Proceedings of the 17th International Scientific and Practical Conference «International Forum: Problems and Scientific Solutions»

(September 26-28, 2026). Melbourne, Australia

No 311

CHEMISTRY AND MATERIALS SCIENCE

Green Synthesis of Benzimidazole Derivatives Using Natural Deep Eutectic Solvents

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Abstract. This article develops an evidence-based strategy for preparing benzimidazole derivatives in natural deep eutectic solvents (NADES). Recent peer-reviewed studies from 2023-2026 were critically combined with an author-designed protocol for the condensation of o-phenylenediamine and aromatic aldehydes. The proposed media are not treated as passive solvent substitutes: their hydrogen-bond networks may activate the aldehyde, support proton transfer, promote ring closure, and influence aerobic aromatization. Betaine- and choline-based mixtures with lactic or malic acid are prioritized, while glycerol-based media serve as lower-acidity controls. The workflow integrates solvent characterization, water-content control, temperature screening, precipitation-based isolation, analytical confirmation, and solvent reuse. Performance is assessed through yield, selectivity, reaction mass efficiency, process mass intensity, E-factor, energy demand, and recovery. No unperformed experiment is presented as measured data; the result is a testable methodological framework for sustainable heterocyclic synthesis.

Keywords: *benzimidazole; NADES; green synthesis; deep eutectic solvent; heterocyclic chemistry; green metrics.*

1. Introduction

Benzimidazole is a fused nitrogen heterocycle used in medicinal chemistry, catalysis, coordination compounds, functional materials, and agrochemicals. The common condensation of o-phenylenediamine with an aldehyde is synthetically attractive, yet conventional procedures may require volatile solvents, strong acids, stoichiometric oxidants, extraction, or chromatography. Recent reviews identify N-heterocycle construction as an important application of deep eutectic media [1]. More directly, a telescopic benzimidazole synthesis in choline chloride/glycerol/water demonstrates that DES-based

processing is relevant to this scaffold [2].

NADES are formed from naturally occurring or bio-derived hydrogen-bond acceptors and donors, including choline derivatives, betaine, organic acids, sugars, and polyols. Their low volatility and adjustable polarity are useful, but natural origin does not automatically prove low toxicity or low life-cycle impact. Contemporary studies therefore recommend precise composition, phase characterization, water measurement, and application-specific safety assessment [3,4]. This article proposes a scientifically transparent route in which literature-supported observations are separated from experimental predictions.

2. Scientific basis

2.1. NADES structure and properties

A homogeneous low-melting mixture should be called a NADES only when eutectic behavior is established or reliably documented. Composition, molar ratio, thermal history, water activity, and purity determine phase stability, acidity, polarity, and viscosity. The dynamic network of hydrogen bonds and ionic interactions can solvate reactants and alter transition-state energies. Small, measured additions of water may reduce viscosity; excess water can disrupt the network and convert the medium into an ordinary aqueous solution [4,5].

2.2. Proposed reaction mechanism

The net aerobic reaction is o-phenylenediamine + Ar-CHO + 1/2 O2 -> 2-aryl-1H-benzimidazole + 2 H2O. An acidic HBD can hydrogen-bond to the aldehyde oxygen and increase carbonyl polarization. Nucleophilic addition, proton transfer, and dehydration form an imine-like intermediate. Intramolecular attack by the second amino group closes the five-membered ring, followed by oxidative aromatization. Reviews of DES catalysis support combined roles for solvation, acid-base activation, and intermediate stabilization [6,7].

The optimum medium should provide balanced activation. Excess acidity can protonate the diamine and suppress nucleophilicity, while a nearly neutral medium may not accelerate condensation. Viscosity can restrict mixing and oxygen transfer. Therefore, solvent composition, temperature, water content, agitation, and exposure to air must be treated as coupled experimental variables rather than optimized independently.

3. Materials and methodology

3.1. Research design and candidate media

Twelve verified sources published from 2023 to 2026 were

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selected across five evidence domains: benzimidazole synthesis in DES, wider heterocycle formation, NADES definition, catalytic behavior, and solvent recovery. Direct benzimidazole evidence [2] was given greater weight than transferable evidence from related imidazoles [11]. Four chemically interpretable candidate media are proposed in Table 1. Homogeneity is a preliminary criterion; DSC or phase-equilibrium evidence is required for a rigorous NADES designation.

Table 1

Author-proposed screening matrix for NADES-assisted benzimidazole synthesis

Candidate medium	Ratio	Expected function	Validation need
Betaine:lactic acid	1:2	Acidic carbonyl activation	DSC, water, pH, viscosity
Choline chloride:lactic acid	1:2	Solvation and proton transfer	DSC, FT-IR, water, viscosity
Choline chloride:malic acid	1:1	Stronger acidic network	DSC/TGA and thermal stability
Betaine:glycerol	1:2	Lower-acidity control	Phase stability and control conversion

3.2. Author-designed experimental workflow

The HBA and HBD are weighed at the selected ratio and mixed at the lowest temperature that gives a stable liquid. Preparation time, mass change, appearance, water content, FT-IR spectrum, viscosity, and, where possible, DSC are recorded. The model reaction contains o-phenylenediamine (1.00 mmol), benzaldehyde (1.00 mmol), and a documented mass of NADES. It is stirred at 60, 80, or 100 degrees C under air and monitored by TLC. Conventional-solvent, HBA-only, HBD-only, and oxygen-limited controls are run under matched conditions.

After maximum conversion, water is added gradually to precipitate the benzimidazole while retaining the hydrophilic NADES components in solution. The solid is filtered, washed, dried, and characterized. Water is removed from the filtrate under reduced pressure; the recovered medium is weighed, re-characterized, and reused. Recovery is accepted only when both solvent mass and catalytic performance remain stable. Figure 1 summarizes the closed-loop design.

