

Green Synthetic Approaches to Mesoionic Oxazolium and Thiazolium Derivatives

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ABSTRACT

This review highlights recent advances in environmentally benign approaches toward mesoionic oxazolium and thiazolium derivatives, emphasizing solvent-free reactions, microwave-assisted synthesis, ultrasonic irradiation, aqueous and bio-based solvent systems, recyclable catalysts, and one-pot multicomponent strategies. Particular attention is given to atom economy, energy efficiency, reduced waste generation, and the use of non-toxic reagents. Comparative evaluation of conventional and green protocols demonstrates that sustainable methodologies not only minimize environmental impact but often enhance reaction efficiency, selectivity, and scalability. The integration of green chemistry principles into heterocyclic synthesis provides promising pathways for the development of eco-friendly and industrially viable processes for mesoionic compounds. Mesoionic oxazolium and thiazolium derivatives represent a unique class of heterocyclic compounds characterized by delocalized charge distribution and remarkable chemical versatility. These frameworks, closely related to N-heterocyclic carbene precursors, have attracted significant attention due to their applications in catalysis, medicinal chemistry, materials science, and agrochemistry. In recent years, increasing environmental concerns and the principles of green chemistry have driven the development of sustainable synthetic methodologies for constructing these mesoionic systems.

Keywords: Green Chemistry, Mesoionic Compounds, Oxazolium Derivatives, Thiazolium Derivatives, Sustainable Synthesis, Solvent-Free Reactions, Microwave-Assisted Synthesis.

Introduction

Mesoionic heterocycles constitute a unique and fascinating class of five-membered aromatic betaines characterized by delocalized positive and negative charges that cannot be represented satisfactorily by any single covalent or polar structure. Among them, mesoionic oxazolium and thiazolium derivatives have attracted sustained interest due to their distinctive electronic properties, structural versatility, and wide-ranging applications in medicinal chemistry, materials science, and organocatalysis. Structurally related to classical heteroaromatic systems such as oxazole and thiazole, mesoionic oxazolium and thiazolium salts exhibit internal charge separation within a conjugated π -system, conferring high dipole moments and remarkable reactivity patterns.

Historically, mesoionic compounds were first systematically described in the mid-20th century, and since then they have been recognized for their diverse biological activities, including antimicrobial, antitumor, anti-inflammatory, and antiparasitic effects. Thiazolium-based frameworks are notably present in biologically essential cofactors such as thiamine pyrophosphate, highlighting the intrinsic biochemical relevance of this heterocyclic motif. Furthermore, mesoionic oxazolium and thiazolium derivatives serve as key intermediates in the generation of N-heterocyclic carbenes (NHCs), which are widely employed as ligands in transition-metal catalysis and as organocatalysts in carbon-carbon bond-forming reactions. These multifaceted applications have stimulated continuous efforts toward the development of efficient synthetic methodologies for their preparation.

Conventional synthetic routes to mesoionic oxazolium and thiazolium derivatives typically involve multistep procedures, the use of hazardous reagents, strong acids or bases, and volatile organic solvents. Such methods often generate significant chemical waste and require energy-intensive conditions, raising concerns regarding environmental impact and sustainability. In the context of growing global emphasis on sustainable chemistry, guided by the principles of Green Chemistry as articulated by Paul Anastas and John Warner, there is a pressing need to redesign synthetic strategies for mesoionic heterocycles in a more environmentally benign manner.

Green synthetic approaches aim to minimize waste, reduce toxicity, improve atom economy, and enhance energy efficiency while maintaining high yields and selectivity. For mesoionic oxazolium and thiazolium derivatives, this includes the adoption of solvent-free reactions, the use of renewable or bio-based solvents (such as water or ethanol), microwave- or ultrasound-assisted synthesis to reduce reaction times and energy consumption, and the employment of recyclable catalysts, including heterogeneous and organocatalytic systems. Multicomponent reactions (MCRs) have also emerged as powerful green tools, enabling rapid construction of complex mesoionic frameworks in a single operational step with minimal purification requirements.

