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CHAPTER 10

Multicomponent Reactions: An Advanced Tool for Organic Synthesis

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Abstract: In organic synthesis, multicomponent reactions (MCRs) have become an effective tool for the synthesis of complex molecules from simple starting materials in a single operation. This review mainly focuses on the key features aligned with green chemistry principles, applications, and challenges associated with the MCRs. The application of MCRs is discussed in different fields, which include the synthesis of natural products, agrochemicals, material science, and pharmaceutical industries. It also covers the difficulties, including the optimization of reaction conditions, selectivity, and scalability of the multicomponent reactions.

Keywords*:* Multicomponent reactions, complex molecule, green chemistry

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1. Introduction

In 1850, Adolph Strecker introduced the idea of multicomponent reactions in the synthesis of amino acids, which was innovative work that set the foundation for the development of the MCRs[1–3]. MCRs received a lot of attention in the middle of the 20th century, and several multicomponent reactions were developed, such as the Biginelli synthesis of dihydropyrimidines, the Hantzsch synthesis of pyridines, etc[4–6]. These MCRs show their potential for the synthesis of molecules and develop their scope in organic synthesis. Multicomponent reactions (MCRs) have become an effective tool in synthesis, allowing composite molecules to be synthesized from the simple starting materials in a one-step reaction[7–9]. In the MCRs synthesis, the rationalized procedure permits the mixing of two or more reactants in a single reaction vessel. This technique considerably contributes to synthetic chemistry by providing a rapid and efficient means of creating a wide range of complex compounds including natural and pharmaceutical products[10,11]. The advantages of MCRs include

- Greater efficiency and productivity.
- Reduced waste production and environmental effects.
- Increased yields and selectivity.
- Simplified reaction protocols and workup process.

2. Important characteristics of multicomponent reactions

Some important features of the multicomponent reaction methods used to synthesize complex molecules are consistent with the principles of green chemistry[12–14], which include,

2.1 ***Atom economy****:* MCRs minimize waste and are made to maximize atom economy. This is achieved by incorporating all reactants into the final product.

2.2 ***Improved selectivity****:* MCRs can provide better selectivity, which lowers the requirement for additional purification of product and increases the total yield product.

2.3 ***Reduced waste****:* MCRs reduce waste production by utilizing all reactants effectively and reducing the number of reaction steps involved in the synthesis.

2.4 ***Reduced energy consumption****:* MCRs frequently operate within optimized conditions, which are generally mild reaction settings, that use less energy.

2.5 ***Use of catalyst****:* The use of a catalyst in MCR requires milder reaction conditions such as optimized temperature and the use of minimal solvent or solvent-free conditions, which minimize the requirement of extra reagents.

2.6 ***Design for degradation****:* Certain MCRs were made to generate molecules that are readily degradable or recyclable.

2.7 ***Enhanced efficiency****:* MCRs were made concise and efficient, which eliminates the number of reaction steps and increases the efficacy of the process.

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2.8 ***Cost-effective:*** The MCRs are cost-effective conventional stepwise synthesis techniques since they do not require expensive reagents or solvents.

