
ENVIRONMENTALLY BENIGN STRATEGIES FOR THE SYNTHESIS AND FUNCTIONALIZATION OF IMIDAZOLIDINE-BASED SYSTEMS

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DOI <https://doi.org/10.30525/978-9934-26-714-7-27>

INTRODUCTION

The field of heterocyclic chemistry has undergone a profound transformation over the last two decades, driven by the escalating necessity to align synthetic methodologies with the principles of green chemistry. Imidazolidine-based systems, specifically heterocyclic ketene amins (HKAs), also identified as cyclic 1,1-enediamines, represent a class of scaffolds with immense structural diversity and significant biological relevance¹. These systems are characterized by a unique electronic architecture wherein the two nitrogen atoms of the imidazolidine ring facilitate a strong “push-pull” effect, donating electron density into an exocyclic double bond that is typically activated by electron-withdrawing groups such as nitro, carbonyl, or cyano moieties². This specific electronic arrangement renders them highly versatile as building blocks for the construction of complex fused heterocycles, including imidazopyridines, imidazoquinolines, and various polycyclic architectures^{3, 4, 5}.

¹ Wang S.-Y., Zhang Z.-W., Yuan L., Jin Y., Zhang C.-H., Lin J. Efficient Synthesis of Bicyclic 2-Pyridinones and 6-Amino-2-pyridinones by the Regioselective Cycloaddition of Nitro Ketene Aminal with 3-Hydroxy-2-aryl-acrylate. *European Journal of Organic Chemistry*. 2022. No. 26. DOI: 10.1002/ejoc.202201268.

² Kong L., Yan S., Lin J. Heterocyclic Ketene Amins: Leading Molecules to Construct Molecular Diversity Fused Heterocyclic Compounds. *Progress in Chemistry*. 2018. Vol. 30, No. 5. P. 639–657. DOI: 10.7536/PC171208.

³ Vala M., Bayat M., Bayat Y. One-pot Synthesis of Dihydro-8H-acenaphtho[1',2':4,5]pyrrolo[1,2-a]imidazole-diol Derivatives. *Molecular Diversity*. 2021. Vol. 25. DOI: 10.1007/s11030-020-10078-2.

⁴ Hooshmand E., Ziyaei A. Nitroalkenes in diverse synthesis of heterocyclic compounds with two or three heteroatoms: recent advances. *Targets in Heterocyclic Systems*. 2019. Vol. 22. DOI: 10.17374/targets.2019.22.119.

⁵ Li M., Zhou Z.-M., Wen L.-R., Qiu Z.-X. Chemistry of heterocyclic ketene amins: construction of imidazo(pyrido)[1,2-a]pyridines and imidazo(pyrido)[3,2,1-ij][1,8]naphthyridines via DABCO-catalyzed tandem annulations. *The Journal of Organic Chemistry*. 2011. Vol. 76, № 9. P. 3054–3063. DOI: 10.1021/jo102167g.

As the global chemical community moves toward carbon neutrality and minimized environmental impact, the traditional reliance on hazardous organic solvents, toxic transition-metal catalysts, and energy-intensive heating protocols has become increasingly untenable^{6, 7}. Consequently, researchers have pioneered a wide array of environmentally benign strategies for the synthesis and functionalization of these systems. These strategies encompass the use of aqueous media, solvent-free mechanochemistry, organocatalysis, and alternative energy sources such as microwave and ultrasound irradiation. Furthermore, the implementation of multicomponent reactions (MCRs) has emerged as a cornerstone of sustainable synthesis, offering high atom economy and reducing the number of purification steps required to achieve structural complexity^{8, 9, 10}.

While recent years have witnessed increasing attention to sustainability, the mechanistic underpinnings of these transformations remain the central factor governing efficiency, regioselectivity, and scalability. The present study therefore evaluates environmentally benign strategies not merely as solvent substitutions but as modifications that interact directly with the intrinsic electronic and conformational properties of the HKA scaffold.

1. Sustainable Synthetic Strategies for Imidazolidine-Based Systems

The evolution of sustainable chemistry in the context of imidazolidine and HKA synthesis is best categorized through the specific green strategies employed to reduce environmental footprints. The following mapping details the most representative publications in this field, categorized by their primary green innovation.

1.1. Resource-Efficient Synthetic Approaches

Resource efficiency represents one of the central pillars of sustainable chemistry. For imidazolidine-based systems and heterocyclic ketene amins

⁶ Kumari M., Haribabu N. Green multicomponent reactions for the synthesis of biologically relevant heterocycles: a sustainable approach. *International Journal of Novel Research and Development*. 2025. Vol. 10. DOI: 10.56975/ijnrd.v10i7.308394.

⁷ Mohlala R. L., Rashamuse T., Coyanis E. 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. *Frontiers in Chemistry*. 2024. Vol. 12. DOI: 10.3389/fchem.2024.1469677.

⁸ Kasana S., Kurmi B., Patel P. Green synthesis of pyridine and their fused system: harnessing the catalytic power of ionic liquids for sustainable and efficient multicomponent reaction. *Current Organic Chemistry*. 2024. Vol. 29. DOI: 10.2174/0113852728331797240903101654.

⁹ Salis C., Mohammadi S., Turazza L., Blandin Y., Garnier M., Hemmert C., Baltas M., Gornitzka H. Mechanochemistry to form substituted imidazoles, imidazolium salts and NHC–gold complexes with fluorine-containing groups. *Molecules*. 2025. Vol. 30, № 3. Article 522. DOI: 10.3390/molecules30030522.

¹⁰ Yu X.-L., Fan Y.-H., Zheng X.-N., Gao J.-F., Zhuang L.-G., Yu Y.-L., Xi J.-H., Zhang D.-W. Synthesis of imidazole-based molecules under ultrasonic irradiation approaches. *Molecules*. 2023. Vol. 28, № 12. Article 4845. DOI: 10.3390/molecules28124845.

(HKAs), this goal is achieved through solvent-free synthesis, mechanochemical activation, multicomponent reactions, and one-pot methodologies. These approaches reduce material consumption, minimize waste generation, and improve atom utilization while maintaining high levels of synthetic performance.

Solvent-Free and Mechanochemical Synthesis

The removal of the solvent phase is perhaps the most direct route to minimizing the E-factor (Environmental Factor) in chemical synthesis, as solvents frequently represent the majority of the mass in a reaction mixture.

In mechanochemical synthesis, the high energy imparted by collisions in a ball mill overcomes the activation energy barriers that would normally require high-temperature reflux. The absence of a solvent means that the reactants are at maximum concentration, which often alters the product selectivity. A prime example is the selective formation of E-regioisomers in the mechanochemical preparation of nitrofurantoin, where the steric constraints of the solid state favor the thermodynamic product more effectively than solution-phase synthesis.

Mechanochemical activation has emerged as an alternative mode of energy input for HKA functionalization. Saha et al. demonstrated¹¹, that high regioselectivity was achieved under milling conditions without liquid media. The absence of solvent increases effective reactant concentration and may alter transition-state organization compared to solution-phase analogues. This methodology utilizes a mixer-mill to facilitate the regioselective functionalization of imidazo-fused systems on a silica gel matrix. The green aspect is the total absence of liquid solvents during the reaction and the use of inexpensive, readily available precursors to generate the active thiocyanating agent *in situ*. The key advantage is the achievement of high yields at ambient temperature within short reaction times – 30 minutes.