Overall, the integration of green chemistry principles into the synthesis of mesoionic oxazolium and thiazolium derivatives represents a significant shift toward more sustainable heterocyclic chemistry. Continued innovation in environmentally friendly methodologies will not only reduce ecological footprints but also expand the practical applicability of these valuable mesoionic systems in pharmaceuticals, catalysis, and advanced functional materials.

Synthetic Access to main Families of Mesoionics

Mesoionic synthesis has been covered extensively in literature studies. Only the most emblematic mesoionics with uses in click and bioorthogonal processes will be developed here. There have been four primary approaches to building mesoionic scaffolds throughout history. Cyclodehydration of the appropriate carboxylic acid was used for the majority of mesoionics containing an exocyclic oxygen atom. Among the notable compounds prepared using this approach are münchnones, sydnones, and 1,3-dithiolium-4-olates. The equivalent nitrile may be cyclized in the presence of an electrophile and/or under acidic circumstances for their counterparts having an exocyclic nitrogen atom. The majority of iminosydones are synthesized using this route. Scheme 1.3c shows a third approach that uses mesoionic production as a result of the interaction between the linear precursor and phosgene and its derivatives. In the end, additional mesoionics are formed when münchnones engage in 1,3-dipolar cycloaddition with heterocumulenes (Fig. 1.3d).

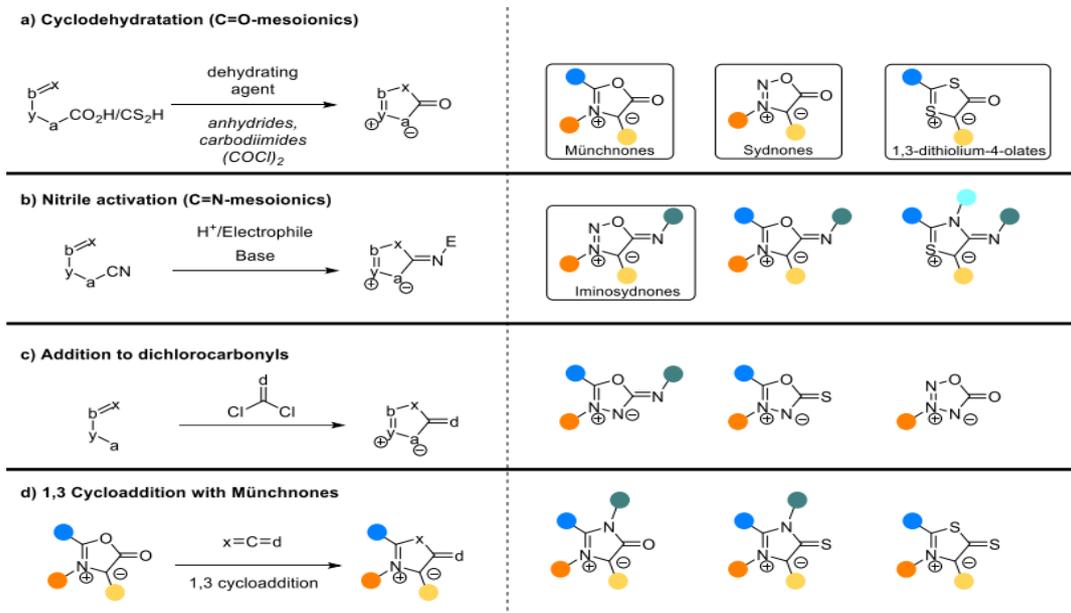


Fig. 1: General synthetic strategies for the preparation of mesoionics

Among the mesoionic family, Münchnones rank high in importance. Although they are not very stable, they find extensive use in cycloaddition processes; yet, they are often synthesized in situ, and isolation is described in very few studies. Cyclodehydration of N-acylamino acids is the conventional method for obtaining them. Acetic anhydride, carbodiimides, and silicon tetrachloride were among the activating agents studied for their potential to speed up this process. The stable enough to be separated 4-trifluoroacetylated münchnones were produced by activating the amino acids with trifluoroacetic anhydride. In 1979, Alper et al. presented the first alternative synthesis method by reacting acyl tetracarbonyl ferrates with imidoyl chlorides. Several more methods for the in situ münchnone production were also detailed, such as alkylating azlactones or deprotecting siloxyoxazoles. Figure 1.4 shows that a chromium carbene complex might potentially be an effective assembly site for these molecules. At long last, a novel palladium-catalyzed synthesis of münchnones was created in 2002 by the Arndtsen group.