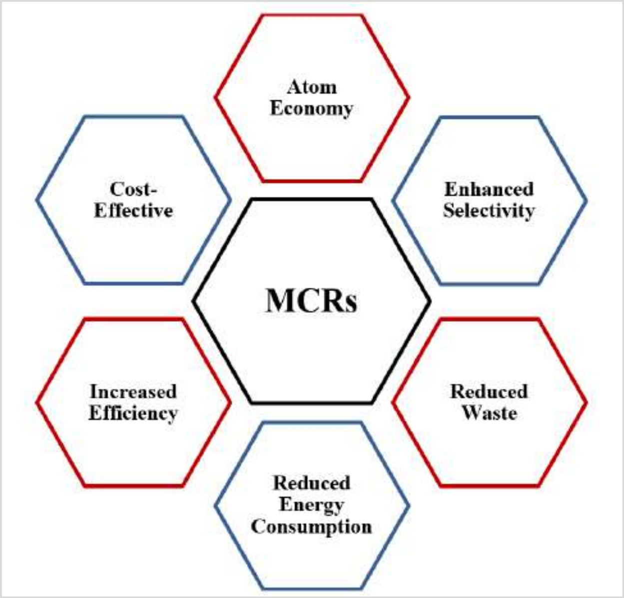


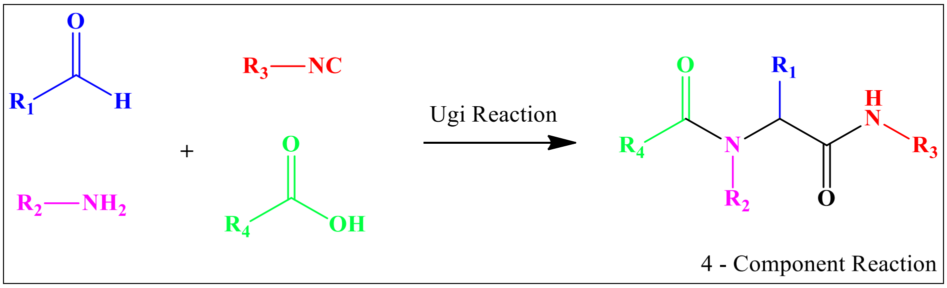
Figure 1: Characteristics of MCRs

Many multicomponent reactions follow the green chemistry principles, allowing the synthesis of complex molecules effectively by making the process cost-effective, reducing waste, and decreasing the environmental effect.[15]

3. Applications of multicomponent reactions

3.1 Peptide synthesis in the pharmaceutical industry

The synthesis of complex molecules such as peptides, natural products, and heterocyclic compounds has made extensive use of MCRs in the pharmaceutical industry. These applications greatly facilitate the synthesis of important intermediates and APIs (active pharmaceutical ingredients) which play an important role in the identification and development of new lead compounds.



Scheme 1

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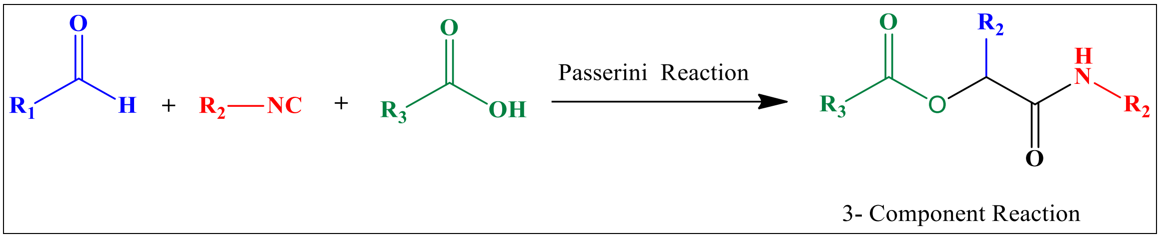
The peptides and peptidomimetics were synthesized using the Ugi reaction, a four-component synthesis (**Scheme 1**) including aldehyde, acid amine, and alkyl isocyanide[16–19].

3.2 Materials Science

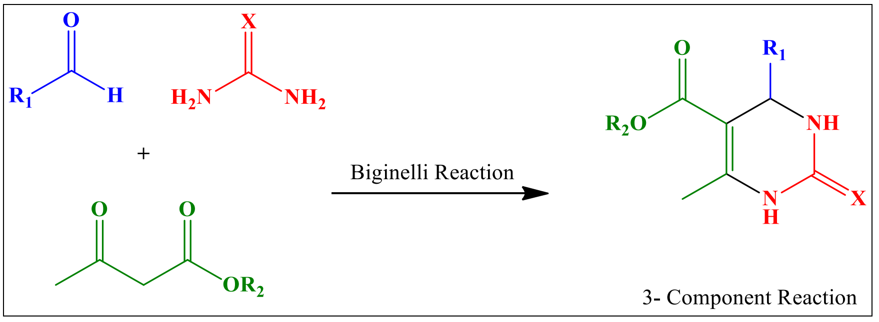
Different materials such as hydrogels, polymers, biomaterials, and metal-organic frameworks (MOFs) have been synthesized using MCRs. Polymeric materials used in the drug delivery have been synthesized using the Passerini reaction, a three-component reaction including aldehyde, alkyl isocyanide, and carboxylic acid (**Scheme 2**)[20–22].