Similarly, in paper¹² the researchers report a highly efficient ball-milling strategy for the quaternization of imidazoles, producing imidazolium salts and NHC-gold complexes. The green benefit lies in the 79–99% yields obtained without solvent use and the circumvention of traditionally long reflux times. This approach is particularly transformative for the synthesis of precursors for gold-based catalysts. Although not limited exclusively to HKAs, these examples illustrate broader mechanochemical principles applicable to imidazolidine-based systems.

¹¹ Saha S., Pinheiro A. B., Chatterjee A., Bhutia Z. T., Banerjee M. A Solvent-Free Mechanochemical Electrophilic C–H Thiocyanation of Indoles and Imidazo[1,2-a]pyridines Using a Cost-Effective Combination of N-Chlorosuccinimide–NaSCN. *Green Chemistry*. 2024. DOI: 10.1039/D4GC00486H.

¹² Salis C., Mohammadi S., Turazza L., Blandin Y., Garnier M., Hemmert C., Baltas M., Gornitzka H. Mechanochemistry to form substituted imidazoles, imidazolium salts and NHC–gold complexes with fluorine-containing groups. *Molecules*. 2025. Vol. 30, № 3. Article 522. DOI: 10.3390/molecules30030522.

Yaqub et al. describe¹³ a solvent-free approach for the construction of fused heterocyclic architectures from ketene amins. The green aspect centers on the reduction of organic waste and the simple purification procedures. The advantage is the broad functional group tolerance and the generation of derivatives with significant pharmacological potential.

The study of direct phosphorylation of heteroarenes under oxygen, metal-free, and solvent-free conditions¹⁴ details the oxidative functionalization of nitrogen heterocycles using atmospheric oxygen as the terminal oxidant. The green aspect is the combination of being metal-free and solvent-free, using air as a benign reagent. The key advantage is the direct access to phosphorylated imidazolidine-related heterocycles with high atom economy.

A four-component reaction for the synthesis of 1,2,4,5-tetrasubstituted imidazoles (Fig. 1) is performed¹⁵ under solvent-free conditions using a novel ionic liquid catalyst. It is worth noting that the authors compared the reaction under different conditions – methanol, ethanol, DMF and DMSO, a solvent-free system. The best yields in the shortest time were shown by the solvent-free approach. The advantage is the short reaction time and excellent yields (average 86%).

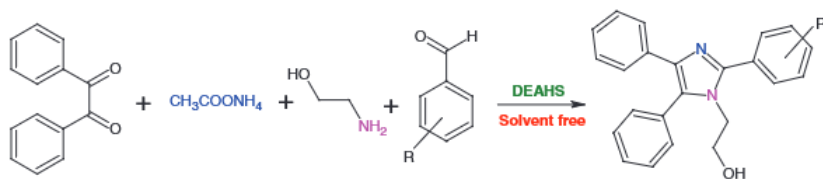


Fig. 1. Synthesis of 1,2,4,5-tetrasubstituted imidazoles

However, mechanochemical protocols introduce variables distinct from solution chemistry. Solid-state diffusion, particle size distribution, and mechanical energy transfer become critical determinants of reproducibility. The selective formation of E-configured products (Fig. 2) in mechanochemical drug

¹³ Yaqub M., Batool J., Mahmood K., Ashraf A., Perveen R., Shafiq Z. Regioselective Synthesis of Fused Ring Heterocyclic Derivatives of Ketene Amins and Their Biological Activities. *Journal of Heterocyclic Chemistry*. 2020. DOI: 10.1002/jhet.4014.

¹⁴ Luo K., Chen Y. Z., Chen L. X., Wu L. Autoxidative C(sp²)-P Formation: Direct Phosphorylation of Heteroarenes under Oxygen, Metal-Free, and Solvent-Free Conditions. *The Journal of Organic Chemistry*. 2016. Vol. 81, No. 11. P. 4682–4689. DOI: 10.1021/acs.joc.6b00592.

¹⁵ Mohamed S., Simpson J., Marzouk A., Talybov A., Abdelhamid A., Abdullayev Y., Abbasov V. Multicomponent Green Synthesis, Spectroscopic and Structural Investigation of Multi-Substituted Imidazoles. Part 1. *Zeitschrift für Naturforschung B*. 2015. Vol. 70. DOI: 10.1515/znb-2015-0067.

synthesis, as reported in the cited study¹⁶, may indicate that crystal-packing constraints contribute to the observed stereochemical outcome. This paper highlights the ball-milling of amino-hydantoin and aldehydes to produce commercial drug molecules. The green aspect is the solvent-, base-, and waste-free stoichiometric processing. The key advantage is the selective formation of the more stable E-regioisomers in pure form without post-reaction workup.

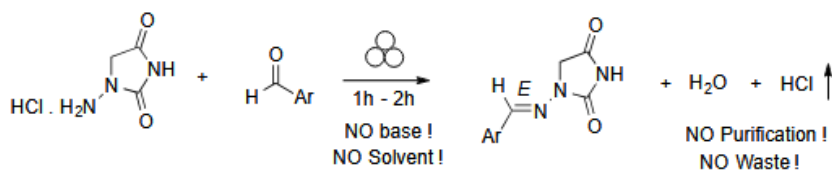


Fig. 2. The selective formation of E-configured products

A solvent-free protocol for the site-selective synthesis of functionalized indoles from HKAs is shown in paper¹⁷. The green aspect is the efficient use of mechanical or thermal energy in the absence of liquid media. The advantage is the construction of complex indole frameworks with high regioselectivity (Fig. 3).



Fig. 3. The synthesis of functionalized indoles from HKAs

Thus, while solvent-free methods reduce solvent mass, their synthetic efficiency must be interpreted in light of solid-state reactivity constraints and scalability considerations.

The management of thiol byproducts generated during the cyclization step deserves particular attention from a green chemistry perspective. The authors

¹⁶ Colacino E., Porcheddu A., Halasz I., Charnay C., Delogu F., Guerra R., Fullenwarth J. Mechanochemistry for “No Solvent, No Base” Preparation of Hydantoin-Based Active Pharmaceutical Ingredients: Nitrofurantoin and Dantrolene. *Green Chemistry*. 2018. Vol. 20, No. 13. P. 2973–2977. DOI: 10.1039/C8GC01345D.

¹⁷ Luo D. Y., Hu X. M., Huang R., Cui S. S., Yan S. J. Base-Promoted Relay Reaction of Heterocyclic Ketene Aminals with o-Difluorobenzene Derivatives for the Highly Site-Selective Synthesis of Functionalized Indoles. *Tetrahedron*. 2021. DOI: 10.1016/j.tet.2021.132275.

of the article¹⁸ discuss two mitigation strategies: chemisorption of the off-gas stream through a 10–15% sodium hydroxide solution, forming reversible alkali metal thiolates (controllable by adjusting alkali concentration or temperature to suppress hydrolysis), and oxidative scrubbing through saturated potassium iodate solution, which converts thiols to the considerably less toxic sulfenic, sulfinic, and sulfonic acids. Both approaches represent practical, low-cost solutions for hazard reduction at the laboratory scale and may serve as starting points for integrated gas-treatment protocols at larger scale.

