn. Moreover, the methods have been presented in detail by ascribing to the corresponding references. Furthermore, the explanation of most of the reaction mechanisms has been given supplying a comprehensive explanation of many reactions, especially heterocyclic chemistry. All these explanations make this book the most authoritative one-volume account of modern green chemistry.

I thank sincerely Prof Ahmet Demirbas, Assoc. Prof. Arif Mermer, PhD student Aslıhan Ayvaz and graduate student Sinem Görkem Demirbas for their help during the preparation of the manuscript and their proofreading.

We are very grateful to Cambridge Scholar Publishing for encouraging us to write this book and thanks to Helen Edwards, Rebecca Gladders and Alison Duffy for contacting us about this.

Hope it helps all readers.

1

INTRODUCTION

Nitrogen-containing heterocyclic compounds frequently take part in the privileged structures named pharmacophores. The prerogative role of such compounds is the ability to act as bond donors/acceptors influencing the medicinal scaffolds and their goal interaction (Amin, Sadek, Abdel-Hameed, et al., 2019).

However, accessing them generally suffers from particular problems, such as a lack of generality, multistep reaction sequences, starting from acyclic precursors, etc. Thus, the successful synthetic strategies yielding heterocyclic scaffolds have remained limited. Therefore, developing new, effective, and environmentally benign methodologies for the focused libraries of such compounds is of great importance (Anies, Pancrazi and Lallemand, 1994; Armstrong, Combs, Tempest, 1996; Ding, Gray, Wu, et al., 2002; 1998; Da Silva, Garden and Pinto, 1999; Dömling, 2000; Bienayme´, Hulme, Oddon, et al., 2003; Gordeev, Patel and Gordon, 1996; Hatamjafari, 2006; Lorsbach, Muegge, 2002; Munoz, Chen, McDonald, 2000; Orru, and de Greef, 2003; Teague, Davis, Leeson, et al., 1999; Wess, Urmann and Sickenberger, 2001; Pelish, Westwood, Feng, et al., 2001).

In 1990, The United States Environmental Protection Agency (USEPA) introduced the term “Green Chemistry” to develop new strategies or revise the old ones that eliminate or minimize (if its use is mandatory) the use of toxic and harmful substances in production processes. For example, using metals or metal complexes as catalysts pollutes water, harming aquatic life and plants and further disrupting the food chain. Moreover, most of these types of catalysts are costly and unavailable commercially.

It should also be noted that the increasing environmental pollution and its destructive impact on the ecosystem have urged scientists to search for new ways to convert the chemical processes constructed at the outset of this century toward eco-friendly procedures. The main target of green chemistry is to convert conventional chemical processes using hazardous reagents, catalysts, and toxic and volatile solvents, into environmentally harmless methods containing renewable and non-hazardous raw materials. Here the major aim is to avoid waste formation in any chemical process rather than the removal of waste formed during production (Dekamin, Karimia, Latifidoost, et al., 2018; Dekamin, Peymana, Karimia, et al., 2016; Demirbas, Mermer, and Demirbas, 2022; Demirbas and Demirbas, 2021; Demirbas and Demirbas, 2020; Khan, Saigal, Shareef, et al., 2018; Mohamadpour, 2021[a]; Mohamadpour, 2021[b]; Chate, Rudrawar, Bondle, et al., 2020; Varma, 2007; Vispute, Zhang, Sanna, et al., 2010; Zarnegar and Safari, 2016).

Indoor air became an important matter of concern since most city dwellers consume up to 80% of their time indoors. Diversified volatile organic compounds (VOCs), particularly formaldehyde (FA) have been accepted as the key participants in air pollution, especially indoors (Araki, Ketema, Bamai, et al., 2020; Bhave and Yeleswarapu, 2020; Chithra and Shiva, 2018; Kumar, Vikrant, and Kim, 2019). FA is known to have carcinogenic and mutagenic activities connected with inhalation and chronic exposure as an industrial chemical (Chen, Zhang, Yang, et al., 2020; Dwivedi and Shukla, 2020; Hassan, El-Abssawy and Khoder, 2018; Hussain, Song, Shah, et al., 2020). A 15-min exposure limit of 100 ppb for FA has been declared by The United States National Institute for Occupational Safety and Health has declared (Durongphan, Amornmettajit, Rungruang, et al., 2020). The highly hazardous nature of FA has urged scientists to develop removal technologies involving thermal catalytic oxidation (Han, Wang, Zhou, et al., 2020; Wang, Ye, Jiang, et al., 2020; Wu, Yi, Tang, et al., 2020), photocatalytic oxidation (Hu, Li, Sun, et al., 2020; Rao, Duo, Long, et al., 2020; Zhu, Hong, Chen, et al., 2020), adsorption (Liu, Jia, Li, et al., 2019; Na, Yoo, Tsang, et al., 2019; Vikrant, Cho, Khan, et al., 2019), and plasma-based techniques (Chang and Lee, 1995; Vikrant, Lim, Younis, et al., 2020).

Some superior properties, such as ease of operation, cost-effectiveness, and operational simplicity have made adsorption-based techniques the most convenient real-world platforms (Khan, Szulejko, Kim, et al., 2019; Vikrant, Cho, Khan, et al., 2019; Vikrant, Deng, Kim, et al., 2019).

Nonetheless, instead of striving to eliminate pollution, it will be the most rational solution to develop strategies to minimize pollution formation. One of the reliable approaches to succeed in this aim is to develop alternative productive strategies with minimized waste and eliminate the use of hazardous solvents. One of the most efficient strategies targeting improving sustainability is multicomponent reactions (MCRs), which lead to higher yields, increased step performance, and decreased reaction times, and also allow purification by more straightforward operations (Bienayme´, Hulme, Oddon et al., 2000; García, Jatczak, Muylaert, et al., 2013; Trost, 2002).