Scheme 2

3.3 Agrochemicals and drug discovery

MCRs have been employed in the production of agrochemicals like pesticides, fungicides, and biopesticides, which makes new and better crop protection. Different heterocyclic compounds have been synthesized using the Biginelli reaction, a three-component reaction between aromatic aldehyde, urea/thiourea, and β-keto ester (**Scheme 3**)[23–25].



Scheme 3

3.4 Combinatorial chemistry

In combinatorial chemistry, MCRs have been utilized to produce a library of chemicals such as heterocyclic compounds, peptides, and other small complex molecules, which are known for their biological activity. Different heterocyclic compounds have been synthesized using the Hantzsch reaction, a three-component reaction involving aldehyde, β-keto ester, and ammonium acetate (**Scheme 4**)[26–28].

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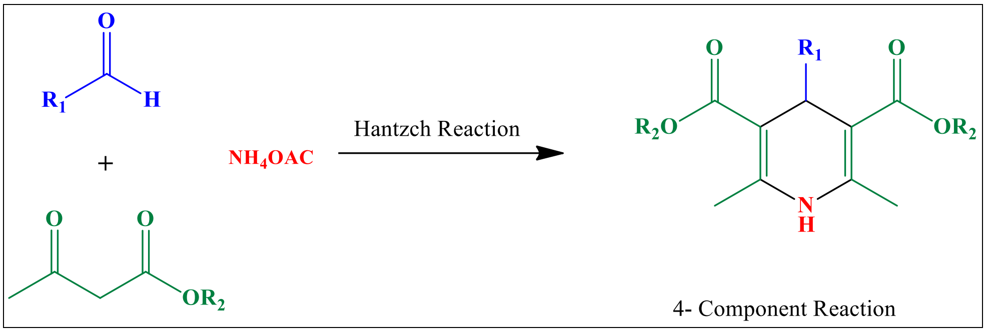
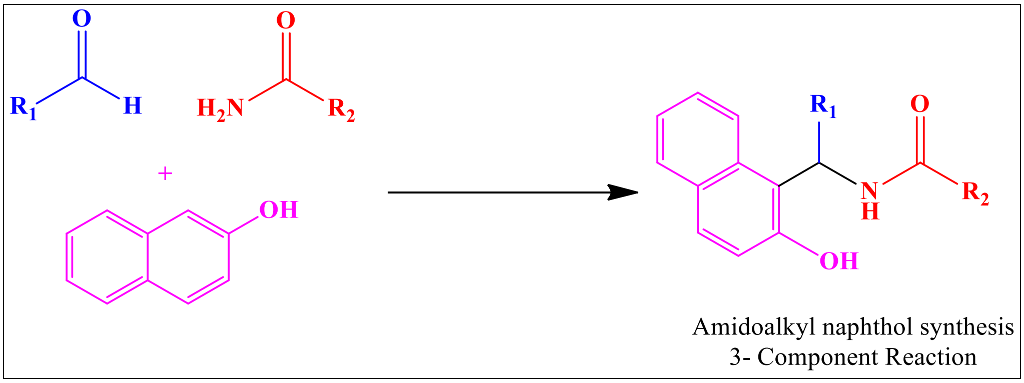


Scheme 4

3.5 Natural Product Synthesis

Natural products like alkaloids and terpenes have been synthesized using MCR because they offer effective and flexible routes for complex molecules (**Scheme 5**). Additionally, it made possible to investigate the structure-activity relation for the development of new alkaloids including derivatives of indole, isoquinoline, and quinolones. These compounds show the application in paint, pigment, and dye industries[29–31].



Scheme 5

4. Challenges in multicomponent reactions

MCRs are always accompanied by a number of difficulties, including

4.1 Optimization of reaction condition

The presence of two or more reactants in the MCRs to achieve high yield and selectivity is a major challenge in the optimization of reaction conditions because the byproduct of the reaction can further complicate the process of MCRs. A thorough understanding of the reaction mechanism regulates several reaction parameters such as temperature, solvent, and use of the catalyst. This approach makes it easier to identify the optimized reaction conditions[32,33].