Green Solvent Systems

Water, ethanol, and deep eutectic solvents (DES) provide sustainable alternatives to traditional dipolar aprotic solvents, often enhancing reaction rates through the “on-water” effect or unique hydrogen-bonding networks.

This foundational work¹⁹ demonstrates the synthesis of imidazolidine-based HKAs from ketene dithioacetals and diamines in water (Fig. 4). The green aspect is the “on-water” acceleration and the total avoidance of acids or bases. The key advantage is the high regioselectivity and yields (90–96%) obtained at room temperature.

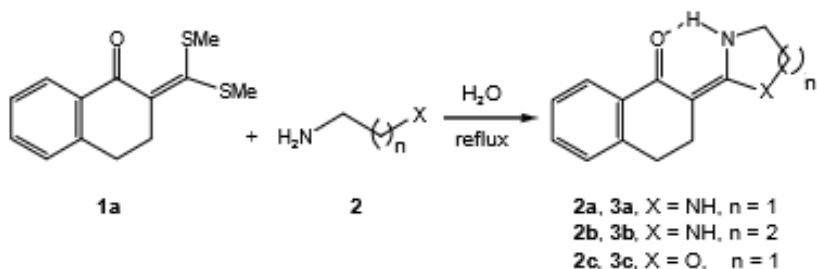


Fig. 4. The synthesis of imidazolidine-based HKAs

The mechanisms of these green syntheses frequently involve a sequence of Knoevenagel condensation, Michael addition, and intramolecular cyclization. In aqueous systems, the hydrophobic effect plays a major role in driving these components together. For instance, in the synthesis of oxa-aza[3.3.3]propellanes (Fig. 6), the insolubility of the ninhydrin-malononitrile adduct in water forces it into proximity with the nitroketene aminal, accelerating the Michael addition step.

¹⁸ Фіголь М. П., Харченко Ю. В. Особливості синтезу кетенаміналей. *Природничі науки*. 2019. № 16. С. 86–89.

¹⁹ Chanu L. G., Singh O. M., Jang S. H., Lee S. G. Regioselective Synthesis of Heterocyclic Ketene N,N-, N,O- and N,S-Acetals in Aqueous Medium. *Bulletin of the Korean Chemical Society*. 2010. Vol. 31, No. 4. P. 859–862. DOI: 10.5012/bkcs.2010.31.04.859.

Wen al.²⁰ report efficient annulation sequences in aqueous media, consistent with preorganization effects and hydrophobic aggregation. This work presents a detailed investigation of the synthesis of fused imidazo-heterocycles using water as the reaction medium. The green aspect is the circumvention of organic solvents and the achievement of high yields at ambient temperature. The advantage is the environmental safety and the broad scope of the aqueous S_NAr reaction.

Water likely influences HKA reactivity via multiple mechanisms:

- hydrogen-bond-assisted polarization of the exocyclic double bond;
- enhanced proximity of hydrophobic reactants (“on-water” effect);
- stabilization of zwitterionic intermediates.

For comparison, an analogous cyclization of ketene amins²¹ (Fig. 5) carried out in an acetonitrile environment required heating for 1 hour, whereas the analogous annulation carried out in water, as reported above, proceeds considerably faster – in just 10 minutes – illustrating the kinetic advantage of the aqueous medium for this reaction class.

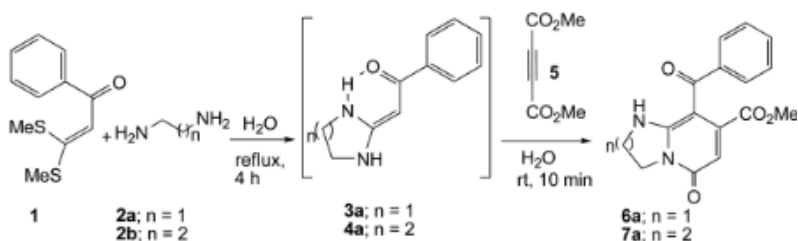


Fig 5. One-pot Synthesis of imidazo[1,2-a]pyridines and pyrido[1,2-a]pyrimidines

Beyond the bicyclic pyridine and pyrimidine scaffolds discussed above, the same aqueous “on-water” principles extend naturally to more complex, multi-ring architectures assembled in a single operation.

These features are especially evident in multicomponent cascade processes, such as the aqueous one-pot synthesis (Fig. 6) reported by Rahimi et al.²², which

²⁰ Wen L. R., Li M., Wang L. J. Synthesis of Imidazo[1,2-a]pyridines and Pyrido[1,2-a]pyrimidines in Water and Their S_NAr Cyclizations. *Bulletin of the Korean Chemical Society*. 2014. Vol. 35, No. 4. P. 995–1000. DOI: 10.5012/bkcs.2014.35.4.995.

²¹ Orlov V. D., Kharchenko Yu. V., Gella I. M., Omel'chenko I. V., Shishkin O. V. Reactions of Ketene Amins with N-Arylmaleimides and Dimethyl Acetylenedicarboxylate, a Direct Pathway to Derivatives of Pyrrolo[1,2-a]imidazole and Imidazo[1,2-a]pyridine. *Chemistry of Heterocyclic Compounds*. 2012. Vol. 48, No. 8. P. 1204–1212.

²² Rahimi Z., Bayat M., Hosseini H. A Highly Chemo- and Regioselective Synthesis of Heterocyclic [3.3.3]Propellanes via Sequential Multicomponent Reactions in Water. *Scientific Reports*. 2025. Vol. 15, 27969. DOI: 10.1038/s41598-025-13577-0.

employs ninhydrin, malononitrile, and nitroketene amins. The green aspect is the use of water as the sole solvent without the need for external catalysts. The advantage is the formation of multiple rings and bonds in one step with high atom economy and easy product separation, the saving of time and cost through sequential one-pot methods.

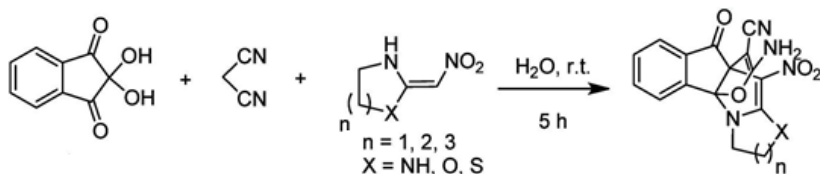


Fig. 6. The synthesis of oxa-aza[3.3.3]propellane derivatives

Notably, aqueous systems often enable direct isolation by precipitation, eliminating chromatographic purification and thereby improving overall process efficiency.