Multicomponent reactions (MCR) can be defined as one-pot operations in which at least three or more components form a single product incorporating most or even all of the starting materials. Consequently, the design and development of MCRs yielding diverse heterocyclic libraries with the desired functionalities, substitution patterns, and diversity have gained great attention. The isolation of the intermediates formed, adding further reagents, and altering the reaction conditions are not needed, which are indispensable in multistep conversions. Moreover, one-pot multicomponent reactions occupy a magnificent position in organic chemistry owing to their selectivity, atom-economical, and energy saving, as well as an environmentally friendly character using more straightforward procedures and equipment. The enormous interest in such one-pot multicomponent reactions has oriented chemists to integrate these methods into eco-friendly methodologies such as combinatorial methods, solid-phase synthesis, and alternative energy sources. These approaches offer opportunities like higher efficiency and convenience (Demirci, Aksakal, Colak, 2017; Hulme and Gore, 2003; Nair, Vinod, Bindu, et al., 2003; Orru and De Greef, 2003; Sadek, Mekheimer, Mohamed, et al., 2012). Moreover, the application of MCR under microwave irradiation has improved the regioselectivity and enhanced the reaction rates for different heterocycles (Abbas, Gomha, Throya et al., 2014; Andrade, Barreto and Silvia, 2008; Bortolini, D'Agostino, Nino et al., 2008; Dömling, 2002; Dömling and Ugi, 2000; El Ashry and Kassem, 2006; Sadek, Mekheimer, Mohamed et al., 2012; Shirole, Kadnor, Tambe, et al., 2017).

Thus, the strategies containing multicomponent approaches have been considered ideal tools for displaying higher efficiency, environmental benignity, cost efficiency, and better atom economy, refraining from tiresome reaction steps, costly purification operations, and comprehensive synthetic procedures (Zhang and Jiang, 2015).

Nevertheless, the quest for this so-called "ideal synthesis" poses the most laborious and challenging task for synthetic chemistry. MCRs represent a reactivity-based notion and are classified according to their respective reaction control, so three scenarios are possible. The first class of MCRs called the domino pathway requires that catalysts, solvents, and reagents all be present in the reaction media from the beginning. Sequential MCRs constitute the second class of MCRs, where the conditions remain fixed during the whole sequence, while the reaction components are added in a well-determined subsequent order step by step. The last class is named consecutive MCRs, where all the components are added stepwise as in sequential MCRs. However, the reaction conditions may need to be changed in each reaction phase. Regardless of class, all three types of MCRs present highly functional and structural variety and tremendous potency to set up novel blockbuster scaffolds (Biesena and Müller, 2021).

The great interest in one-pot MRC has stimulated scientists to combine these methodologies with ecologically benign strategies such as alternative energy sources, combinatorial methods, and solvent-free reaction media, which offer opportunities like higher efficiency and convenience. In addition, the microwave-supported administration of MCR enhances the reaction rates and improves the regioselectivity of different heterocyclic scaffolds. Thus, the combined multicomponent processes have been considered ideal strategies leading to higher efficacy and environmental compatibility with atom economy, avoiding tedious reaction steps and expensive purification processes (Demirbas, Mermer, Demirbas, 2022).

Synthetic procedures under microwave irradiation (MAOS) have been implemented as a productive tool for many organic reactions. The methodology leads the organic reactions to proceed with short reaction times and high yields for pure products. It has been seen that reaction times reduce from days or hours to minutes when the microwave irradiation technique is integrated with the one-pot multicomponent reactions efficiently (Zhang and Jiang, 2015).

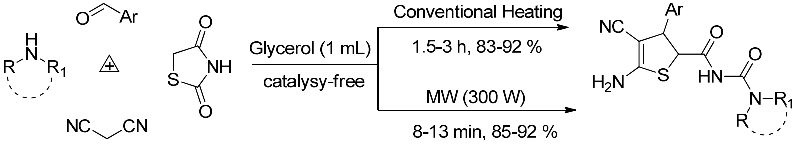
1.1. Microwave Irradiated Reactions

In recent years, Microwave irradiated methods have become a hot spot of investigation with great utility alone or in combination with multicomponent reaction techniques. In most cases, microwave-mediated methods have resulted in a drastic reduction of reaction times, straightforward workup procedures, and drastically increased product yields compared to conventional heating. Thus, microwave irradiation has been implemented successfully for a broad array of reaction types and has become a frequently used tool in organic synthesis. In fact, in this method, a high-frequency wave is used to heat the reagents to a high temperature in a short time. The heating mechanism of microwave irradiation is explained by two main processes: dipolar polarization and ionic conduction. Microwave heating of homogeneous media occurs when an oscillating microwave electromagnetic field interacts with several species (molecule or ion) that are polarizable. The straight warming up without heating the reaction vessel occurs when the polarized molecules or ions fight to line up with the electromagnetic field by rotating, bumping into, and rubbing against each other. Therefore, it is clear that the combination of multicomponent reaction techniques and microwave superheating offers a synergistic effect than the application of the two methods individually (Mermer, Demirbas, Demirbas, et al., 2018; Demirbas, Mermer and Demirbas, 2022).

Moreover, the limitation of fossil energy sources has led to the discovery of renewable and more efficient energy sources to provide the requisite heat has become more significant. In this context, the high efficiency of microwave irradiation compared to conventional heating at the proceeding of chemical reactions has resulted in its fast-growing applications in diversified types of chemical conversions.

