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# GREEN SYNTHESIS OF BENZIMIDAZOLES USING A RECYCLABLE DEEP EUTECTIC SOLVENT

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**Abstract**

Benzimidazoles sit at the core of several marketed anthelmintic, antiulcer and antihypertensive drugs, yet their classical synthesis relies on strong acids, high temperatures and volatile organic solvents. This review summarises what has been published on the use of deep eutectic solvents, particularly choline chloride mixtures, as recyclable media for forming the benzimidazole ring. It covers the classical condensation routes, the physical chemistry of eutectic mixtures, reported recycling behaviour, green metrics and toxicity questions. The literature suggests that these solvents can act as medium and mild catalyst together, but recycling data are often limited to a few cycles. No new experimental data are reported here. Standardised metrics and residual-solvent studies are still missing.

## 1. INTRODUCTION

The benzimidazole nucleus, a benzene ring fused to an imidazole, is one of the most frequently met heterocycles in medicinal chemistry. It appears in the proton pump inhibitor omeprazole, in the anthelmintics albendazole and mebendazole, and in the angiotensin receptor blocker telmisartan [1, 2, 3]. The scaffold resembles the purine bases closely enough to interact with many biological targets, which partly explains its reputation as a privileged structure. Demand for the building block is therefore steady, and so is the pressure on the way it is made. Process chemists are asked not only for yield and purity but also for a lower solvent burden and less hazardous waste [4].

Biological behaviour explains some of that persistence. The anthelmintic benzimidazoles bind to parasite β-tubulin and block microtubule assembly, a selective action that has kept the class in veterinary and human use

for decades [3]. Proton pump inhibitors, by contrast, depend on the benzimidazole as part of a prodrug that converts to a reactive sulfenamide in acid surroundings [1]. Antiviral, anticancer and antihistamine candidates have broadened the picture further [2]. Because so many different programmes start from the same bicyclic core, an improvement to the way the ring is built can in principle benefit many projects at once, which is the practical argument for studying solvent choice in this one reaction.

Most of the classical routes to 2-substituted benzimidazoles start from o-phenylenediamine. Condensation with a carboxylic acid under strongly acidic, high-temperature conditions, first described by Phillips in the 1920s, is still the textbook method [5]. Condensation with an aldehyde followed by oxidative cyclisation is the other common option [6]. Both routes tend to use dimethylformamide, toluene or chlorinated solvents, and both generate aqueous waste once the mixture is neutralised. These practical details matter because solvents typically make up most of the mass used in a pharmaceutical synthesis, a point that the E factor literature has made repeatedly [4, 7].

Interest in alternative media has grown in step with the principles of green chemistry reviewed by Anastas and Kirchhoff [8]. Water, supercritical carbon dioxide, ionic liquids and bio-derived solvents have all been tried [9, 10]. Deep eutectic solvents (DES) joined that list in 2003, when a mixture of choline chloride and urea was reported to stay liquid at room temperature even though each component melts well above 100 °C [11]. This review draws on the published literature to describe how such solvents have been applied to benzimidazole formation, what is known about recycling them, and where the evidence is thin. It reports no new experimental data.

## 2. CLASSICAL ROUTES TO THE BENZIMIDAZOLE RING

The Phillips condensation heats o-phenylenediamine with a carboxylic acid in dilute mineral acid, typically hydrochloric acid, and produces the 2-substituted benzimidazole by loss of two molecules of water [5]. It works well for aliphatic acids and less well for aromatic ones, which often need polyphosphoric acid or sealed-tube temperatures. Work-up involves neutralisation with a base, which generates salt-laden waste. For a medicinal chemist making a small library this is acceptable. For a manufacturing plant it is a recurring cost, and the corrosive reagents add equipment demands that rarely appear in the original papers.

The aldehyde route avoids the harshest acid conditions. The diamine and aldehyde first give a Schiff base, which cyclises to a benzimidazoline and is then oxidised to the aromatic ring [6]. Oxidants reported in the older literature include sodium metabisulfite, copper salts, hydrogen peroxide with acid, and simply air. The reaction is attractive because aldehydes are cheap and varied, but selectivity can be a problem. Mixtures of 2-substituted and 1,2-disubstituted products arise when two aldehyde molecules react, and the balance depends on the solvent, stoichiometry and catalyst [2, 6]. Which of these routes is chosen in practice often depends more on the availability of the aldehyde than on any deep mechanistic preference.

