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Original Article

# Sustainable Approaches to Isoxazole Synthesis: A Green Chemistry Perspective

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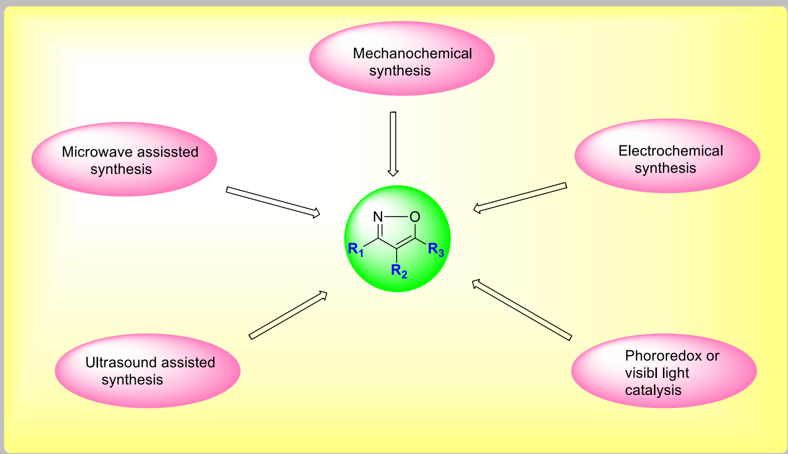
***Abstract***

*Isoxazoles are versatile heterocycles valued for their biological and material applications, driving continued interest in efficient and environmentally responsible methods for their construction. This work highlights recent sustainable strategies for synthesizing isoxazole frameworks utilizing green chemistry principles. Emphasis is placed on solvent-reduced or solvent-free conditions, the adoption of renewable or bio-derived starting materials, and the use of benign solvents such as water or ethanol. Energy-efficient activation techniques including microwave irradiation, ultrasound, and mechanochemistry are discussed alongside emerging catalytic systems designed to minimize waste and improve atom economy. Together, these innovations demonstrate how greener methodologies can deliver high yields, improved selectivity, and reduced environmental impact. The findings underscore the growing potential of sustainable design in advancing heterocyclic synthesis for pharmaceutical and materials applications.*

***Keywords-*** *Isoxazole synthesis, green chemistry, Sustainable organic synthesis, Eco-friendly catalysis, Atom economy, Renewable feedstock, Solvent-minimized methods, Microwave assisted synthesis, ultrasound-assisted synthesis, Mechanochemistry, Photocatalytic redox catalysis.*




## Introduction

Isoxazoles constitute a privileged class of five-membered heterocycles widely recognized for their diverse applications in pharmaceuticals, agrochemicals, natural product synthesis, and functional materials. Their presence in bioactive molecules such as anti-inflammatory agents, antimicrobial drugs, and CNS-active compounds has continually driven interest in developing efficient synthetic routes to these motifs. [1,2] Traditional methodologies for constructing isoxazole frameworks often rely on **toxic** solvents, hazardous reagents, stoichiometric oxidants, or energy-intensive conditions, which contribute to environmental burdens and limit scalability. Consequently, there is a growing need to redesign these synthetic strategies to align with modern sustainability goals. [3,4]



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Green chemistry provides a guiding framework for achieving environmentally responsible synthesis by emphasizing waste reduction, atom economy, safer reaction conditions, renewable feedstock, and energy efficiency. [5] In the context of isoxazole construction, applying green chemistry principles has led to the emergence of innovative methodologies that reduce ecological impact while maintaining or enhancing reaction efficiency. These developments include the adoption of green solvents such as water and bio-based media, benign catalysts including biocatalysts and recyclable heterogeneous catalysts, and alternative activation technologies like microwave irradiation, mechanochemistry, and photo redox catalysis. Furthermore, domino, multi-component, and one-pot strategies have gained importance for minimizing reaction steps and waste generation. [6]

Recent advances in sustainable isoxazole synthesis underscore the possibility of achieving high selectivity, broad functional-group tolerance, and scalable reaction conditions while adhering to environmental safety standards. By integrating the core principles of green chemistry into heterocycle construction, researchers can expand the utility of isoxazoles in numerous application areas without compromising ecological responsibility. This review (or section) explores these sustainable approaches in detail, highlighting key methodologies, technological innovations, and future prospects for greener isoxazole synthesis. [1,6]