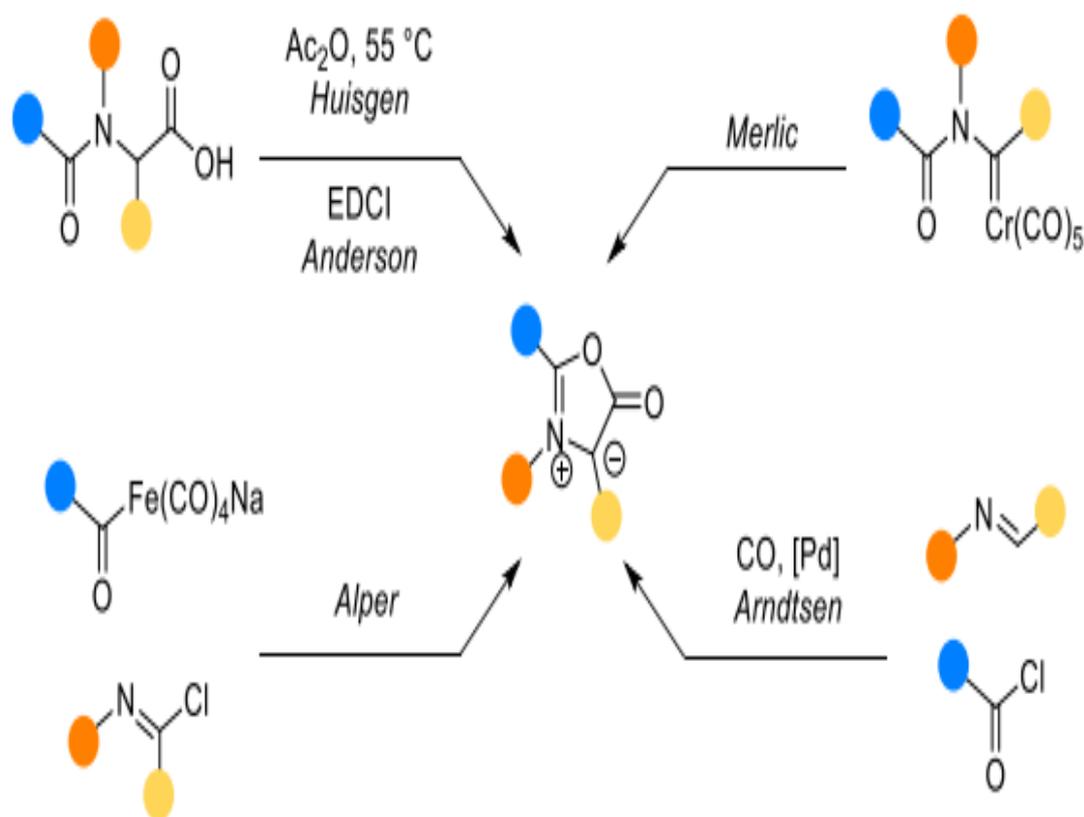
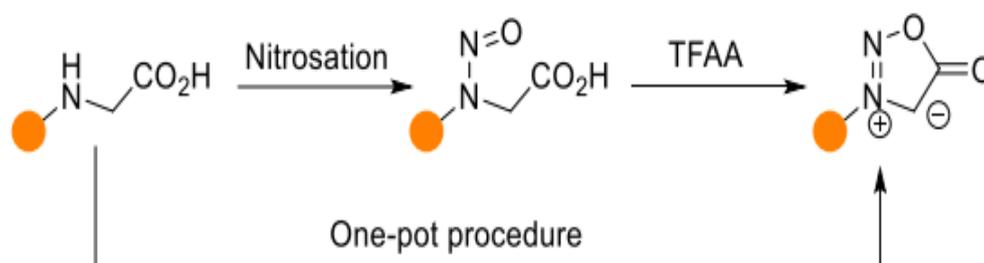