It is well known that microwave chemistry relies on the ability of the reaction mixture to absorb microwave energy efficiently, taking advantage of microwave dielectric heating phenomena such as dipolar polarization and ionic conduction mechanisms. It is accepted that the capability of any reaction mixture to absorb microwave energy efficiently constitutes the basis of microwave chemistry. The absorption of energy and then conversion into heating depends on the polarity of the reaction media. The performance of such energy and heat dispersion is a function of the dielectric properties of the reaction media. Therefore, MW energy is absorbed more efficiently by the molecules with higher dielectric constant while less by the reagents with lower polarity (Demirbas, Mermer and Demirbas, 2022; Demirbas and Demirbas, 2020).

However, such solvents should be avoided as much as possible since they pose a risk of explosion. It is best to avoid the use of solvents altogether. However, when the solvent is mandatory, solvents such as glycerol, which have high performance in absorbing and transmitting MW energy to the reactants, and are non-flammable and non-volatile, should be preferred. An example of a glycerol-mediated four-component reaction in which glycerol has been used as the solvent and the reaction time was shortened from 1,5-3h to 8-13 min when using MW has been reported by Kordnezhadian and coworkers for the synthesis 2-(*N*-carbamoylacetamide)-substituted-2,3-dihydrothiophenes (Scheme 1) (Kordnezhadian, Mohsen and Khalafi, 2020).



Scheme 1. One-pot four-component synthesis of dihydrothiophene derivatives in glycerol at 90°C under conventional heating or MW irradiation.

There are an enormous amount of examples of MW irradiated multicomponent reactions in a green and suitable solvent or without solvent. Examples of these will be presented in the following sections.

As mentioned above, greener energy inputs have a prominent role in promoting chemical reactions. In this perspective, ultrasound comes forward with alternatives involving milling processes and microwave irradiation. Compared to traditional heating, it is clear that the use of ultrasound irradiation for synthetic targets generally provides a higher yield, shorter reaction time, and selectivity (Javed, Mason, Phull et al; 1995; Banerjee, 2017; Nomura and Koda, 2015; Penteado, Monti, Sancineto et al., 2018).

1.2. Ultrasound-Irradiated Reactions

Ultrasound, which is any sound wave in frequencies above the normal hearing range of the human ear (i.e., above 16 kHz) (Savun-Hekimoglu, 2020), has a vast amount of application areas, such as in the food and pharmaceutical industries (Mason, 1996; Rastogi, 2011; Wang, Kang, Zhang et al., 2018), waste management (Gogate, Mujumdar and Pandit, 2003; Savun-Hekimoglu, Ince, 2019; Savun-Hekimoglu, Ince, 2017; Ignole and Khedkar, 2012; Kerboua, Hamdaoui and Al-Zahrani, 2021; Monsef, Ghiyasiyan-Arani, Amiri et al., 2020; Naddeo, Belgiorno, Kassino, 2010; Nejumal, Manoj, Aravind et al., 2014; Serna-Galvis, Silva-

Agredo, Botero-Coy et al., 2019; Yousef, Khataee, Hassandoost, et al., 2020; Yadav, Ali and Khan, 2020; Zinatloo-Ajabshir, Baladi, Amiri et al., 2020), extraction processing (Ebringerova and Hromadkova, 2010; Filho, Sousa, Rodrigues, et al, 2020; Juliano, Bainczyk, Swiergo, et al., 2017; Kulkarni, Rathod and 2014; Kumari, Tiwari, Hossain, 2018; Martinez, Delso, Aguilar et al., 2020; Ojha, Aznar, O'Donnell et al., 2020; Paniwnyk, Beaufoy, Lorimer et al., 2001; Paniwnyk, Cai, Albu, 2009), analytical chemistry (Robin, Tanter and Pernot, 2017; Seidi and Yamini, 2012; Wieland, Tauber, Gasser et al., 2019), the production of nanoparticles (Asfaram, Ghaedi, Abidi et al., 2018; Bayrami, Aliogkli, Pouran et al; 2019; Chatel, 2019; Dheyab, Azizi, Jameel, 2021; Ersan, Kipcak, Ozen et al., 2020; Islam, Paul, Burheim et al., 2019; Machado, dos Santos, Januario et al., 2021), and waste treatment (Paniwnyk, Cai, Albu, 2009; Mermer, Demirci, Basoglu-Ozdemir, et al., 2017).

Sonochemistry is interested in the reactions stimulated by shock waves produced by localized pressure and by radicals, which form in or around bubbles caused by the thermal decomposition of molecules in the system due to ultrasonic cavitation (Machado, dos Santos, Januario et al., 2021).

1.2.1. The Phenomenon of Acoustic Cavitation

Four theories have been proposed to clarify sonochemical effects:

1. Electrical theory,
2. Hot-spot theory,
3. Supercritical theory,
4. Plasma discharge theory.

Among them, the most accepted named acoustic cavitation effect basis on the formation, growth, and implosion of bubbles with a life span of a few microseconds. At these points in the reaction medium, the temperature and pressure reach levels of 5000◦C and 10,000 atm, respectively (Wu, Guo, 2013). The collapse of these bubbles supplies the activation energy required by the reaction (Ando and Kimura, 2003; Bremer, 1994). There are several types of the cavitation process, such as hydrodynamic, acoustic, particle, and optical cavitation derived from the related ultrasonic and experimental parameters such as acoustic power, frequency, solvents, reactor shape, vapor pressure, temperature, viscosity, surface tension, etc. (Kuna, Behling, Valange et al., 2017; Shah, Pandit and Moholkar 1999).