**Figure-1**

**Green synthesis Methods for isoxazole:**

**Solvent-Free / Mechanochemical Synthesis:**

Mechanochemistry has emerged as a potent green-chemistry technique for creating isoxazole rings without the need for organic solvents, high temperatures, or harmful reagents. Mechanical energy (grinding, milling, shearing) creates bonds rather than dissolving reactants in a solvent, thus lowering waste and energy usage. Mechanochemical approach for synthesis of isoxazole mainly includes, cyclocondensation reaction between β-diketones / β-ketoesters & hydroxylamine hydrochloride results in **3,5**-disubstituted isoxazoles and 1,3-Dipolar cycloaddition reaction between Nitrile oxide reacts with alkynes/alkenes results in **3,4- or 3,5-substituted isoxazoles. [7,8]** (Figure-2)

| Green Method | Reaction | Key Features | Benifits |
|---|---|---|---|
| Solvent-Free / Mechanochemical Synthesis | Cyclization of β-dicarbonyls with hydroxylamine<br>1,3-dipolar cycloadditions. | Reactions performed via grinding or ball milling.<br>No solvent needed; short reaction times. | • Avoids hazardous oxidants.<br>• High regioselectivity<br>• No need for chromatographic purification<br>• Eliminates solvents, reduces waste, energy efficiency. |

**Table-1: Solvent-Free / Mechanochemical synthesis**

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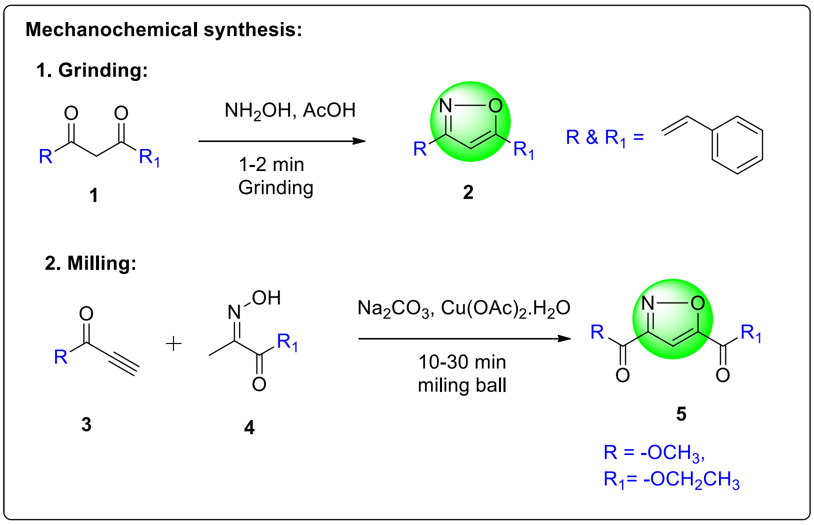


**Figure-2: Solvent-Free / Mechanochemical synthesis**

**Microwave assistance**

Microwave irradiation is widely recognized as an efficient green-chemistry tool for accelerating heterocyclic transformations with electromagnetic waves (2.45 GHz) by direct heating molecules through dipole rotation & ionic conduction which provides volumetric, uniform heating inside the reaction mixture including the formation of isoxazole rings with minimum energy consumption and reducing the toxic solvent requirement aligning with the green chemistry. Microwave assisted approach involves synthesis of isoxazole reaction between nitrile oxide with alkynes. Also, oxidative cyclisation between oxime and green oxidant (such as H2O2 & oxone) under microwave condition. [9] (Figure-3)

Microwave assisted reactions are excellent for cyclocondensation and 1,3-dipolar cycloaddition. [10,11]

| Green Method | Reaction | Key Features | Benifits |
|---|---|---|---|
| Microwave assistance | 1,3-dipolar cycloadditions. | electromagnetic waves (2.45 GHz)<br>Fast heating.<br>Minutes-scale reactions. | • Higher yields and cleaner profiles.<br>• Reduced time cycle.<br>• Cleaner reaction<br>• Green solvents. |
| | Oxidative Cyclisation | | |