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4.2 Scalability of reaction

In MCRs, it is a major problem in scaling to industrial levels while preserving the efficiency and selectivity of the reaction. Some aspects need to be carefully taken into consideration such as the availability of the reactor, appropriate reaction conditions, and management of the formation of byproducts and impurities at large-scale production. It is necessary to develop new reactor technologies and processes that overcome these issues to scale up MCRs effectively[34,35].

4.3 Sustainability of reaction

To create more sustainable MCRs, starting materials produced from biomass such as lipids, amino acids, and proteins were used. The essential component is the use of environmentally friendly solvents, such as water, ionic liquids, and supercritical fluids. Creating energy-efficient conditions, such as photochemical reactions, microwaves, and sonication-assisted synthesis significantly reduces energy consumption and also decreases waste production accompanying MCRs[36,37].

4.4 Selectivity of reaction

It can be difficult to control the selectivity of the MCRs when several reaction routes are possible. The reactant ratio, selection of the catalyst, and optimized reaction condition in terms of choice of solvent, temperature, and time are some of the variables that also affect the selectivity of MCRs[38,39].

5. Conclusion

Multicomponent reactions (MCRs) provide a rapid and effective method for the synthesis of complex molecules in the field of organic synthesis. The MCRs show the many potential applications in the synthesis of natural products and the synthesized new compounds. The MCRs must overcome certain challenges for future research such as optimized reaction conditions, which show increased efficiency and selectivity while scaling up at industrial levels.

References

1. Domling, Recent Developments in Isocyanide Based Multicomponent Reactions in applied chemistry, *Chem. Rev.* 106 (**2006**) 17-89. https://doi.org/10.1021/cr0505728.
2. L. Weber, Multi-component reactions and evolutionary chemistry, *Combinatorial chemistry*, 7 (**2002**) 143–147.
3. H. B. de Lima, G. M. das Neves, I. L. Gonçalves, A. A. Merlo, Vera L. Eifler-Lima, Multicomponent Reactions in the Last 30 Years: How are we Today?, *J. Braz. Chem. Soc. 35,* **(2024)**, 1-33. https://dx.doi.org/10.21577/0103-5053.20240075.
4. L.F. Tietze, G. Brasche, K.M. Gericke, Domino Reactions in Organic Synthesis, 2 (**2006**) 1-632. https://doi.org/10.1021/cr950027e.

ISBN: 978-93-95369-49-7 (electronic) 978-93-95369-48-0 (paperback)

5. K.C. Nicolaou, D.J. Edmonds, P.G. Bulger, Natural Product Synthesis Cascade Reactions in Total Synthesis, *Angewandte Chemie,* 45 (**2006**) 7134–7186. https://doi.org/10.1002/anie.200601872.

6. M. F. Litvic, M. Litvic, I. Cepanec V. Vinkovic, Hantzsch Synthesis of 2,6-Dimethyl-3,5-dimethoxycarbonyl-4- (*o*-methoxyphenyl)-1,4-dihydropyridine; a Novel Cyclisation Leading to an Unusual Formation of 1-Amino-2-methoxycarbonyl- 3,5-bis(*o*-methoxyphenyl)-4-oxa-cyclohexan-1-ene, *Molecule, 12* (**2007**) 2546–2558. https://doi.org/10.3390/12112546.

7. T. Gaich, P. S. Baran, Aiming for the Ideal Synthesis, *J. Org. Chem*., 75 (**2010**) 4657–4673. https://doi.org/10.1021/jo1006812.

8. Groenendaal, D.J. Vugts, R.F. Schmitz, F.J.J. De Kanter, E. Ruijter, M.B. Groen, R.V.A. Orru, A Multicomponent Synthesis of Triazinane Diones, *J. Org. Chem,* 73 (**2008**) 719–722. https://doi.org/10.1021/jo701973d.