A one-pot three-component reaction performed in ethanol under catalyst-free conditions is discussed by Saeedi et al.²³. The green aspect is the use of an environmentally benign solvent and the absence of toxic additives. As evidenced by the optimization data presented in Table 1, water proved to be an ineffective medium for this transformation, likely due to the limited solubility of the starting materials. However, the highest efficiency was achieved using ethanol as a sustainable solvent under catalyst-free conditions. Specifically, the reaction in refluxing ethanol (see Table 1, Entry 5) afforded the target product in an 88% yield, and eliminates the need for additional acidic or basic additives, which aligns with the principles of green chemistry. The advantage is the high yield and simple workup involving only filtration and washing.

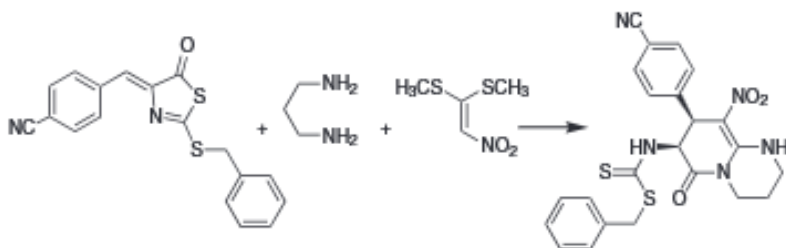


Fig. 7. The one-pot three-component reaction

²³ Saeedi M., Khoshdoun M., Mohammadi A., Halvagar M., Amani V. Synthesis of Functionalized Bicyclic Pyridones Containing Dithiocarbamate Group Using Thioazlactones, Diamines and Nitroketene Dithioacetal. *SynOpen*. 2021. DOI: 10.1055/a-1492-9229.

Table 1

The reaction conditions for the synthesis of bicyclic pyridines

Entry	Catalyst (mol%)	Solvent	Temp (°C)	Yield (%) ^b
1	–	EtOH	r.t.	NR
2	–	CHCl ₃	r.t.	NR
3	–	H ₂ O	r.t.	NR
4	–	H ₂ O	reflux	NR
5	–	EtOH	reflux	88
6	PTSA (30)	EtOH	reflux	64
7	Et ₃ N (30)	EtOH	reflux	45

Further details on the ethanol-mediated synthesis of bicyclic pyridones are provided in article²⁴. The green aspect is the high purity of the products which requires no chromatography. The advantage is the high efficiency and diastereoselectivity of the domino amidation.

This review and earlier research summary^{25, 26}, together highlight the use of Choline Chloride/Urea (DES) for the synthesis of imidazonaphthyridines. The environmental efficiency of this protocol is underscored by the dual role of the Deep Eutectic Solvent (DES), which functions simultaneously as a biodegradable medium and a Lewis acid catalyst. In this capacity, the DES facilitates the reaction by activating both the carbonyl and cyano groups through a robust hydrogen-bonding network (Fig. 8), thereby enhancing the electrophilicity of the reactants without the need for additional volatile organic solvents.

While solvent selection plays a central role in reducing the environmental footprint of HKA synthesis, the sustainability of a process is also strongly influenced by the nature of the catalyst employed. The development of recyclable, non-toxic, and highly efficient catalytic systems therefore represents a complementary strategy for improving both environmental and economic performance.

²⁴ Wang S.-Y., Zhang Z.-W., Yuan L., Jin Y., Zhang C.-H., Lin J. Efficient Synthesis of Bicyclic 2-Pyridinones and 6-Amino-2-pyridinones by the Regioselective Cycloaddition of Nitro Ketene Aminoal with 3-Hydroxy-2-aryl-acrylate. *European Journal of Organic Chemistry*. 2022. No. 26. DOI: 10.1002/ejoc.202201268.

²⁵ Hooshmand E., Ziyaei A. Nitroalkenes in Diverse Synthesis of Heterocyclic Compounds with Two or Three Heteroatoms: Recent Advances. *Targets in Heterocyclic Systems*. 2019. Vol. 22. DOI: 10.17374/targets.2019.22.119.

²⁶ Shaabani A., Hooshmand S. E.; Tabatabaei A. T. Synthesis of fully substituted naphthyridines: A novel domino four-component reaction in a deep eutectic solvent system based on choline chloride/urea. *Tetrahedron Lett.* 2015, 57, 351–353.

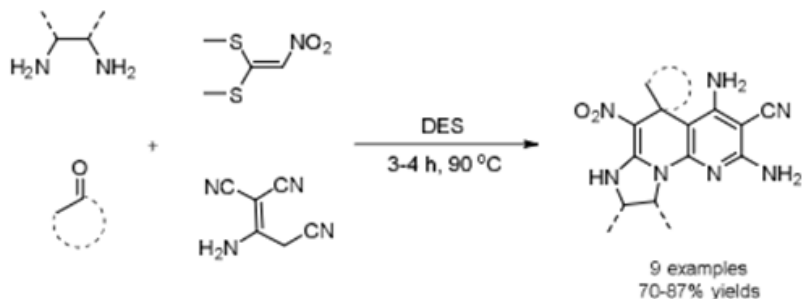


Fig. 8. Using DES in synthesis

1.2. Green Catalytic Strategies

Sustainable catalysis involves the use of recyclable heterogeneous catalysts or small organic molecules that mimic the efficacy of metals without the associated toxicity.

Mohamed et al.²⁷ investigated the catalytic power of a simple ionic liquid in the multicomponent synthesis of imidazole. An environmental aspect is the possibility of multiple use of the catalyst – for at least four cycles and the elimination of chromatographic purification. This approach allows for a reduction in the cost of the final product and the avoidance of the use of aggressive Lewis acids.

The study²⁸ utilizes a biodegradable amino acid as an organocatalyst. The green aspect is the use of a non-toxic, bio-based catalyst in a one-pot assembly. The advantage is the high structural diversity achieved with a simple experimental setup.

In the study by Albalawi et al.²⁹, microwave activation was compared with conventional heating methods for the synthesis of functionalized imidazolium-based ionic liquids. The green aspect is the use of ionic liquids as environmentally friendly solvents and catalysts. The advantage is the increased purity and yield obtained in just minutes.

²⁷ Mohamed S., Simpson J., Marzouk A., Talybov A., Abdelhamid A., Abdullayev Y., Abbasov V. Multicomponent Green Synthesis, Spectroscopic and Structural Investigation of Multi-Substituted Imidazoles. Part 1. *Zeitschrift für Naturforschung B*. 2015. Vol. 70. DOI: 10.1515/znb-2015-0067.

²⁸ Fu L., Lin W., Hu M.-H., Liu X.-C., Huang Z.-B., Shi D.-Q. Efficient Synthesis of Functionalized Benzo[b][1,8]naphthyridine Derivatives via Three-Component Reaction Catalyzed by L-Proline. *ACS Combinatorial Science*. 2014. Vol. 16, No. 5. P. 238–243. DOI: 10.1021/co4001524.

²⁹ Albalawi A., El-Sayed W., Aljuhani A., Almutairi S., Rezki N., Aouad M., Messali M. Microwave-Assisted Synthesis of Some Potential Bioactive Imidazolium-Based Room-Temperature Ionic Liquids. *Molecules*. 2018. Vol. 23. Article 1727. DOI: 10.3390/molecules23071727.