**Table-2: Microwave assisted synthesis**

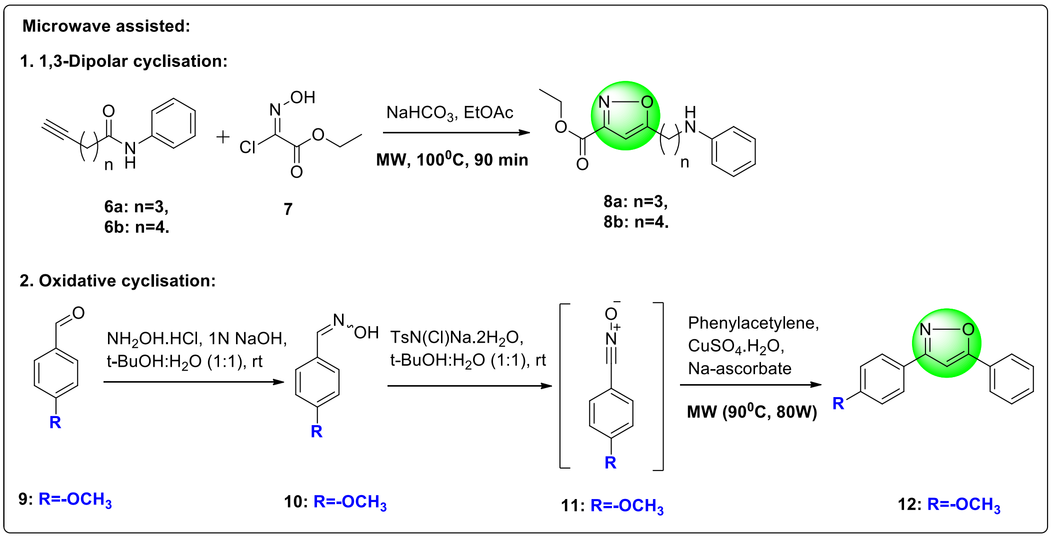


**Figure-3: Microwave assisted synthesis**

**Ultrasound-Assisted:**

An effective green activation technique for heterocycle synthesis, including isoxazoles, is ultrasound irradiation with sound waves (usually 20–40 kHz). Under otherwise mild bulk circumstances, acoustic cavitation promotes cleaner and faster reactions by producing localized high temperatures and pressures for incredibly brief periods of time. Ultrasound assisted useful for sonochemical 1,3-dipolar cycloadditions [6] (Figure-4), condensations [6]

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(Figure-4) & oxidative cyclisation [12] (Figure-4) under mild conditions. [13,14]

| Green Method | Reaction | Key Features | Benifits |
|---|---|---|---|
| Ultrasound assistance | Sonochemical 1,3-dipolar cycloadditions. | Sound waves (usually 20–40 kHz) Acoustic cavitation enhances reaction rate. Mild temperatures | • Higher yields and cleaner profiles. • Reduced time cycle. • Cleaner reaction • Green solvents. |
| | Condensation reaction | | |
| | Oxidative Cyclisation | | |