9. G. Bosica, K. Baldacchino, R. Abdilla, R. De Nittis, Green Organic Synthesis via Multicomponent Reactions, *Xjenza Online,* 9 (**2021**) 173–179. https://doi.org/10.7423/XJENZA.2021.3.10.

10. Domling, W. Wang, K. Wang, Chemistry and Biology Of Multicomponent Reactions, *Chem. Rev.*,112, (**2012**) 3083-3135. https://doi.org/10.1021/cr100233r.

11. J. Zhu, Recent Developments in the Isonitrile-Based Multicomponent Synthesis of Heterocycles, *Eur. J. Org. Chem.,* (2003) 1133-1144. https://doi.org/10.1002/ejoc.200390167.

12. R. L. Mohlala,T. J. Rashamuse, E. M. Coyanis, Multicomponent reactions as an efficient and facile alternative route in organic synthesis and applications, (**2023**) 1.39. https://doi:10.20944/preprints202306.0345.v1.

13. Á.Cores, J. Clerigué, E. Orocio-Rodríguez J. C. Menéndez, Multicomponent Reactions for the Synthesis of Active Pharmaceutical Ingredients, *Pharmaceuticals*, 15 (**2022**) 1-42. https://doi.org/10.3390/ph15081009.

14. R. L. Mohlala, T. J. Rashamuse E. M. Coyanis, Highlighting multicomponent reactions as an efficient and facile alternative route in the chemical synthesis of organic-based molecules: a tremendous growth in the past 5 years, *Front. Chem.,* 12, (**2024**) 1-22. https://doi.org/10.3389/fchem.2024.1469677.

15. W. Zhang, Multicomponent Reactions (MCRs), *Pot, Atom, and Step Economy (PASE) Synthesis*, (**2021**) 27-41. https://doi.org/10.1007/978-3-030-22596-4_4.

16. Yang, Y. Zhao, Y. Wei, C. Fu, L. Tao, Ugi Reaction in Polymer Chemistry: Syntheses, Applications and Prospectives, *Polymer Chemistry*, (**2015**) 1-3. https://doi.org/10.1039/C5PY01398D.

ISBN: 978-93-95369-49-7 (electronic) 978-93-95369-48-0 (paperback)|

17. J. Zhang, P. Yu, S. Li, H. Sun, S. Xiang, J.J. Wang, K.N. Houk, B. Tan, Asymmetric phosphoric acid – catalyzed four-component Ugi reaction, *Research,* 1087 (**2018**) 361-372. https://doi.org/10.1126/science.aas8707.

18. R.O. Rocha, M.O. Rodrigues, B.A.D. Neto, Review on the Ugi Multicomponent Reaction Mechanism and the Use of Fluorescent Derivatives as Functional Chromophores, *ACS Omega*, 5 (**2020**) 972-979. https://doi.org/10.1021/acsomega.9b03684.

19. Y. Tao, Z. Wang, Y. Tao, Polypeptoids synthesis based on Ugi reaction: Advances and perspectives, *Biopolymers*, (**2019**) 1-11. https://doi.org/10.1002/bip.23288.

20. K. N. Onwukamike, S. Grelier, E. Grau, H. Cramail, M. A. R. Meier, On the direct use of CO_2 in multicomponent reactions : introducing the Passerini four component reaction, *RSC Adv.,* 8 (**2018**) 31490–31495. https://doi.org/10.1039/c8ra07150k.

21. L. Banfi, L. Ban, A. Basso, , C. Lambruschini, L. Moni, R. Riva Chemical Science*, Chem. Sci,*. 12 (**2021**) 15445–15472. https://doi.org/10.1039/D1SC03810A.

22. A.R. Kazemizadeh, A. Ramazani, Synthetic Applications of Passerini Reaction, *Current Organic Chemistry,* 16 (**2012**) 418–450.

23. Mushtaq, A. Munawar, B. Parveen, S. Javed, A. Fawad, Z. Kulsoom, G. Ali, Recent advances in the synthesis of dihydropyrimidinones via biginelli reaction, *J. Iran. Chem. Soc,*. 21 (***2024***) 2565–2586. https://doi.org/10.1007/s13738-024-03100-z.