Catalysis has been the main strategy for softening these conditions. Lewis acids, supported acids, nanoparticles and organocatalysts have all been described, and many of them improve yield or reduce time [2, 6]. The weakness is that the catalyst frequently has to be separated and either discarded or regenerated, and the reaction is still run in an organic solvent. Microwave heating, reviewed by Loupy and colleagues, shortens reaction times from hours to minutes and was widely adopted for benzimidazole libraries [12]. Faster heating does not, however, change the solvent problem, which is what motivated the search for media that could do more than dissolve the reagents.

Solvent-free and aqueous variants have also been tried, usually by grinding the diamine with an aldehyde and a solid acid, or by heating in water with a surfactant. These approaches deserve credit for removing organic solvent altogether, though they bring their own difficulties. Solid-state reactions are

hard to stir and to scale, and the heat release cannot be controlled as easily as in solution. Water as a medium often needs a catalyst or high temperature because the organic substrates dissolve poorly [2, 10]. The practical gap that remains is a liquid medium that dissolves both reagents, tolerates moderate heating and can be recovered, which is the niche that eutectic mixtures are intended to fill.

Alongside the synthetic literature, solvent selection guides have given chemists a common vocabulary for judging a medium. The CHEM21 guide ranks common solvents as recommended, problematic or hazardous, and places dimethylformamide among those to be replaced [13]. Jessop argued that a solvent has to be judged on safety, health, environmental and energy grounds together, including the energy needed for recovery [14]. Any replacement for the traditional solvents in benzimidazole chemistry therefore has to be judged against these frameworks, not simply against the claim that it is non-volatile. The same frameworks are used in the sections below to judge claims made for eutectic media.

## 3. DEEP EUTECTIC SOLVENTS AS REACTION MEDIA

A deep eutectic solvent is a mixture of a hydrogen-bond acceptor and a hydrogen-bond donor whose melting point is far lower than that of either component. The classic example combines choline chloride with urea in a 1:2 molar ratio, giving a liquid below 15 °C [11]. Hydrogen bonding between the chloride ion and the donor disrupts the crystal lattice of the salt, and that is the usual explanation for the depression of the freezing point [15, 16]. Other donors include glycerol, ethylene glycol, carboxylic acids and sugars. Changing the donor changes viscosity, polarity and acidity, which is why the mixtures are often called designer solvents [16, 17, 18].

The attraction for synthesis is a combination of properties. Vapour pressures are very low, many components are cheap and commercially available, and several mixtures are made simply by warming and stirring the two solids, with no solvent and no by-product [15, 19]. Some mixtures derive entirely from primary metabolites such as choline, sugars and organic acids, and these have been called natural deep eutectic solvents [20, 21]. The idea that such a mixture could serve both as solvent and as catalyst is one of the main reasons organic chemists took an interest, and the review by Alonso and colleagues documents the wide range of reactions in which this has been tried [19].

Preparation is straightforward, and that simplicity is part of the appeal. The two components are weighed in the stated molar ratio, heated gently to roughly 60 to 80 °C, and stirred until a clear liquid forms, which typically takes under an hour [15, 22]. No purification is needed because the process is a simple mixing step with complete atom economy [23]. Reviews also stress that composition governs behaviour. Moving the molar ratio of choline chloride to donor, or adding a few per cent of water, shifts viscosity and conductivity noticeably, and so a reaction developed in one batch of mixture may not transfer directly to another prepared with a different water content [16, 18].

There are also real drawbacks. Viscosity is the most obvious, since choline chloride and glycerol or urea mixtures can be hundreds of times more viscous than water at room temperature, and mass transfer suffers unless the mixture is heated [15, 18]. Water uptake from the air changes the composition and can alter reactivity, so published procedures that do not report water content are hard to reproduce. Florindo and colleagues showed how strongly the carboxylic acid partner changes the physical properties of cholinium chloride mixtures, underlining that no single DES behaves like another [24]. Describing them as a single solvent class is convenient but misleading.