The methodology described by Phadtare et al.³⁰ introduces HBOB as an efficient, low-cost green catalyst. The green aspect is the high catalytic efficiency (70–95% yields) under mild conditions. The advantage is the accessibility of perimidine-based scaffolds which are related to the imidazolidine architecture.

The study by Zendeheel et al.³¹ explores the use of HPA supported on NaY zeolites. The green aspect is the high dispersion and recyclability of the solid acid catalyst. The advantage is the easy separation of the catalyst from the reaction mixture and high acidic strength.

Collectively, the reviewed catalytic methodologies demonstrate that environmentally benign catalysts can successfully replace more hazardous conventional systems without compromising reaction efficiency. The combination of catalyst recyclability, operational simplicity, and high product yields highlights the important role of green catalysis in the sustainable synthesis of imidazolidine-based systems.

1.3. Energy-Efficient Technologies for Green Synthesis

Microwave irradiation, ultrasound-assisted synthesis, and continuous-flow technologies represent some of the most advanced tools of modern green chemistry. These approaches improve energy efficiency, reduce reaction times, and frequently enhance selectivity while minimizing solvent and resource consumption. As a result, they have become increasingly important for the sustainable synthesis and functionalization of imidazolidine-based systems and related heterocycles.

In the study by Albalawi et al.³², a microwave-assisted approach was employed for the synthesis of imidazolidine-derived salts. The results demonstrated that microwave irradiation afforded satisfactory yields while substantially reducing reaction times compared with conventional heating methods.

The work of Sangi et al.³³ details the use of microwave energy to synthesize 2-(nitromethylene)imidazolidine derivatives (Fig. 9). The green aspect lies in the combination of rapid microwave-assisted synthesis with streamlined biological evaluation, reducing overall experimental time and resource consumption.

³⁰ Phadtare S. B., Vijayraghavan R., Shankarling G. S., MacFarlane D. R. Efficient Synthesis of 2,3-Dihydro-1H-Perimidine Derivatives Using HBOB as a Novel Solid Acid Catalyst. *Australian Journal of Chemistry*. 2012. Vol. 65. P. 86–90. DOI: 10.1071/CH11381.

³¹ Zendeheel M., Mobinikhaledi A., Alikhani H., Jafari N. Preparation of Heteropoly Acid/Porous Hybrid Materials and Investigation of Their Catalytic Behavior in the Synthesis of Perimidine. *Journal of the Chinese Chemical Society*. 2010. Vol. 57. P. 683–689. DOI: 10.1002/jccs.201000095.

³² Albalawi A., El-Sayed W., Aljuhani A., Almutairi S., Rezki N., Aouad M., Messali M. Microwave-Assisted Synthesis of Some Potential Bioactive Imidazolium-Based Room-Temperature Ionic Liquids. *Molecules*. 2018. Vol. 23. Article 1727. DOI: 10.3390/molecules23071727.

³³ Sangi D., Monteiro J., Vanzolini K., Cass Q., Paixão M., Correa A. Microwave-Assisted Synthesis of N-Heterocycles and Their Evaluation Using an Acetylcholinesterase Immobilized Capillary Reactor. *Journal of the Brazilian Chemical Society*. 2014. DOI: 10.5935/0103-5053.20140056.

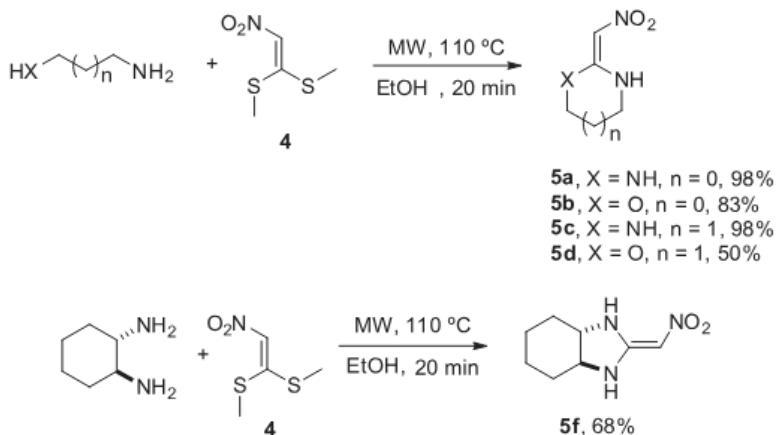


Fig. 9. The synthesis of 2-(nitromethylene)imidazolidine derivatives

A notable example is provided by Savych et al.³⁴, they use alternative energy to drive the condensation and annulation of chromones with HKAs (Fig. 10). The green aspect is the one-pot multicomponent strategy that saves energy and solvent. The advantage is the efficient generation of structurally complex phosphatase inhibitors through a single synthetic operation.

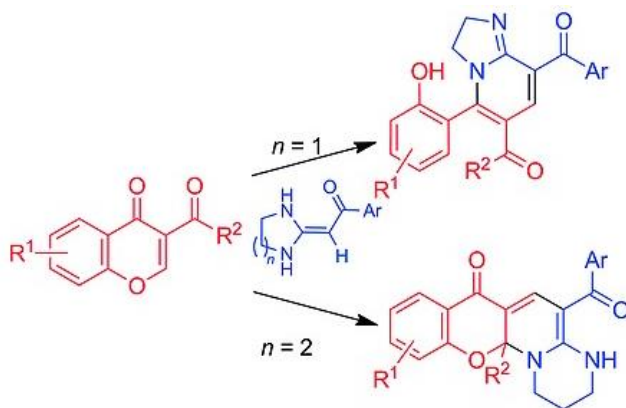


Fig. 10. The condensation and annulation of chromones with HKAs

³⁴ Savych I., Ejaz S. A., Shah S. J. A., Iaroshenko V. O., Villinger A., Sosnovskikh V. Y., Iqbal J., Abbasi A., Langer P. Reactions of 3-Acylchromones with Heterocyclic Ketene Aminals: One-Pot Synthesis and Phosphatase Inhibitory Activity of Fused Pyridine Derivatives. *European Journal of Organic Chemistry*. 2017. P. 186–202. DOI: 10.1002/ejoc.201601138.

Ran et al.³⁵ leverages microwave heating for the rapid synthesis of fluorophores from HKAs. The green aspect is the solvent-free conditions combined with efficient energy transfer. The advantage is the production of highly pure fluorophores suitable for imaging applications with minimal environmental footprint.

While conventional imidazole derivatives synthesis is limited by poor efficiency, ultrasound-assisted protocols offer a robust solution aligned with green chemistry principles. Recent developments^{36, 37} demonstrate that ultrasonic irradiation enhances classical named reactions, delivering superior yields, improved selectivity, and reduced environmental footprints. The beneficial effects of sonochemical activation are generally attributed to acoustic cavitation, which generates localized high-energy microenvironments capable of promoting efficient bond formation under relatively mild bulk conditions. Consequently, ultrasound-assisted synthesis represents a valuable and sustainable strategy for the preparation of heterocyclic compounds.

1.4. Trend Analysis

The shift toward sustainable methodologies is most clearly visible when examining the quantitative metrics of atom economy, E-factor, and reaction efficiency.