24. H. Nagarajaiah, A. Mukhopadhyay, J.N. Moorthy, Biginelli reaction : an overview, *Tetrahedron Lett.,* 57 (**2016**) 5135–5149. https://doi.org/10.1016/j.tetlet.2016.09.047.

25. R.P. Herrera, E. Marqués-lópez, Multicomponent Reactions: Concepts and Applications for Design and Synthesis, (**2015**) 1.9.

26. G. Liu, R. Pan, Y. Wei, L. Tao, The Hantzsch Reaction in Polymer Chemistry : From Synthetic Methods to Applications, *Macromol. Rapid Commu,* 2000459 (**2020**) 1–10. https://doi.org/10.1002/marc.202000459.

27. M. Abdella, A. M. Abdelmoniem, I. A. Abdelhamid A.H.M. Elwahy, Synthesis of heterocyclic compounds via Michael and Hantzsch reactions, *J Heterocyclic Chem.*, 43 (**2020**) 1–48. https://doi.org/10.1002/jhet.3883.

28. H.S. Sohal, A review on recent trends in synthesis and applications of 1,4-dihydropyridines, *Materials Today Proceeding,* (**2021**) 1–8. https://doi.org/10.1016/j.matpr.2021.08.209.

29. N.S. Suryawanshi, P. Jain, Bronsted acidic ionic liquid as an efficient and reusable catalyst for one-pot synthesis of 1-amidoalkyl 2-naphthols under solvent-free conditions, *Orient. J. Chem.,* 26 (**2010**) 1525–1528. https://doi.org/10.1016/j.tetlet.2009.07.116.

30. A.H.M. Elwahy, Synthesis of heterocyclic compounds via Michael and Hantzsch reactions, *J Heterocyclic Chem.,* (**2020**) 1476–1523. https://doi.org/10.1002/jhet.3883.

ISBN: 978-93-95369-49-7 (electronic) 978-93-95369-48-0 (paperback) |

31. Z. Karimi-Jaberi, M. Jokar, S.Z. Abbasi, Efficient synthesis of 1-amidoalkyl-2-naphthols by one-pot, three-component reaction under solvent-free conditions, *J. of Chem.* (**2013**) 1–6. https://doi.org/10.1155/2013/341649.

32. M.A. Fouad, H. Abdel-hamid, M.S. Ayoup, Two decades of recent advances of Ugi reactions : synthetic and pharmaceutical applications, *RSC Adv.*, 10 (**2020**) 42644–42681. https://doi.org/10.1039/d0ra07501a.

33. S. Alsolami, H. S. Alorfi, K. A. Alamry, M.A. Hussein, One-pot multicomponent polymerization towards heterocyclic polymers: a mini review, *RSC Adv.,*14 (**2024**) 1757–1781. https://doi.org/10.1039/d3ra07278a.

34. `L. Weber, 12 Discovery of New MCRs , Chemical Evolution and Lead Optimization, (**2003**) 1-2.

35. Dömling, A.D. Alqahtani, General Introduction to MCRs : Past , Present , and Future, (**2015**) 1-12.

36. De Graaff, E. Ruijter, R.V.A. Orru, Recent developments in asymmetric multicomponent reactions, *Chem. Soc. Rev.,* 41 (**2012**) 3969–4009. https://doi.org/10.1039/c2cs15361k.

37. K. Yang, Q. Song, Enantioselective three-component reaction to access chiral a -vinyl phosphonates, *Chem Catal.,* 3 (**2023**) 100539-100542. https://doi.org/10.1016/j.checat.2023.100539.

38. S.A. Kiledal, R. Jourdain, S. Vellalath, D. Romo, Multicomponent Enantioselective Synthesis of Tetrahydropyridazinones Employing Chiral α,β-Unsaturated Acylammonium Salts, *Org. Lett.*, 23 (**2021**) 6622-6627. https://doi.org/10.1021/acs.orglett.1c02044.

39. C. Lambruschini, A. Basso, L. Ban, Integrating biocatalysis and multicomponent reactions, *Drug Discovery Today: Technologies*, 7 (**2018**) 1–7. https://doi.org/10.1016/j.ddtec.2018.06.004.

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