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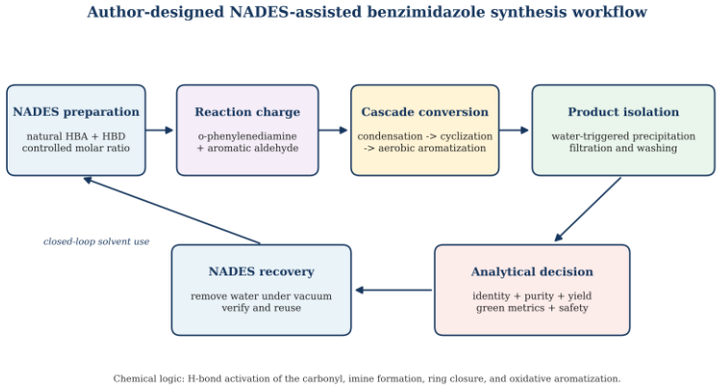

Figure 1

Author-designed NADES-assisted benzimidazole synthesis and solvent-reuse workflow

Source: developed by the authors for the present methodological study.

3.3. Identification and green metrics

Identity is verified by melting point, FT-IR, 1H NMR, and 13C NMR; mass spectrometry and chromatographic purity are added where available. Conversion and isolated yield are reported separately because product solubility can distort recovery. The assessment includes reaction mass efficiency, process mass intensity, E-factor, temperature-time energy demand, solvent recovery, and retained activity over reuse cycles. Water, extraction solvent, washing liquid, drying agents, and regeneration energy are included in the mass balance [8].

4. Results of the critical evidence synthesis and discussion

4.1. Feasibility and expected substrate effects

Recent evidence supports the feasibility of DES-enabled heterocycle construction but does not justify assuming uniformly high yield. The direct telescopic benzimidazole study [2] and broader heterocycle review [1] show that eutectic media can support sequential bond formation. A 2025 imidazole study further demonstrates dual solvent-catalyst behavior, water-triggered isolation, and reuse [11]. These results justify laboratory screening of natural acidic media, while the 2025 NADES review clarifies that mixture-specific characterization remains essential [9].

The substrate panel should include benzaldehyde, electron-poor and electron-rich para-substituted aldehydes, an ortho-substituted aldehyde, and a heteroaromatic aldehyde.

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Electron-withdrawing groups may accelerate nucleophilic addition, whereas steric congestion may slow condensation or cyclization. Conversion must be measured independently of isolated yield because a product that remains soluble in the NADES-water phase can appear unreactive despite substantial chemical conversion.

4.2. Water, viscosity, and selectivity

Water has two opposing effects. A controlled amount can lower viscosity, improve mixing, and increase oxygen transfer; excessive water can weaken the organized hydrogen-bond network and change substrate partitioning. The experimental record should therefore state water as a measured mass fraction. Temperature must be evaluated together with water content because heating also reduces viscosity and may remove water. Chemoselectivity should be followed for both dihydrobenzimidazole intermediates and 1,2-disubstituted products, since reaction rate alone does not establish a clean green route.

4.3. Recovery, safety, and the green claim

The main process advantage is possible elimination of chromatography: water addition may precipitate the product and permit filtration. Recovered NADES should be compared with fresh material by mass, FT-IR, water content, and viscosity over at least five cycles. Regeneration and disposal are part of the environmental assessment, since downstream operations may dominate the burden of a low-volatility medium [8].

Low vapor pressure reduces inhalation and VOC emissions but does not eliminate toxicity. Acidity, osmotic effects, impurities, and interactions between components can change biological behavior. A metal-containing or strongly synthetic DES should not be relabeled as natural. Recent perspectives in pharmaceutical and asymmetric catalysis accordingly present NADES as multifunctional media while emphasizing industrial relevance, safety, and compositional limitations [9,10,12].

5. Optimization and validation

Optimization proceeds sequentially: feasibility screening, temperature-water-loading optimization, substrate scope, work-up comparison, reuse, and gram-scale confirmation. Each optimized condition is repeated independently at least three times and reported as mean plus standard deviation. A condition advances only when it combines reproducible conversion, clean selectivity, simple isolation,

and favorable mass metrics. Mechanistic controls compare the complete NADES with its separate HBA and HBD, vary oxygen exposure, and test defined water levels.

Mechanistic interpretation should rely on converging evidence. Carbonyl-band shifts in FT-IR may support hydrogen bonding but do not alone prove catalytic activation. Initial-rate comparisons between the complete NADES, its separate components, and an acidity-matched control can distinguish network effects from ordinary acid catalysis. Independent synthetic replicates must not be replaced by repeated instrumental measurements of one batch. Reporting individual results, confidence intervals, spectra, and complete mass calculations makes the optimization auditable and prevents a favorable isolated yield from concealing poor conversion or solvent-intensive recovery.

6. Limitations

This article proposes a research design and does not report new experimental yields, spectra, toxicity values, or recycling percentages. Laboratory validation is therefore required before superiority over a conventional route can be claimed. Other limitations are inconsistent DES terminology and limited mixture-specific safety data. Future work should combine phase analysis, kinetics, spectroscopy, broader substrate scope, and life-cycle assessment using fully disclosed solvent composition and recovery procedures.

7. Conclusion

NADES can potentially combine solvation, carbonyl activation, proton transfer, low volatility, and recoverability in benzimidazole synthesis. The proposed method prioritizes choline- and betaine-based acidic media, compares them with a lower-acidity control, and evaluates the entire reaction-isolation-reuse cycle. Its central requirement is verification: eutectic behavior, product identity, purity, solvent stability, safety, and complete green metrics must all support the final claim.

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