## 4. DES-MEDIATED BENZIMIDAZOLE FORMATION

Several groups have reported that condensation of o-phenylenediamine with aromatic aldehydes proceeds in choline chloride-based mixtures without any added acid or metal, at moderate temperatures and often within an hour or two. The proposed explanation is that the hydrogen-bond donor activates the carbonyl group while the

chloride stabilises the intermediate, an argument that echoes the general mechanistic discussion in the reviews [15, 17, 19]. Where the aldehyde carries electron-withdrawing groups, reactions are generally reported to be faster, which is consistent with a rate-limiting nucleophilic attack on the carbonyl. The overall picture across these papers is of a medium that behaves as a mild Brønsted acid.

Work-up is often simple. After the reaction, water is added and the product, which is usually poorly water-soluble, precipitates and is collected by filtration. The aqueous phase, which now contains the eutectic mixture, can be evaporated to remove the added water and reused [15, 19]. This is the feature that makes the approach attractive for green chemistry, because it replaces extraction with organic solvent by filtration and water removal. It is worth remembering that evaporating water from a viscous mixture consumes energy, a cost that some reports leave out when they describe the procedure as solvent-free or low-energy [14].

Reported recycling is the weakest part of the evidence. Papers commonly show that the DES can be reused for three to five cycles with a modest drop in yield, and some state that the recovered mixture shows unchanged spectroscopic features [17, 19]. Few go further. Accumulating water, small amounts of unreacted diamine and oligomeric by-products can all build up in the recovered phase, and a mixture that looks fine by infrared spectroscopy may still differ in composition. Characterisation of the recovered solvent by nuclear magnetic resonance and Karl Fischer titration would answer the question properly, but it is the exception in the published procedures.

Monitoring of these reactions has mostly relied on simple tools. Thin-layer chromatography follows consumption of the diamine, and product identity is confirmed by melting point, infrared and NMR spectroscopy [6, 19]. In viscous media, sampling and dilution for chromatography are less convenient than in a volatile solvent, and signals from the eutectic components can overlap with those of the product if the sample is not carefully worked up. High-performance liquid chromatography would give a more quantitative view of by-product formation, particularly the 1,2-disubstituted impurity, but few of the published studies report impurity profiles at the level a pharmaceutical analyst would expect [2, 25].

A second point concerns the nature of the cyclisation step. In an aldehyde route, an oxidant is still needed to aromatise the benzimidazoline. Many DES papers rely on air, and in some the eutectic medium itself is suggested to facilitate the oxidation, though direct mechanistic proof is limited [6, 19]. Where a mild oxidant is added, the question becomes whether it persists in the recycled solvent. Variation in this single step helps explain why yields for apparently similar substrates differ between laboratories, and why careful side-by-side comparison with a conventional solvent under the same conditions is more informative than a bare yield figure.

Carboxylic acid routes have been explored less often in DES, probably because the high temperatures required to drive dehydration sit uncomfortably with viscous mixtures that absorb water. Where an acidic donor such as a carboxylic acid or a sugar acid forms part of the mixture, the medium may supply both the acid catalyst and the polar environment, and this has been proposed as a way to bring the Phillips reaction closer to mild conditions [15, 24]. Evidence remains sparse, and the more reliable conclusion from the literature is that aldehyde condensation is where the current benefits of deep eutectic media are best documented.

Substrate scope reported across the aldehyde papers covers electron-rich and electron-poor aromatic aldehydes, heteroaromatic aldehydes and, less convincingly, aliphatic aldehydes. Sterically hindered ortho-substituted aldehydes tend to give lower yields, while substituted diamines give a regiochemistry question when the two nitrogens are no longer equivalent [2, 6]. Papers rarely test substrates with acid-sensitive protecting groups, which is a pity, because that is exactly where a mildly acidic medium might cause trouble in drug-like molecules. Readers wanting to apply the method to a late-stage intermediate should treat the typical substrate table as a

guide to simple building blocks only.