In fact, the formation of acoustic cavitation includes 3 stages:

1. Nucleation,
2. Bubble growth known as expansion as well,
3. Implosive collapse.

Firstly, microbubbles, which are trapped in micro-slits of small particles in the liquid, generate cavitation nuclei, where the cavities are formed depending on the purity and type of the liquid. After that, since the acoustic intensity is low and lasts a few more acoustic cycles before expansion, a small cavity develops rapidly and expands by rectified diffusion. The third moment is when the cavity grows to an ultimate size and can no longer absorb energy, and a violent implosion occurs. At this point, the extreme pressure and temperature provide an extraordinary reaction media behaving a high-energy microreactor that leads to molecular fragmentation of the gases trapped in the collapsing cavities. However, there are some reactions that the cavitation effect can not explain. This indicates a broader need for investigation of the occurrence of chemical transformations by ultrasonic irradiation (Vinatoru and Mason, 2019; Vinatoru and Mason, 2021). Depending on how particles vibrate in the reaction media, ultrasound waves are classified into four types: plate/Lamb waves, transverse/shear waves, longitudinal compression waves, and surface/Rayleigh waves (Pilli, Bhunia, LeBlanc et al., 2011; Wu, Teh and Hay, 2013).

Concerning frequency, ultrasound can be examined in three classes: power ultrasound (20–100 kHz), high-frequency ultrasound (100 kHz –1 MHz), and diagnostic ultrasound (1–500 MHz). Among them, the one used most widely is the first class to accelerate physical and chemical transformations. In most cases, the increasing potency also improves the reaction rate. Another parameter that should be observed is temperature because, in many cases, the increased temperature causes decreased cavitational effects (Machado, dos Santos, Januario et al., 2021).

1.2.2. Ultrasonic Waves Promoting Chemical Reactions

It should not be forgotten that the existing bonds are broken (sonolysis), and new bonds are formed in also sonochemistry (Li, Dong, Zhang, et al., 2021). Ultrasonic waves with frequencies above 20 kHz in a liquid can break bonds and generate free radicals having the capacity to support a series of chemical conversions. When water is used as a solvent, hydroxyl and hydrogen radical form, and oxidation-reduction reactions occur (Ahmadian-Fard-Fini, Ghanbari, Amiri et al., 2021; Vinatoru, Mason, and Luche, 2021).

Luche and coworkers have divided sonochemical reactions into three groups (Vinatoru, Mason and Luche, 2021).

- **Homogeneous sonochemistry:** The reactions taking part in this category proceed in a radical way, in which the intermediates being radical or radical ions are produced by cavitation in the homogeneous media. In such cases, sonication supports reactions through radicals and ionic reactions are not affected by such irradiation. This could be considered real sonochemistry.
- **Heterogenous sonochemistry:** Reactions taking place owing to the mechanical effect of the waves disseminating in a heterogeneous media, which proceed via the formation of ionic intermediates, would be induced by the cavitational agitation effect; this would be the “false” sonochemistry.
- **Sonocatalysis:** In heterogeneous reactions with mixed mechanisms containing radicals and ions, the radical path would be promoted via sonication, with a cumulative application of the general mechanical effect of heterogeneous sonochemistry.

Concerning the relationship between catalysis and sonochemistry, it is clear that the implosion of a cavitation bubble improves the dispersion of the catalyst in the reaction media leading to the formation of highly reactive areas on the surface of the catalyst particles and also increasing the dissemination of reagents on the surface of the catalyst. The combination of these processes makes it possible for reactions that do not take place because of the low kinetic energy unless the presence of such promotes, normally. In case a solid catalyst is used, sometimes a synergistic effect between ultrasound and catalyst is observed. Cavitation bubbles form preferably on the particle surface via heterogeneous nucleation. The implosion of the bubbles is asymmetric, so physical and chemical conditions due to this process finish stimulating the activation or formation of catalytic sites (Amaniampong and Jerome, 2020).

2

NITROGEN-CONTAINING MULTICOMPONENT REACTIONS

In this book, one-pot multicomponent reactions, most of which promoted by microwave- or ultrasound irradiation, using nitrogen-containing reagents have been presented. In the fist chapter, the multicomponent reactions using amines as reagent have been submitted.

2.1. Multicomponent Reactions Using Amines as Reagent

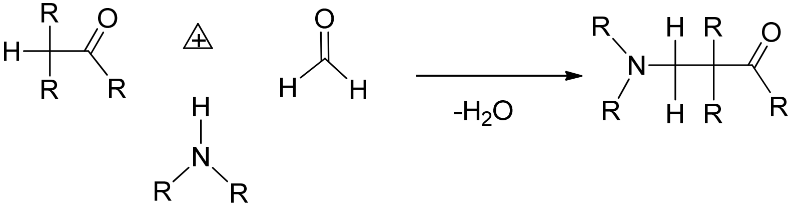
2.1.1. Mannich Reaction

Undoubtedly, one of the most well-known nitrogen-containing multicomponent reactions is the Mannich reaction. This three-component reaction contains the condensation of a primary or secondary amine or an active hydrogen component such as ketones, nitroalkanes, β-keto esters, β-cyanoacids, an enolizable carbonyl compound, and a nonenolizable aldehyde to generate aminomethylated products, which are also named as Mannich bases. The β-amino carbonyl compounds are considered advanced synthetic intermediates, taking part in the synthetic pathway of production of significant natural and pharmaceutical products. β-Amino carbonyl compounds constitute a significant and essential part of *N*-based heterocyclics attracting the attention of pharmaceutical industries due to their biological activities such as antibacterial, antitumor, and anti-inflammatory activity. They are also basic building blocks leading to the formation of several prominent molecules, such as peptides, amino alcohols, and lactams, and as precursors for the synthesis of amino acids (Machado, dos Santos, Januarion, 2021, Müller, Nandi, Jamatia, Ramen et al., 2020; Goesmann and Waldmann, 1999; Davis, Zhang, Anilkumar, 2003; Fujita, Nagasawa, Uto, Hashimoto et al., 2004).

When it comes to bioactive compounds, the fragment linked to the parent amine by the Mannich condensation increases the lipophilic character of the total molecules at physiological pH values via decreasing their protonation, the final effect of which of is an increase of absorption through bio-membranes (Roman, 2015; Oloyede, Wiilie and Adeeko, 2014).