The longitudinal analysis of the literature reveals several significant trends. Firstly, there is a clear trajectory from “green-solvent-assisted” methods toward “solvent-free” mechanochemical methods. In the early 2010s, the primary focus was on replacing hazardous chlorinated solvents with water or ethanol. By 2020, increasing attention was directed toward mechanochemical and solvent-free methodologies, which emerged as one of the most promising approaches for reducing solvent consumption and minimizing process waste.

Secondly, the complexity of the “one-pot” reactions has increased. While early methods focused on 3-component reactions, recent protocols often involve 4- or even 5-component cascades, enabling the formation of multiple covalent bonds in a single operation. This reduces the cumulative environmental impact associated with intermediate isolation and purification.

³⁵ Ran X., Zhou Q., Zhang J., Wang S., Wang G., Yang H., Liu X., Wang Z., Yu X. A Solvent-Free and Efficient Synthesis of Bicyclic 2-Pyridone Derivatives for Endoplasmic Reticulum Imaging. *Organic Chemistry Frontiers*. 2021. Vol. 8. DOI: 10.1039/D1QO00350J.

³⁶ Yu X.-L., Fan Y.-H., Zheng X.-N., Gao J.-F., Zhuang L.-G., Yu Y.-L., Xi J.-H., Zhang D.-W. Synthesis of Imidazole-Based Molecules under Ultrasonic Irradiation Approaches. *Molecules*. 2023. Vol. 28, No. 12. Article 4845. DOI: 10.3390/molecules28124845.

³⁷ Messali M., Aouad M. R., El-Sayed W. S., Al-Sheikh Ali A., Ben Hadda T., Hammouti B. New Eco-Friendly 1-Alkyl-3-(4-phenoxybutyl) Imidazolium-Based Ionic Liquids Derivatives: A Green Ultrasound-Assisted Synthesis, Characterization, Antibacterial Activity and POM Analyses. *Molecules*. 2014. Vol. 19, No. 8. P. 11741–11759. DOI: 10.3390/molecules190811741.

Thirdly, there is an increasing emphasis on catalyst life-cycle. The use of heterogeneous, recyclable catalysts and biodegradable organocatalysts like *L*-proline has become an increasingly important consideration in contemporary green chemistry research. Finally, the adoption of alternative energy (microwave and ultrasound) has evolved from a novelty to a practical tool for achieving high purity and speed, particularly in the synthesis of pharmaceuticals and imaging agents.

A significant finding of this review is that “green” claims in many publications lack quantitative support³⁸. While yields are reported with high precision, metrics such as Process Mass Intensity (PMI) or Reaction Mass Efficiency (RME) are rarely calculated. For example, many studies describe their work as “efficient” and “green” while using large excesses of reagents (e.g., 2-5 equivalents) or large volumes of solvent for washing.

Without quantitative data, it is impossible to distinguish between a “green-labeled” process and a truly sustainable one. Sheldon’s E-factor³⁹ remains among the most widely accepted metrics for evaluating waste generation, including solvents and catalysts. The available literature suggests that mechanochemical and multicomponent protocols frequently provide the most favorable balance between atom economy, waste reduction, and operational simplicity. However, meaningful comparison between different methodologies remains difficult because sustainability metrics are reported inconsistently across studies. Broader adoption of standardized parameters such as E-factor, PMI, and RME would greatly improve the objective assessment of green synthetic methodologies.

Although the reviewed methodologies share the common objective of reducing the environmental impact of chemical synthesis, they achieve this goal through different mechanisms, including solvent replacement, waste minimization, catalyst recyclability, and energy-efficient activation. Consequently, each strategy possesses characteristic strengths and limitations that influence its applicability in both laboratory and industrial settings. The main advantages and challenges associated with the principal green approaches employed in the synthesis of imidazolidine-based systems are summarized in Table 2.

Overall, the comparative analysis confirms that sustainable synthesis is best achieved through the integration of multiple green chemistry principles rather than reliance on a single strategy. Future developments are likely to focus on combining resource-efficient reaction design, environmentally benign media, recyclable catalysts, and energy-efficient technologies within unified synthetic platforms.

³⁸ Constable D., Curzons A., Cunningham V. Metrics to “Green” Chemistry – Which Are the Best? *Green Chemistry*. 2002. Vol. 4. P. 521–527. DOI: 10.1039/B206169B.

³⁹ Sheldon R. The E Factor at 30: A Passion for Pollution Prevention. *Green Chemistry*. 2023. Vol. 25. P. 1704–1728. DOI: 10.1039/D2GC04747K.

Table 2

**Comparative Assessment of the Main Green Strategies Employed
in the Synthesis of Imidazolidine-Based Systems**

Green strategy	Main advantages	Main limitations
Water	Non-toxic, inexpensive, readily available	Limited solubility of many substrates
DES	Solvent and catalyst in one medium	High viscosity, difficult product separation
Mechanochemistry	Minimal solvent consumption, low E-factor	Scale-up and reproducibility challenges
Microwave	Rapid heating, short reaction times	Specialized equipment required
Ultrasound	Mild conditions, enhanced mass transfer	Limited scalability for industrial applications

2. Structure–Reactivity Relationships and Green Functionalization

The success of sustainable methodologies in HKA chemistry is fundamentally linked to the distinctive electronic structure of these compounds. Functionalization strategies that utilize the inherent reactivity of the imidazolidine ring allow for the construction of highly complex molecules without unnecessary derivatization steps.

The imidazolidine ring, particularly in its 2-alkylidene form (the HKA), possesses a unique electronic profile that enables its high reactivity in green media. The two nitrogen atoms exert a cooperative electron-donating mesomeric effect, donating electron density to the α -carbon of the exocyclic double bond. This creates a highly nucleophilic center, which is further activated by the presence of electron-withdrawing groups (NO_2 , CN, COR) on the β -carbon.

This “push-pull” system is stabilized by internal hydrogen bonding, typically between the NH group of the imidazolidine ring and the electronegative atoms of the substituent on the exocyclic double bond. This hydrogen bonding plays a critical role in the regioselectivity of multicomponent reactions. In water, these hydrogen-bonding patterns are influenced by the surrounding solvent molecules, which can either stabilize the transition state through the “on-water” effect or provide an acidic/basic environment that catalyzes the ring-closing steps.

The publication⁴⁰ describes a sophisticated cascade where HKAs react with aldehydes and active methylene compounds. The green aspect is the formation

⁴⁰ Li M., Shao P., Wang S.-W., Kong W., Wen L.-R. Four-Component Cascade Heteroannulation of Heterocyclic Ketene Aminals: Synthesis of Functionalized Tetrahydroimidazo[1,2-a]pyridine Derivatives. *The Journal of Organic Chemistry*. 2012. Vol. 77, No. 20. P. 8956–8967. DOI: 10.1021/jo3013836.

of multiple C-C and C-N bonds in a single operation. The advantage is the high atom economy and the elimination of intermediate purification.