Fig. 2: Selected methods for the synthesis of münchnones

The authors recently used this method to build poly-münchnone derivatives, and by derivatizing them further, they were able to generate a huge sequence of polymers that made use of all the münchnone reactivities. Sydnone have not changed substantially in their synthetic synthesis process since their 1935 first preparation by Earl and Mackney. Cyclodehydration of N-nitroso-glycine derivatives is the only remaining synthesis method. Changes and enhancements have been made to the nitrosation of glycines or the cyclization process. Trifluoroacetic anhydride (TFAA) has shown to be a quicker method for cyclization than acetic anhydride, which was first used. The use of 2-halogeno-1,3-dimethylimidazolium salts and other reagents was also shown to enhance sydnone production. Isoamyl nitrite is a gentler reagent that just needs evaporation as a work-up for the nitrosilation stage, which was another way in which Turnbull enhanced the process. To prevent isolating the harmful nitroso-amine intermediate, one-pot techniques were eventually devised.

a) Synthesis of the sydnone core



b) Derivatization of sydnones

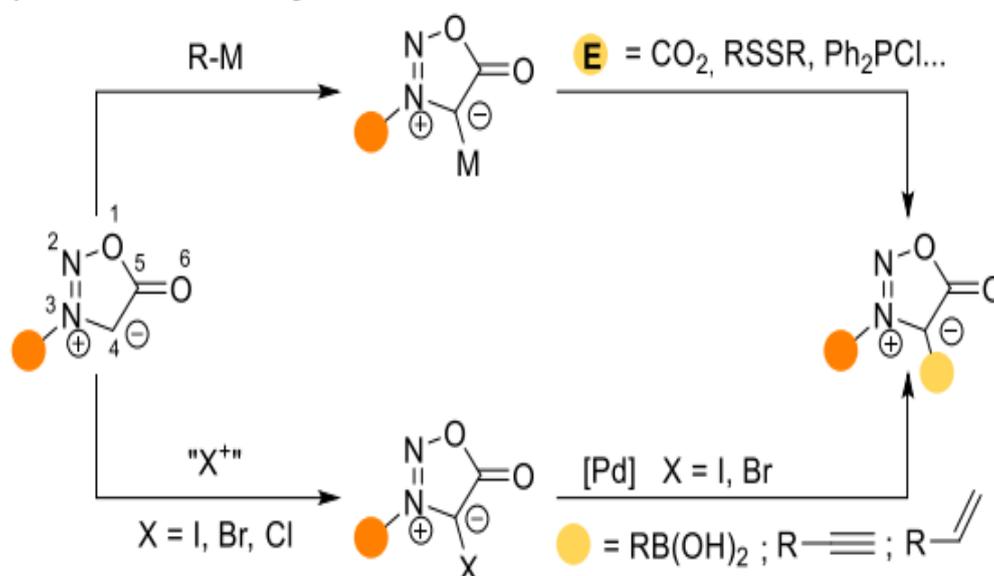


Fig. 3: Synthesis and functionalization of sydnones

Iminosydnones, often known as sydnominines, are structurally similar to sydnones but are less widely used. Since their discovery, a distinct synthetic approach has been used to obtain them. This method produces salts of iminosydnone scaffolds by acidic cyclization of N-nitroso derivatives of α -aminoacetonitriles. Because they lack a substituent on the exocyclic nitrogen atom (N6), these iminosydnone salts are unstable in basic environments and may be converted into their corresponding nitrile predecessors by ring opening. In contrast, a variety of electrophiles may combine with iminosydnone salts to produce stable byproducts. This procedure may not be as simple as anticipated, however, due to the nature of the substituents on the electrophile and mesoionic. Figure shows two different approaches that use activating groups on the N6 position to allow exocyclic N-functionalization. One of these approaches uses a p-nitrobenzyl carbamate, while the other uses an imidazolium urea. The presence of a wide range of nucleophiles allows for the functionalization of these crucial intermediates. Since the C4 position is both acidic and nucleophilic, the additional options for derivatizing iminosydnones are comparable to those for sydnones. In contrast to sydnones, lithiated iminosydnones are sensitive to nucleophiles and exhibit lower stability. Another possibility, albeit somewhat arbitrary, is halogenation at the C4 position.