**Table-3: Ultrasound assisted synthesis**

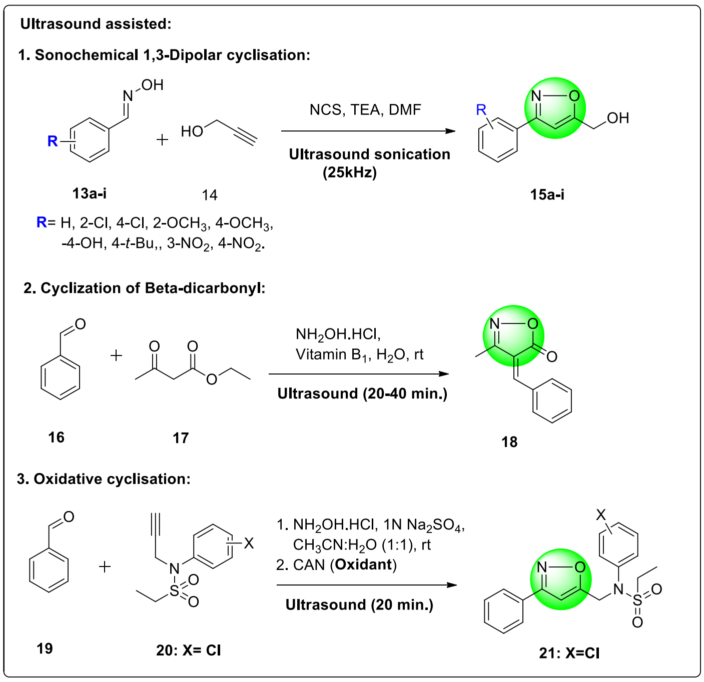


**Figure-4:** Ultrasound Assisted synthesis

**Photoredox or Visible-Light Catalysis:**

Visible-light photoredox catalysis has emerged as a powerful and sustainable method for constructing **isoxazole** frameworks. This strategy uses *low-energy visible light* (blue, green, or white LEDs) in combination with **organic dyes** or **transition-metal photo catalysts** to generate reactive radical or ionic species under mild, environmentally friendly conditions. These photoredox reaction involves visible light-induced 1,3-dipolar cycloaddition reaction between nitrile oxides and alkynes to form substituted isoxazoles. Also, photocatalytic or oxidative cyclisation of alkenes or oximes using visible light results in the formation of isoxazoles. [15,16] (Figure-5)

| Green Method | Reaction | Key Features | Benifits |
|---|---|---|---|
| Photoredox / Visible-Light Catalysis | 1,3-dipolar cycloadditions. | Light-driven oxidation steps. Avoids harsh oxidants. Mild & selective. | • Avoids hazardous oxidants. • Energy efficiency. |
| | Visible-light generation of nitrile oxides | | |

**Table-4: Photo redox or visible catalysis**

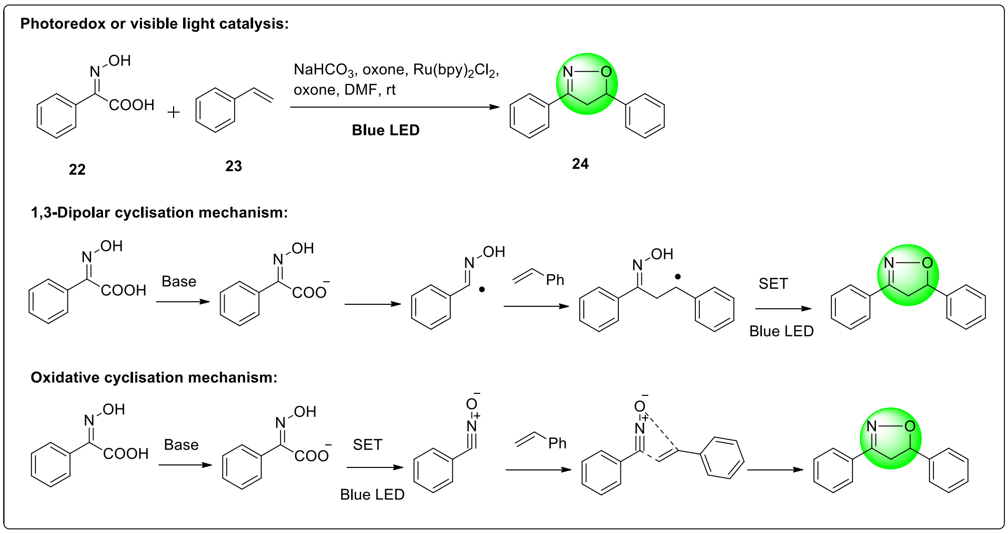


**Figure-5: Photo redox or visible catalysis**

**Electrochemical Synthesis:**

By using electric current as a clean reagent to drive oxidation, reduction, or radical processes, electrochemical synthesis (also known as "green electro synthesis") does away with the requirement for heavy-metal catalysts, hazardous reagents, or stoichiometric oxidants. Electrochemistry has emerged as a potent and sustainable technique for isoxazole synthesis, allowing for the effective production of the isoxazole ring under benign and ecologically benign conditions. This electrochemical synthesis of isoxazole consist three different methods. Electrochemical Oxidation of Oximes to Nitrile Oxides undergoes 1,3-dipolar cyclisation with alkynes or alkenes to form isoxazoles. Also, anodic Oxidative Cyclization of Oxime Ethers through radical reaction form isoxazoles. [17,18] (Figure-6)