Yu et al.⁴¹ focus on the construction of tetracyclic architectures from readily available precursors (Fig. 11). The green aspect is the one-pot multicomponent nature of the reaction. The advantage is the creation of complex biologically active frameworks with high efficiency.

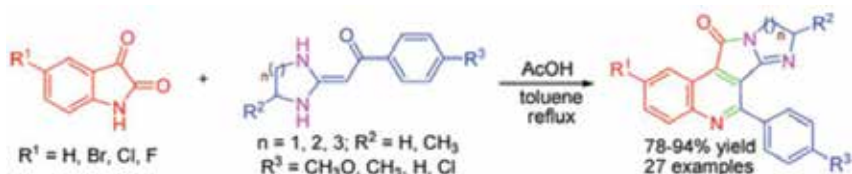


Fig. 11. The synthesis of substituted imidazopyrroloquinoline derivatives

Wen et al.⁴² demonstrate how the electronic properties of the HKA can be tuned for regioselective synthesis (Fig. 12). The green aspect is the high step economy of the MCR. The advantage is the rapid access to naphthyridine frameworks which are rare in traditional synthesis.

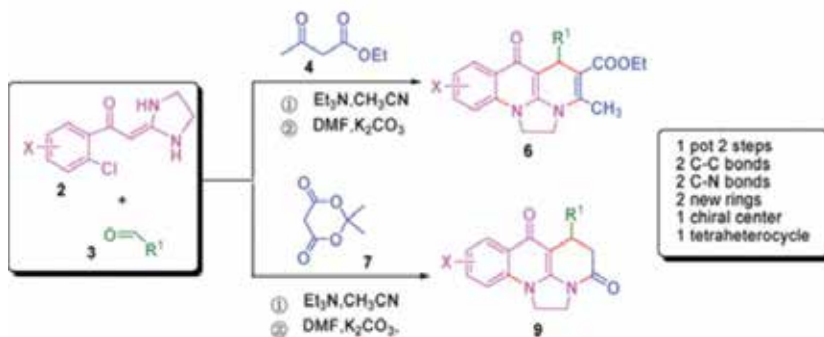


Fig. 12. The synthesis of tetrahydrobenzo[b]imidazo[3,2,1-ij][1,8]naphthyridine derivatives

⁴¹ Yu F., Yan S., Hu L., Wang Y., Lin J. Cascade Reaction of Isatins with Heterocyclic Ketene Aminals: Synthesis of Imidazopyrroloquinoline Derivatives. *Organic Letters*. 2011. Vol. 13, No. 18. P. 4782–4785. DOI: 10.1021/ol201783d.

⁴² Wen L. R., Liu C., Li M., Wang L. J. Modulating the Reactivity of Heterocyclic Ketene Aminals in MCR: Selective Construction of Tetrahydrobenzo[b]imidazo[3,2,1-ij]naphthyridines. *The Journal of Organic Chemistry*. 2010. Vol. 75, No. 22. P. 7605–7614. DOI: 10.1021/jo101454q.

Collectively, these studies demonstrate that the intrinsic nucleophilicity of HKAs enables efficient multicomponent and cascade transformations, allowing the rapid construction of polycyclic frameworks with high atom economy and minimal intermediate handling.

Chen et al.⁴³ utilize ethanol as a green solvent for the assembly of imidazopyridinium salts (Fig. 13). The green aspect is the high atom economy (94%) and the use of sustainable reaction media. The advantage is the direct synthesis of functionalized materials for materials science and medicine.

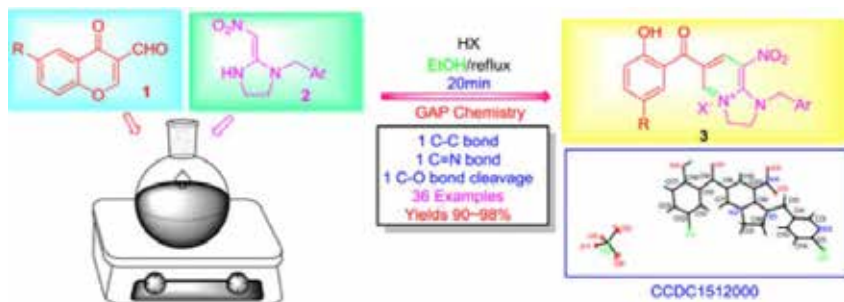


Fig. 13. The synthesis of functionalized bicyclic pyridinium derivatives

The versatility of HKAs is further illustrated by site-selective relay reactions with difluorobenzenes reported by Luo et al.⁴⁴, already discussed above in the context of solvent-free synthesis, can also be read from the perspective of functionalization strategy: it constitutes a relay reaction between HKAs and difluorobenzenes whose green aspect is the base-promoted site-selectivity that avoids transition metals. The advantage is the environmental safety and high yield of the indole products.

Functionalization strategies have shifted toward C-H activation and metal-free relay reactions. The use of CaCl_2 as a promoter in the reaction of HKAs with fluorinated benzaldehydes provides an excellent example of green functionalization principles in practice. By sequestering the byproduct hydrofluoric acid as solid CaF_2 , the protocol mitigates the hazards associated with fluorine chemistry while maintaining high atom economy. This strategy

⁴³ Chen L., Huang R., Du X. X., Yan S. J., Lin J. One-Pot Synthesis of Highly Functionalized Bicyclic Imidazopyridinium Derivatives in Ethanol. *ACS Sustainable Chemistry & Engineering*. 2017. Vol. 5, No. 2. P. 1899–1905. DOI: 10.1021/acssuschemeng.6b02622.

⁴⁴ Luo D. Y., Hu X. M., Huang R., Cui S. S., Yan S. J. Base-Promoted Relay Reaction of Heterocyclic Ketene Aminals with o-Difluorobenzene Derivatives for the Highly Site-Selective Synthesis of Functionalized Indoles. *Tetrahedron*. 2021. DOI: 10.1016/j.tet.2021.132275.

illustrates how reagent design can simultaneously improve reaction selectivity, operational safety, and waste management.

Beyond substrate-controlled reactivity, catalyst selection also plays an important role in sustainable functionalization strategies. Furthermore, the integration of organocatalysis, such as *L*-proline-mediated synthesis, allows for the formation of complex bicyclic systems under mild conditions. These organocatalysts are often biodegradable and non-toxic, addressing the sustainability issues associated with transition metals like Palladium or Rhodium that require expensive ligands and careful removal from final pharmaceutical products.

Overall, the unique electronic structure of HKAs provides an exceptional platform for sustainable functionalization. Their intrinsic nucleophilicity, ability to participate in multicomponent cascades, and compatibility with environmentally benign catalysts and reaction media enable the efficient synthesis of structurally diverse heterocyclic frameworks while minimizing waste generation and process complexity. These features explain why HKAs continue to attract considerable attention as versatile building blocks in green heterocyclic chemistry.

3. Applications and Industrial Feasibility

The practical utility of imidazolidine-based systems is widespread, spanning agriculture, medicine, and materials science.