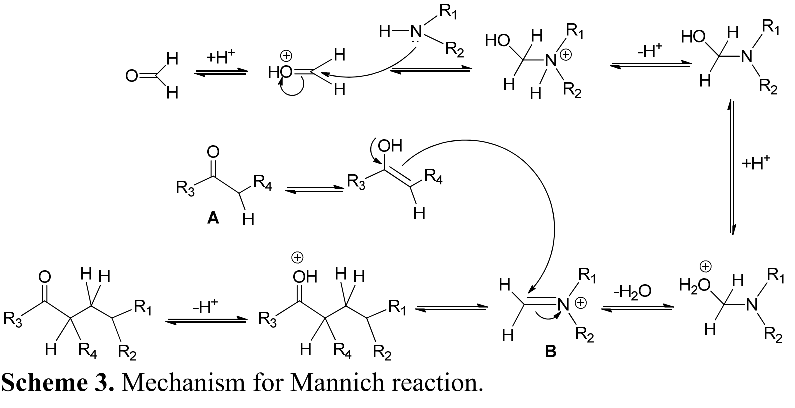
In addition, the primary function of Mannich products is to make molecules solubility in aqueous solvents by converting them to aminium salts (Zhao, Wei, Su, 2009). Until today, the *N*-Mannich reaction has been implemented to produce *N*- containing prodrugs successfully (Scheme 2) (Demirci, Aksakal, Colak, 2017; Dongare, Chavan, Bhale, et al., 2016).

The iminium compound produced by aldehyde behaves as the acceptor in the reaction (Blicke, 2011).



Scheme 2. General representation of the Mannich reaction.

The accepted mechanism starts with a nucleophilic attack of amine-nitrogen to the carbonyl carbon (Scheme 3).

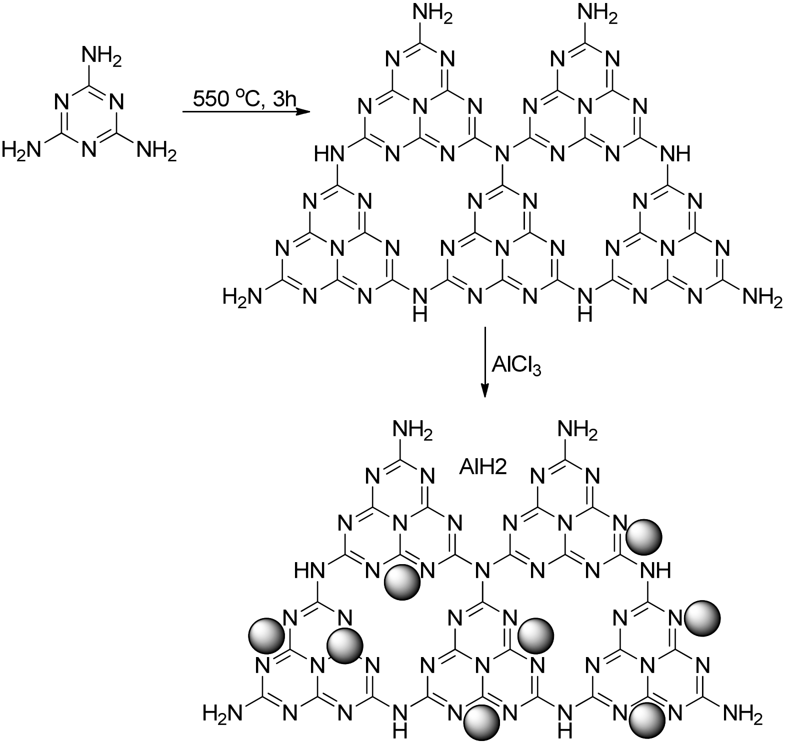


Scheme 3. Mechanism for Mannich reaction.

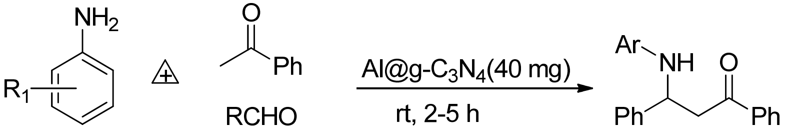
The compound with activated α-CH (**A**) tautomerizes to its enol form then it attacks to imminium ion (**B**) (Blicke, 2011).

Despite all their advantages and usefulness, Mannich reactions can suffer from some drawbacks involving harsh reaction conditions, long reaction times, etc. To avoid these disadvantages, some Mannich reactions, which include a minimum amount of a catalyst, such as $InCl_3$, $AlCl_3$, $SnCl_4$, etc. have been reported.

Besides, various acidic compounds, such as heteropolyacids and sulfonic acid, and metal or metal oxide nanoparticles, such as sulfated alumina and zirconia, have also been used as efficient catalysts. However, these catalytic reactions also have various disadvantages, such as long reaction times, low yields, and non-green procedures with expensive catalysts and higher energy consumption. The discovery of a catalyst, which is quickly recovered with the preferred properties involving high activity and selectivity, and environmental benignity has become an exciting area in organic chemistry. Besides other catalysts in varied structures, carbon nitrides are a group of polymeric materials consisting of carbon and nitrogen. The combination of nitrogen atoms in the carbon architecture improves functional, chemical, and electrical properties. One of the first reported polymers with preferred properties involving high thermal, chemical, water, and corrosion resistance and high hardness is graphitic carbon nitride, g-C_3N_4, with the main structure of $(C_3N_3H)_n$. The g-C_3N_4 has an *N*-bridged poly(tri-s-triazine) planar structure with a high degree of condensation. These materials are easily obtained on a large scale from cost-effective substances such as urea and melamine under solvent-free media. Metals doped g-C_3N_4 has the ability to improve their catalytic efficacy since there are plenty of free amino groups on the C_3N_4 spine, and metal ions can easily bind to these groups (Heydri, Azizi, Mirjafari, Mahmoudi et al., 2022). In this connection, Heydari's group has used the Al-doped g-C_3N_4 (Al@ g-C_3N_4) nanosheets as an efficient heterogeneous catalyst for Mannich reaction at room temperature (Scheme 4, Scheme 5) (Heydari, Azizi, Mirjafari, Mahmoudi, et al., 2022).