| Green Method | Reaction | Key Features | Benifits |
|---|---|---|---|
| Electrochemical Synthesis | 1,3-dipolar cycloadditions of nitrile oxide with alkyne or alkene | Electrons act as clean oxidants. No stoichiometric chemical oxidants required. | • inherently green oxidation.<br>• High atom economy<br>• Mild condition<br>• Electricity replaces toxic oxidants<br>• Waste prevention |

**Table-5: Electrochemical Synthesis**

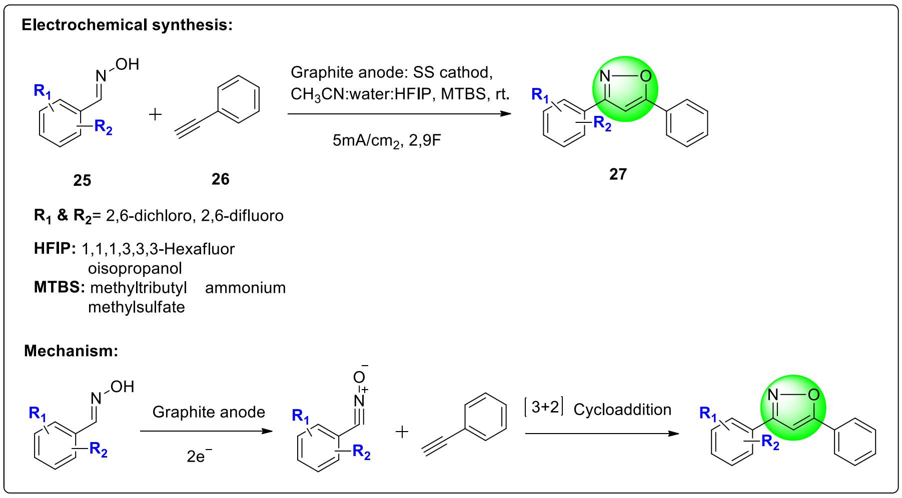


**Table-6: Electrochemical Synthesis**

**Conclusion**

The advancement of environmentally conscious heterocyclic chemistry depends on the creation of sustainable and energy-efficient methods for the synthesis of isoxazoles. Significant gains in reaction efficiency, selectivity, and environmental effect are shown by the green techniques covered, which range from solvent-free and mechanochemical methods to microwave, ultrasonic, photoredox, and electrochemical approaches. Together, these techniques cut down on hazardous waste, use fewer solvents, provide quicker reaction times, and need less energy than traditional approaches.

All things considered, incorporating green chemistry concepts into the synthesis of isoxazoles offers a feasible route toward more sustainable and clean chemical processes. The eco-efficiency and usefulness of isoxazole-based synthesis in both academic and industrial contexts will be further improved by ongoing research into catalyst-free systems, renewable energy sources, and scalable greener technologies.

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**Conflicts of interest**

The authors declare that there are no conflicts of interest regarding the publication of this paper.