Agrochemical and Toxicological Context

Imidazolidine is a structural component of neonicotinoids like imidacloprid, which revolutionized pest management but also raised significant environmental concerns regarding their impact on pollinators. Although the environmental concerns associated with certain neonicotinoids arise primarily from their biological activity rather than their synthesis, the development of greener synthetic routes can reduce the overall environmental footprint associated with their production. Beyond agrochemical applications, imidazolidine derivatives have also attracted interest in medicinal chemistry. For example, the discovery of 2-(nitromethylene)imidazolidine as a lead compound for Alzheimer's treatment highlights the versatility of the imidazolidine scaffold and its applicability across distinct areas of bioactive compound development. The development of green methodologies for these compounds contributes to minimizing the environmental footprint of their production.

Materials and Corrosion Inhibition

In materials science, functionalized imidazolium-based ionic liquids are frequently employed as alternative low-volatility reaction media and anti-bacterial agents. Their synthesis via microwave irradiation provides

a high-efficiency route to these materials. Beyond their role as reaction media, imidazole-derived compounds also serve as functional materials. Moreover, the use of amino acid-derived imidazoles as corrosion inhibitors demonstrates how green synthetic metrics (high AE, low E-factor) can lead to environmentally friendly functional materials that protect infrastructure without releasing toxic substances into the marine environment.

Industrial Feasibility and Scalability

The assessment of industrial feasibility suggests that while “on-water” and solvent-free methods are highly attractive, they face challenges in heat dissipation and mass transfer at very large scales. Continuous-flow technologies offer one promising approach to addressing these limitations. Flow systems allow precise control of reaction conditions, heat transfer, and residence time, and can be integrated with microwave or ultrasound activation when appropriate. The fact that many of these green products can be isolated by simple filtration rather than energy-intensive distillation or chromatography is a major economic incentive for industrial adoption.

From an industrial perspective, the attractiveness of green HKA synthesis is closely linked to process simplification. Reduced solvent consumption, elimination of chromatographic purification, shorter reaction times, and the possibility of catalyst recycling contribute directly to lower operating costs and reduced energy demand. These factors may partially offset the costs associated with specialized equipment such as ball mills, microwave reactors, or continuous-flow systems.

Overall, the diverse applications of imidazolidine-based systems in agriculture, medicine, materials science, and corrosion protection demonstrate the broad practical relevance of these compounds. At the same time, the development of sustainable synthetic methodologies enhances their industrial attractiveness by reducing waste generation, energy consumption, and dependence on hazardous reagents. Although challenges related to scale-up and process optimization remain, the combination of green chemistry principles with the intrinsic versatility of HKAs provides a strong foundation for the future development of sustainable industrial processes based on HKA chemistry.

CONCLUSIONS

The synthesis and functionalization of imidazolidine-based systems have undergone substantial development over the past fifteen years, evolving from predominantly conventional synthetic approaches toward methodologies increasingly aligned with the principles of green chemistry. The literature reviewed demonstrates that heterocyclic ketene aminated (HKAs) constitute highly versatile building blocks capable of participating in multicomponent,

cascade, and regioselective transformations that provide rapid access to structurally complex heterocyclic frameworks. The unique push–pull electronic structure of HKAs facilitates efficient functionalization under mild reaction conditions, enabling the development of sustainable synthetic methodologies with high regioselectivity and step economy.

The most significant advances have been associated with the replacement of hazardous solvents by water, ethanol, and deep eutectic solvents, the development of solvent-free and mechanochemical protocols, the implementation of recyclable catalytic systems, and the adoption of energy-efficient activation techniques such as microwave irradiation and ultrasound. These approaches have improved the sustainability of synthetic processes while generally maintaining high levels of reaction efficiency, selectivity, and product yield.

At the same time, the review highlights the importance of evaluating sustainability using comprehensive quantitative metrics rather than relying solely on qualitative “green” claims. Although numerous studies report excellent yields and operational simplicity, parameters such as Process Mass Intensity, Reaction Mass Efficiency, life-cycle assessment, and solvent-adjusted E-factors remain insufficiently reported. Consequently, objective comparison of alternative methodologies is often difficult.

The analysis of the reviewed literature leads to several general conclusions.

Green chemistry strategies applied to HKA synthesis demonstrably improve environmental profiles without systematic sacrifice of yield or selectivity.

Water emerges as the most versatile and broadly applicable solvent substitute across the reaction types surveyed, offering kinetic benefits, simplified workup, and elimination of occupational hazards.

Solvent elimination (solvent-free and mechanochemical approaches) is most effective when coupled with careful optimization of reagent purity and product isolation protocols.

Multicomponent reactions in green media represent the highest-efficiency strategy, combining atom economy, step economy, and reduced waste generation in a single operation.

Despite the substantial progress achieved over the past decade, several scientific and technological challenges remain unresolved. Analysis of the current literature reveals a number of research directions that could further enhance the sustainability, efficiency, and industrial applicability of HKA-based synthetic methodologies.

Based on the gaps and limitations identified in the reviewed literature, the following directions appear most promising for future research:

- Systematic optimization of solvent-free routes to HKA precursors, with attention to reagent purity, mixing efficiency, and scalable isolation procedures.

- Development of integrated off-gas and byproduct capture systems for reactions generating volatile or malodorous side-products such as thiols, enabling greener process profiles at preparative scale.
- Broader reporting of full mass balances, solvent-adjusted E-factors, and life-cycle assessments for HKA syntheses, to allow meaningful cross-study comparison of green metrics.
- Exploration of catalytic activation in aqueous systems – including organocatalysis, photocatalysis, and biocatalysis – as routes to enantioselective HKA functionalization under physiological or near-physiological conditions.
- Application of machine learning and AI-assisted optimization to predict the reaction conditions that simultaneously minimize waste and maximize atom economy for complex multicomponent assemblies involving imidazolidine scaffolds.

SUMMARY

This review examines recent advances in the sustainable synthesis and functionalization of imidazolidine-based systems, with particular emphasis on heterocyclic ketene aminals (HKAs) as versatile building blocks for heterocyclic chemistry. The analysis covers literature published between 2010 and 2025 and focuses on the application of green chemistry principles to the construction of structurally complex imidazolidine derivatives. Special attention is given to solvent-free and mechanochemical methodologies, the use of environmentally benign reaction media such as water, ethanol, and deep eutectic solvents, as well as recyclable catalytic systems and energy-efficient activation techniques. The role of the unique electronic structure of HKAs in promoting regioselective and multicomponent transformations under mild conditions is discussed. Comparative evaluation of sustainable synthetic strategies demonstrates the advantages of multicomponent and cascade reactions in terms of atom economy, step economy, and waste minimization. Current trends in green HKA chemistry reveal a shift from simple solvent substitution toward integrated approaches combining resource efficiency, catalyst recyclability, and alternative energy inputs. The review also considers the practical applications of imidazolidine-based compounds in agriculture, medicinal chemistry, materials science, and corrosion protection, together with aspects of industrial feasibility and scalability. Particular attention is devoted to the critical assessment of sustainability metrics and the limitations of qualitative “green” claims in the absence of comprehensive quantitative evaluation. The findings highlight the considerable potential of HKA-based methodologies for the development of more sustainable synthetic processes and identify key directions for future research in green heterocyclic chemistry.

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