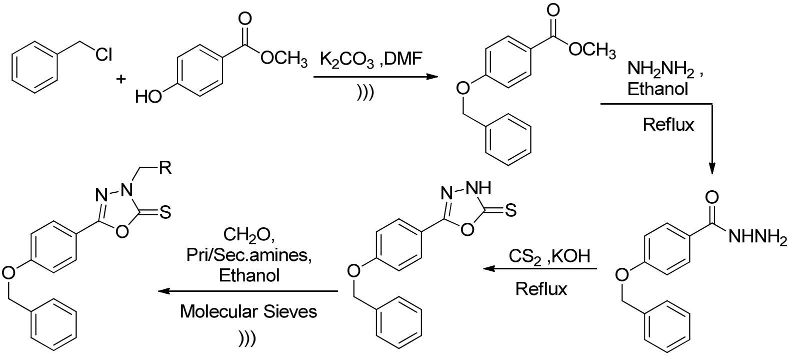
Scheme 4. Preparation of Al@g-C_3N_4.



Scheme 5. Al@g-C_3N_4 catalyzed three-component Mannich reaction.

The literature survey has revealed that the *S*-Mannich reaction is also possible besides *N*-Mannich reactions depending on the reaction conditions and structural convenience (Demirbas, Mermer and Demirbas, 2022; Demirbas and Demirbas, 2021; Demirbas and Demirbas, 2020; Nimbalkar, Tupe, Vazquez, Khan, et al., 2016).

Molecular sieves- and ultrasound-promoted Mannich reaction using 1,3,4-oxadiazole-2-thiones as a carbonyl component has been reported by Nimbalkar et al. In this example, the complete conversion has taken 18-20 hours under reflux conditions, while the same Mannich reaction has been completed in 1-2 hours in the US irradiated method (Scheme 6) (Nimbalkar, Tupe, Seijas et al., 2016).



Scheme 6. Molecular sieves- and ultrasound-promoted Mannich reaction.

Some bioactive compounds containing penicillin, cephalosporin, or fluoroquinolone core have been obtained through an MW-supported Mannich reaction, in which the components containing a thione function were used as a carbonyl component have been reported by Demirbas' group (Fig. 1) (Basoglu-Ozdemir, Demirbas, Demirbas, et al., 2018; Demirbas, Ceylan, Demirbas, 2007; Demirci, Mermer, Ak, Aksakal, Colak et al., 2017); Uygun-Cebeci, Basoglu-Ozdemir, Ceylan, et al.,2017; Uygun-Cebeci, Demirbas, Basoglu-Ozdemir, 2018).

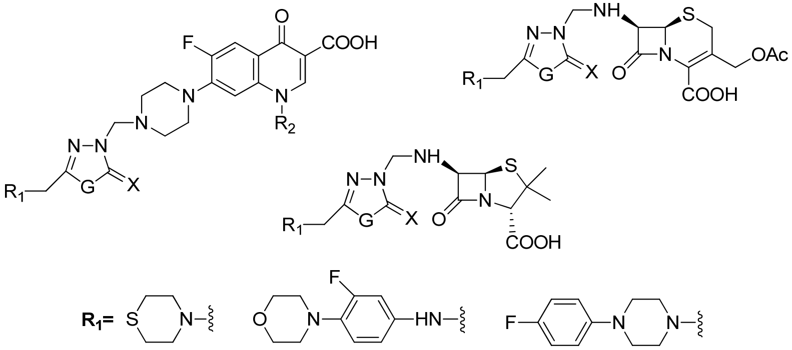
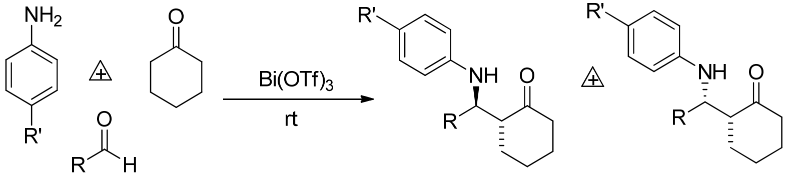


Figure 1. Some bioactive compounds containing fluoroquinolone, penicillin, or cephalosporine core.

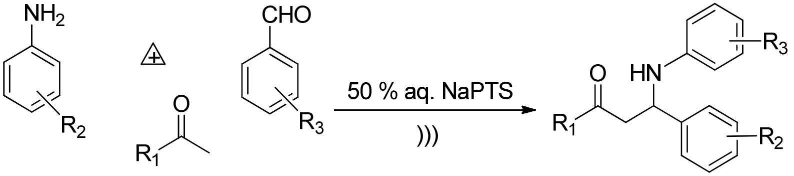
Classical Mannich reactions generally proceed with a reaction time between 3-10 hours. However, combining these reactions with promoting techniques such as MW or US will accelerate the reaction. There are many studies in this field in the literature (Basoglu-Ozdemir, Demirbas, Demirbas, Ayaz et al., 2018; Demirbas, Mermer and Demirbas, 2022; Mermer, Demirci, Ozdemir, Demirbas et al., 2017; Ozdemir, Demirbas, Demirbas, et al., 2018; Ram and Pandey, 1974).