**Reference**

1. Martis, G. J., & Gaonkar, S. L. (2025). *Advances in isoxazole chemistry and their role in drug discovery. RSC Advances*, **15**.
2. Wang, X., Hu, Q., Tang, H., & Pan, X. (2023). *Isoxazole/Isoxazoline Skeleton in the Structural Modification of Natural Products: A Review. Pharmaceuticals*, **16**(2), 228.
3. *RSC Advances* — "Copper(II)-catalyzed synthesis of 3,5-disubstituted isoxazoles … require stoichiometric oxidants such as TEMPO, hypervalent iodine, DDQ, etc., which pose environmental burden."
4. *Pharmaceuticals* — Chen, M.-T. et al., *The Green and Effective Synthesis of Isoxazole-Based Molecules Under Ultrasonic Irradiation Approaches*, Pharmaceuticals **2025**, 18 (8), 1179.
5. Anastas, P. T. & Warner, J. C. *Green Chemistry: Theory and Practice.* Oxford University Press, 1998.
6. Mei-Tong Chen, Yao-Rong Li, Zhao-Qi Wang, Shan Jiang, Zan-Hui Jia & Da-Wei Zhang, "The Green and Effective Synthesis of Isoxazole-Based Molecules Under Ultrasonic Irradiation Approaches," *Pharmaceuticals* **18**, 1179 (2025).
7. Hernandez, R. R., Burchell-Reyes, K., Braga, A. P., Lopez, J. K., & Forgione, P. (2022). Solvent-free synthesis of 3, 5-isoxazoles via 1, 3-dipolar cycloaddition of terminal alkynes and hydroxyimidoyl chlorides over Cu/$Al_2O_3$ surface under ball-milling conditions. RSC Advances, 12(11), 6396-6402.
8. Hernández, J. G.; Bolm, C. "Chapter on Mechanochemical Heterocycle Synthesis" *J. Org. Chem.*, 2017, 82, 4007–4019.
9. Koufaki, Maria; Fotopoulou, Theano; Kapetanou, Marianna; Heropoulos, Georgios A.; Gonos, Efstathios S.; Chondrogianni, Niki . (2014). *Microwave-assisted synthesis of 3,5-disubstituted isoxazoles and evaluation of their anti-ageing activity. European Journal of Medicinal Chemistry, 83(), 508–515.* doi: 10.1016/j.ejmech.2014.06.046
10. Kappe, C. O. "Microwave-Assisted Synthesis of Heterocycles Including Isoxazoles." *Chem. Rev.*, 2008, 108, 1052–1094.
11. Varma, R. S.; Dahiya, R.; Kumar, S. "Microwave-Assisted Solvent-Free Synthesis of Isoxazoles." *Tetrahedron Letters*, 1997, 38, 7029–7032.
12. Alaoui, Soukaina; Driowya, Mohsine; Demange, Luc; Benhida, Rachid; Bougrin, Khalid. (2018). *Ultrasound-assisted facile one-pot sequential synthesis of novel sulfonamide-isoxazoles using cerium (IV) ammonium nitrate (CAN) as an efficient oxidant in aqueous medium. Ultrasonics Sonochemistry, 40(), 289–297.* doi: 10.1016/j.ultsonch.2017.07.019
13. Mason, T. J.; Peters, D. "Practical Sonochemistry: Uses and Applications of Ultrasound in Chemistry." **Horwood Publishing, 2002.**
14. Naik, P. N.; Sastry, G. N. "Ultrasound-Assisted Synthesis of Isoxazole and Related Heterocycles." *Ultrasonics Sonochemistry*, 2013, 20, 120–126.
15. Svejstrup, Thomas; Zawodny, Wojciech; Douglas, James J; Bidgelli, Damon; Sheikh, Nadeem S.; Leonori, Daniele. (2016). *Visible-Light-Mediated Generation of Nitrile Oxides for the Photoredox Synthesis of Isoxazolines and Isoxazoles. Chem. Commun.* doi:10.1039/C6CC06029C.
16. Hari, D. P.; König, B. "The Photocatalyzed Synthesis of Heterocycles." *Chemical Communications*, 2014, **50**, 6688–6699.
17. Silja Hofmann; Johannes Winter; Tobias Prenzel; Maríade Jesús Gálvez-Vázquez; Siegfried R.Waldvoge**.** **"**Electrochemical Synthesis of Isoxazoles and Isoxazolines via Anodic Oxidation of Oximes**."** ChemElectroChem; 2023; page 1-8. doi.org/10.1002/celc.202300434.
18. Rodrigo, E.; Waser, J. "Electrochemistry for the Construction of N–O and N–O–C Bonds in Heterocycles." ***Angewandte*** *Chemie International Edition*, 2015, **54**, 12466–12470.