## 5. GREEN METRICS AND SAFETY

Metrics give a more honest picture than adjectives. The E factor, defined by Sheldon as the mass of waste per mass of product, counts everything that is not the product, including solvents and aqueous work-up [7]. Atom economy, introduced by Trost, looks at the stoichiometry of the reaction alone [23]. Constable and colleagues compared several mass-based metrics and concluded that no single measure is enough on its own [26]. For a DES process, the E factor is heavily influenced by how many times the solvent is reused, which is why a claim of recyclability needs numbers behind it. A medium recovered once is not very different from one used once.

The representative findings gathered in table 1 span solvent properties, synthetic routes, green metrics and toxicity for benzimidazole synthesis in eutectic media. They show that the better-documented entries concern the properties of the mixtures themselves and the behaviour of the aldehyde route, while entries on long-term recycling and on toxicity are fewer. The grouping of entries by theme (fig. 1) reflects this unevenness. Evidence on how the solvent behaves in the reaction is considerably more abundant than evidence on what happens to it afterwards, and the second kind is exactly what a process chemist would need.

Toxicity is the issue that most often gets overlooked. Early enthusiasm treated DES as inherently benign because the components are cheap and often natural, but Hayyan and colleagues reported that some mixtures showed measurable toxicity towards bacteria and brine shrimp, and that the mixture can be more toxic than its components [27]. Later studies of choline chloride mixtures found that biodegradability and toxicity depend on the hydrogen-bond donor [28, 29]. Wen and colleagues observed that toxicity rose with the nature of the donor and with concentration [30]. The sensible position is that each mixture needs its own assessment, not a blanket assumption.

Energy is the metric that deserves more attention. Heating a viscous mixture to 80 or 100 °C for a couple of hours is not obviously cheaper than refluxing a low-boiling solvent for the same time, and the removal of water during recovery adds a further load [14, 31]. The comparison also depends on scale. At laboratory scale, heating blocks and rotary evaporators hide the real energy costs, whereas at plant scale heat integration and solvent recovery by distillation are well-established for conventional solvents [4, 32]. A fair assessment would put both options through the same calculation, and the few papers that have attempted this report a mixed picture.

For pharmaceutical use there is a further layer of regulation. The ICH guideline on residual solvents classifies solvents by toxicity and sets permitted daily exposures, but it was written for volatile organic solvents and does not directly cover non-volatile media such as DES [25]. Choline chloride, urea and glycerol are not among the listed solvents, so in practice a manufacturer would have to show that the medium is removed from the active ingredient by crystallisation and washing, and demonstrate control through validated analytical methods. Metal residues are a separate question, addressed by the European guideline on residues of metal catalysts and reagents, and are relevant if any metal catalyst is used [33].

**Table 1: Representative published findings on benzimidazole synthesis in deep eutectic and related media**

| Topic | Reported finding | Ref. |
|---|---|---|
| Choline chloride:urea 1:2 molar ratio | Liquid at room temperature although both components melt above 100 °C; the first widely cited DES | [11, 15] |
| Hydrogen-bond donor choice | Donor alters viscosity, polarity and acidity, so each mixture behaves differently | [16, 24] |
| Natural DES sugars, organic acids | Prepared from primary metabolites; proposed as media for green technology | [20, 21] |
| Phillips condensation diamine plus acid | Requires strong acid and heat; neutralisation produces salt waste | [5, 6] |
| Aldehyde cyclisation oxidative | Milder conditions but mixtures of 2-substituted and 1,2-disubstituted products may form | [2, 6] |

| Topic | Reported finding | Ref. |
|---|---|---|
| Aldehyde route in choline chloride DES | Mild Brønsted acid behaviour reported; product isolated by water precipitation | [15, 19] |
| Microwave heating | Shortens reaction times but leaves the solvent issue unchanged | [12] |
| E factor | Waste mass per product mass; strongly dependent on the number of solvent reuse cycles | [4, 7] |
| Solvent selection guides | Rank dimethylformamide as hazardous and favour recovery-aware assessment | [13, 14] |
| Toxicity of DES | Some mixtures more toxic than their components; donor-dependent biodegradability | [27, 28, 29] |
| Residual solvent control | ICH limits written for volatile solvents; non-volatile media need case-by-case justification | [25, 33] |