Scheme 7. Synthesis of *β*-aminoketones via Bi(OTf)$_3$.4H$_2$O catalyzed Mannich reaction.

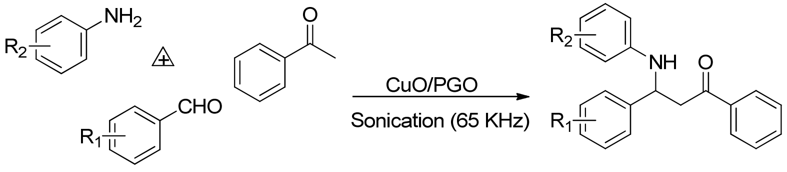
As an example, the Bismuth(III) triflate-catalyzed reaction performed by Ozturkcan et al in water at room temperature can be given as an ultrasound-promoted Mannich reaction (Ozturkcan, Turhan and Turgut, 2012) (Scheme 7). The authors reported that while this reaction takes place in 5,3-8 hours at room temperature, this time is reduced to 1-2 hours with ultrasound irradiation.

The statement “hydrotropes” means water-soluble surface-active compounds in various classes that enhance the solubility in the aqueous media even at higher concentrations. Generally, they consist of hydrophobic and hydrophilic fragments, where the hydrophobic part should be too small to stimulate micelle formation. Kamble's group has described an ultrasound-mediated synthetic pathway affording β-amino carbonyl compounds in an aqueous hydrotropic solution (Kamble, Kumbhar, Rashinkar, et al., 2012) (Scheme 8).



Scheme 8. Ultrasound mediated synthesis of β-aminocarbonyl compounds in NaPTS solution.

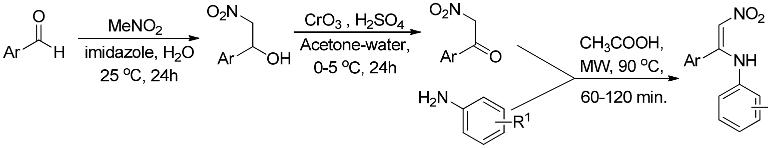
Considering that both acids and metal oxide nanoparticles have been used affording Mannich bases, it seems that the attachment of metal oxide nanoparticles on an acidic GO (PGO) surface would generate a new nanocatalyst accelerating the formation of β-aminocarbonyl compounds.



Scheme 9. Ultrasound-promoted green synthesis of 3-anilino-1,3-diphenyl-1-propanones via Mannich reaction catalyzed by CuO/PGO nanoparticles.

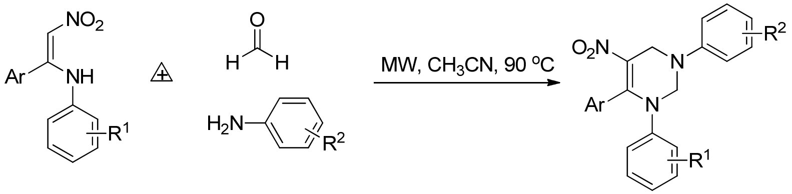
In this context, Dash's group has developed a highly efficient heterogeneous nanocatalyst, CuO/PGO (CuO Phosphate Graphene Oxide), and used it as the catalyst for the Mannich reaction yielding 3-aniline-1,3-diphenyl-1-propanone derivatives under ultrasound irradiation (Scheme 9) (Achary, Nayaka, Barik, et al., 2020). It has been observed that this nanocatalyst is supremely active toward all the reaction types with a shorter reaction period and less energy consumption compared to other traditionally available catalysts.

One of the most efficient ways to afford pyrimidine derivatives starts from reactive enamines, which can be obtained by different methods (Gülbenek, Yıldırım and Yıldırım, 2022). In this context, Yıldırım's group has reported a study leading to the formation of some nitropyrimidine derivatives, which contain the use of reactive enamines (Scheme 10).



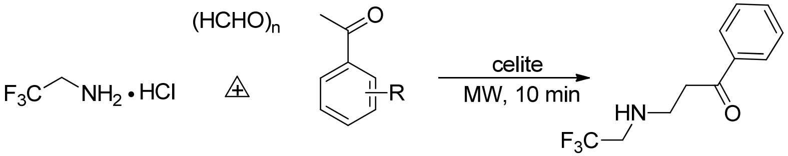
Scheme 10. Synthesis of *β*-nitroenamines under MW irradiated conditions.

Firstly, the synthesis of 2-nitro-1-arylethan-1-ol has been achieved via a three-step reaction starting from the reaction between benzaldehyde and nitromethane in the mixture of water-imidazole. It has been followed by the oxidation the nitro compound to 2-nitro-1-arylethanone using Jones reagent in good yields. In the third step, the desired *β*-nitroenamines have been obtained from the microwave-promoted reaction of 2-nitro-1-arylethanone with several anilines in acetic acid. To obtain the target 5-nitro-1,2,3,4-tetrahydropyrimidines, the treatment of *β*-nitroenamines with various aniline derivatives in the presence of formaldehyde has been used. For this conversion, two methods, traditional heating and MW irradiation, have been used. In the conventional method, the reaction has taken 8-18 hours to complete, while in the MW-assisted method, the reaction has been completed in 40-85 minutes (Scheme 11) (Gulbenek, Yıldırım and Yıldırım, 2022).



Scheme 11. MW Irradiated synthesis of 5-nitro-1,2,3,4-tetrahydropyrimidines.

Recently, Jin et al have reported a microwave-irradiated Fisher indolization reaction, where some advancements have been observed in the reaction time and yields. In this context, the trifluoroethyl group has been introduced through the Mannich reaction under microwave heating, generating secondary or tertiary amines (Scheme 12) (Jin, Su and Yu, 2021).