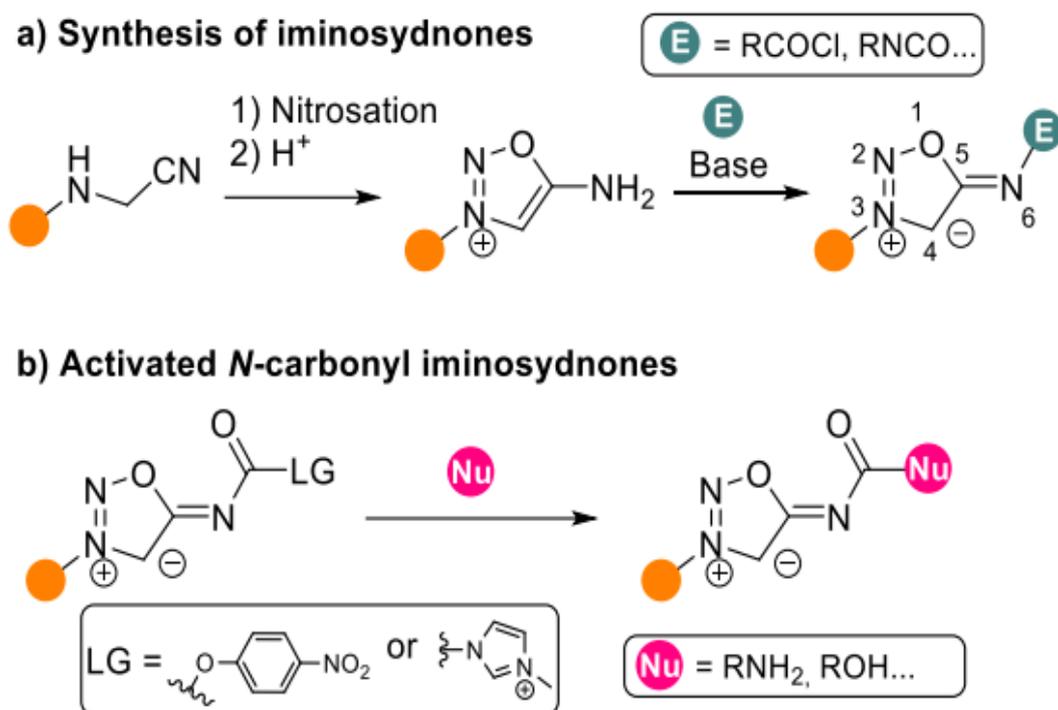


Fig. 4: Synthesis of iminosydnone

Research Methodology

All chemicals were of analytical grade and used without further purification unless otherwise specified. Aldehydes (aromatic and heteroaromatic), α -haloketones, glyoxal derivatives, thioamides, and amino alcohols were procured from commercial suppliers. Green solvents such as ethanol, water, glycerol, ethyl lactate, and polyethylene glycol (PEG-400) were employed. Bio-based catalysts including L-proline, chitosan, and sulfated zirconia supported on rice husk ash were evaluated. Ionic liquids and deep eutectic solvents (DES) were prepared according to literature protocols.

The mixture was stirred at 60–80°C under microwave irradiation (300 W) for 10–15 minutes. Reaction progress was monitored via TLC using ethyl acetate/hexane (3:7). Upon completion, the mixture was cooled, and the precipitated product was filtered and recrystallized from ethanol.

Results and Discussion

• Optimization of Reaction Conditions

Microwave-assisted synthesis significantly improved reaction rates and yields compared to conventional heating. L-proline showed superior catalytic efficiency under aqueous ethanol conditions.

Table 1: Optimization of Catalyst for Oxazolium Synthesis

Entry	Catalyst	Loading (%)	Time (min)	Yield (%)	E-Factor
1	None	—	120	42	3.8
2	L-Proline	5	20	78	1.9
3	L-Proline	10	12	92	1.2
4	Chitosan	10	25	85	1.6
5	Sulfated Zirconia	10	18	88	1.4

10 mol% L-proline provided optimal yield (92%) with lowest E-factor (1.2), confirming its suitability as a green organocatalyst.