## 6. LIMITATIONS AND FUTURE DIRECTIONS

Several limitations of the literature need to be stated plainly. Most reports are from academic laboratories working at the gram scale or less, with substrates chosen to show the method at its best. Comparisons with conventional solvents under identical conditions are the exception. Water content and viscosity are rarely reported, and recycling is usually demonstrated over a handful of cycles. For a pharmaceutical process, where batch-to-batch consistency is the first requirement, these gaps are not trivial, and they make it difficult to say whether a given DES method is genuinely greener than a well-optimised conventional one [4, 14].

Reproducibility deserves its own mention. Many procedures give the DES composition as a molar ratio but say nothing about the grade of choline chloride, which is hygroscopic and may contain water from the start. Reaction temperatures are sometimes quoted as bath temperatures and not internal ones, which in a viscous medium can differ by several degrees. Yields of isolated product are generally given, but purity data are less consistent [6, 19]. A discipline of reporting that mirrors what is expected for conventional methods would help readers judge whether differences between papers reflect chemistry or merely handling [22, 26].

Another gap is the link between laboratory chemistry and quality systems. Pharmaceutical manufacturers work under validated processes in which every solvent, reagent and recovery step is justified in the regulatory file. Reusing a recovered eutectic phase in a later batch raises questions of cross-contamination and of carry-over that regulators would expect to see addressed with data [25, 33]. Such studies have rarely been published, which is understandable for academic work, but their absence means that industrial uptake is hard to judge from the open literature alone. Such gaps are understandable but they limit what can be concluded.

Life-cycle thinking would close some of the gaps. The energy required to remove water from the recovered mixture, the production footprint of the components, and the fate of the spent solvent all enter the calculation, and Clarke and colleagues have argued that green solvent claims should be tested against all three [31]. Sheldon has similarly noted that solvent-related waste dominates the mass of most fine chemical processes, so the choice of medium has a large effect on the metrics [32]. A DES process that needs repeated evaporation of large volumes of water may not look so favourable when judged in this way.

Future work could usefully focus on a small number of well-characterised mixtures instead of an ever-growing list of new ones. Reporting water content, viscosity and recovered-solvent composition as routine data would allow results from different laboratories to be compared. Continuous-flow operation with heated, low-viscosity mixtures is an obvious engineering direction. Toxicity and biodegradability screening should be built into method development, and regulatory dialogue about how non-volatile media fit into residual-solvent control would help translation to manufacturing [25, 33]. Until then, deep eutectic solvents remain a promising but incompletely validated option.

## 7. CONCLUSION

Deep eutectic solvents, especially choline chloride mixtures, have been presented in the published literature as plausible replacements for volatile organic solvents in the formation of the benzimidazole ring. Their strongest case rests on the aldehyde condensation route, where the hydrogen-bond-donating medium appears to behave as a mild acid and where isolation by precipitation with water is straightforward [15, 19]. Low cost and ready availability of the components add to the appeal, and the physical chemistry of the mixtures is now reasonably well understood [11, 16, 17].

The weaknesses are equally clear. Recycling data seldom extend beyond a few cycles, recovered solvents are rarely characterised, toxicity varies between mixtures, and regulatory frameworks for residual solvents were not written with these media in mind [25, 27]. A fair reading is that the approach is promising for laboratory-scale synthesis and worthy of further development, but claims of sustainability should be supported by metrics, life-cycle data and analytical evidence before the method is carried into pharmaceutical manufacturing [7, 14, 31].

## 8. ABBREVIATIONS

DES-Deep eutectic solvent, ICH-International Council for Harmonisation, CHEM21-Chemical manufacturing methods for the 21st century pharmaceutical industry, E factor-Environmental factor (mass of waste per mass of product), NMR-Nuclear magnetic resonance

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All the authors have contributed equally.

## 11. CONFLICT OF INTERESTS

Declared none

## 12. REFERENCES

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