Scheme 12. Microwave-supported Mannich reactions yielding secondary amines. Advantages: operational simplicity, trifluoroethylamine derivatives, minimal environmental impact, ease of product purification, solvent and catalyst-free conditions, functional group tolerance.

An ultrasound-irradiated Mannich reaction leading to the formation of aminomethylated daidzein derivatives had been described by Yuan et al. Daidzein (7,4′-dihydroxyisoflavone), which is used to reduce menopause symptoms, protect against osteoporosis, and prevention of cardiovascular disease, is one of the most abundant isoflavonoids taken part in legumes, especially soybeans. Moreover, the alcohol-dehydrogenase (ADH) inhibition effect of daidzein has also been reported. However, its boundary absorption upon oral use due to the low solubility of daidzein in water makes it inconvenient to be used as a natural additive in medicine or foodstuff (Yuan, Yang, Mai, et al., 2015). In recent years, different methods have been developed for a library of daidzein to increase bioavailability and adsorption. Among them, a convenient Atherton-Todd reaction affording a series of 7-O-phosphorylated daidzein derivatives has been reported by Chen and Xiao (Chen, Shi, Qu, et al., 2007; Xiao, Yang, Mao, et al., 2012; Yuan, Yang, Mai, et al., 2015).

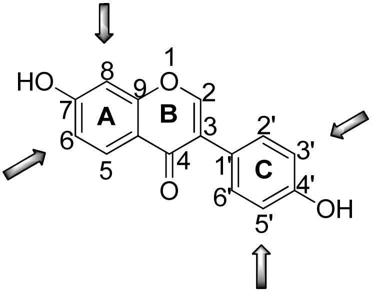
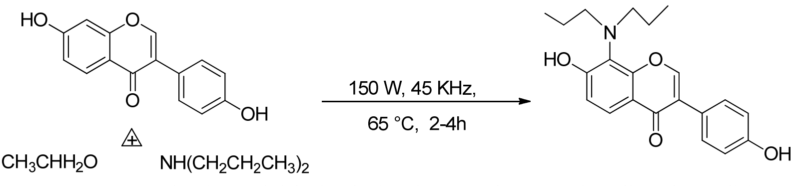


Figure 2. Structure of daidzein and possible sites for the Mannich reaction.

7-O-glycosides of daidzein derivatives have also been obtained using 2,2,2-trifluoro-*N*-(*p*-methoxyphenyl)acetamidates as the glycosyl donors (Fig. 2) (Al-Maharik and Botting, 2008; Al-Maharik and Botting, 2006; Yuan, Yang, Mai, et al., 2015).

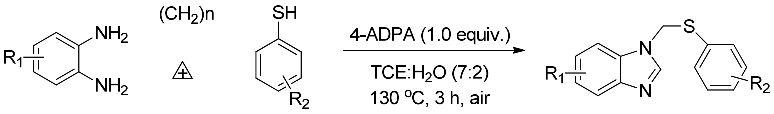
Although the presence of many daidzein derivatives synthesized through various procedures, most of the efforts have focused on the reaction at the C-7 and/or C-4' position, and reactions taking place at the C-8 position or other positions are quite rare (Yuan, Yang, Mai et al., 2015).

Yuan and coworkers have reported the aminomethylation reaction of daidzein, under ultrasonic irradiation in the presence of an amine and formaldehyde in DMF. The regioselectivity analysis has shown that the products obtained are 8-aminomethylated derivatives among the other possible isomers (Scheme 13).



Scheme 13. Synthesis of daidrein derivatives under MW irradiated conditions.

A base-promoted three-component reaction closely related to the Mannich condensation and resulting in a chemo-selective ring closure has been reported by Deng's group (Scheme 14). The reaction has proceeded in the mixture of 4-aminodiphenylamine (4-ADPA) and 1,1,1,2-tetrachloroethane (TCE): H_2O (7:2) mixture at 130°C for 3h and displayed well tolerance against various functional groups. One C-S and three new C-N bonds has formed in a single attempt with high chemoselectivity. The studies on defining the mechanism have shown that firstly diamine reacts with formaldehyde to generate a diimine intermediate followed by nucleophilic attack by thiophenol anion to provide the desired product via a cyclization (Tian, Yuan, Xiao, et al., 2019).

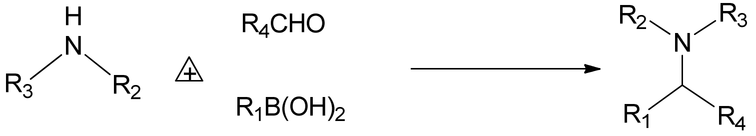


Scheme 14. Synthess of *N*-thiomethyl benzimidazoles.

2.1.1.1. Petasis reaction

In 1993, Petasis et al described a new type of MCR known as the Petasis borono−Mannich reaction (simply the Petasis reaction, PR) between (*E*)-vinylboronic acid, paraformaldehyde, and a secondary amine to afford allylamines (Petasis and Akritopoulou, 1993). Since a different mechanism different from the traditional Mannich reaction has been proposed, the term "Petasis borono Mannich reaction" may not precisely define the nature of this boron-based MCR (Arend, Westermann and Risch, 1998).

The term "borono−Mannich reaction" improperly points to the direct reaction of boronic acid with electrophilic iminium ion assortments. Whereas the term "Petasis" has also been used for several other conversions such as Petasis−Ferrier rearrangement and Petasis olefination reaction (Scheme 15) (Petatis and Bzowej, 1990; Petatis and Lu, 1996).



Scheme 15. General represantation of the Petatis reaction.

The Former shows the conversion of cyclic enol acetals to tetrahydrofurans or tetrahydropyrans through a Lewis-acid-supported oxygen-to-carbon transposition pathway, while the latter means an aldehyde or ketone olefination via the formation of a four-membered