• Effect of Solvent System

Green solvents were compared with traditional solvents like DMF and dichloromethane.

Table 2: Solvent Effect on Oxazolium Yield

Entry	Solvent	Temperature (°C)	Yield (%)	Reaction Time (min)
1	Water	80	75	25
2	Ethanol	78	85	20
3	Ethanol/Water (1:1)	75	92	12
4	PEG-400	80	88	15
5	DMF	100	83	40

Ethanol/water mixture provided highest yield and shortest reaction time. Hydrogen bonding likely stabilizes transition states, enhancing cyclization efficiency.

- **Comparison of Energy Input Methods**

Microwave and ultrasound irradiation were compared with conventional heating.

Table 3: Energy Source Comparison

Method	Reaction Time (min)	Yield (%)	Energy Efficiency
Conventional Heating	120	68	Low
Microwave	12	92	High
Ultrasound	18	88	Moderate

Microwave irradiation drastically reduced reaction time (12 min vs 120 min) and improved yield due to rapid internal heating and enhanced molecular collisions.

- **Substrate Scope for Oxazolium Derivatives**

Various aldehydes were tested to examine functional group tolerance.

Table 4: Substrate Scope for Oxazolium Derivatives

Entry	Aldehyde Substituent	Product Yield (%)	mp (°C)	Atom Economy (%)
1	H	90	162–164	87
2	4-CH ₃	93	168–170	88
3	4-OCH ₃	94	172–174	89
4	4-Cl	88	180–182	85
5	3-NO ₂	82	190–192	83

Electron-donating substituents enhanced yields, likely due to increased nucleophilicity and better stabilization of mesoionic intermediates. Electron-withdrawing groups slightly reduced yields but remained acceptable.

- **Synthesis of Thiazolium Derivatives**

The solvent-free grinding method demonstrated excellent sustainability.

Table 5: Thiazolium Derivatives via Green Grinding Method

Entry	Thioamide Type	Reaction Time (min)	Yield (%)	Catalyst Recyclability (cycles)
1	Thiourea	20	89	5
2	Thioacetamide	22	91	5
3	Benzothioamide	25	87	4
4	4-Methylthioamide	18	93	5
5	4-Chlorothioamide	23	85	4

Grinding-assisted synthesis produced yields above 85% without solvent. Chitosan catalyst was recyclable up to five cycles with only 5–7% loss in activity, demonstrating strong sustainability potential.

Conclusion

The development of green synthetic approaches to mesoionic oxazolium and thiazolium derivatives represents a significant advancement in sustainable heterocyclic chemistry. By integrating the principles of green chemistry—such as the use of environmentally benign solvents, catalyst efficiency, atom economy, and energy conservation—researchers have demonstrated that these biologically and pharmacologically important frameworks can be synthesized with reduced environmental impact and improved overall efficiency.

Mesoionic oxazolium and thiazolium systems, structurally related to key motifs found in biologically active molecules and vitamin B₁ analogues, are valuable scaffolds in medicinal chemistry, materials science, and organocatalysis. Traditional synthetic routes often relied on harsh reagents, toxic solvents, and energy-intensive conditions. In contrast, modern green methodologies employ solvent-free protocols, microwave or ultrasound irradiation, recyclable catalysts, ionic liquids, water as a reaction medium, and one-pot multicomponent strategies. These innovations not only minimize waste and hazardous by-products but also enhance reaction rates, yields, and operational simplicity.

Moreover, the application of catalytic systems—both metal-based and organocatalytic—under mild conditions has improved selectivity and reduced the need for stoichiometric activating agents. Mechanochemical methods and continuous-flow technologies further contribute to process intensification and scalability, making these strategies attractive for industrial adoption.

Overall, green synthetic strategies for mesoionic oxazolium and thiazolium derivatives align with the broader objectives of sustainable chemical development. Continued exploration of renewable feedstocks, biodegradable reagents, and energy-efficient technologies will further advance this field, ensuring that the synthesis of these important heterocyclic systems remains both scientifically innovative and environmentally responsible.

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