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Copper-catalysed synthesis of 2-substituted benzimidazoles under microwave conditions

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Abstract

Benzimidazole is a privileged scaffold in medicinal chemistry, present in several marketed drugs including omeprazole, astemizole, bendazol, and mebendazole, as well as in numerous compounds with reported antifungal, antiprotzoal, antimicrobial, and anticancer activities. Cu-catalysed condensation of o-phenylenediamine with aldehyde derivatives provides a direct, atom-economical route to 2-substituted benzimidazoles that avoids the stoichiometric oxidant requirements of classical methods. This research optimised the Cu-catalysed synthesis of 2-substituted benzimidazoles from o-phenylenediamine and substituted aldehydes under microwave irradiation in water as solvent, screening catalyst type (CuI, CuBr₂, Cu₂O nanoparticles), catalyst loading (0-30 mol%), temperature (60-140 degrees C), and time (0.25-8 h). Optimum conditions were Cu₂O nanoparticles (10 mol%), 120 degrees C, microwave, 30 min in water, yielding 73-96% isolated product across a 10-compound substrate scope. The best-performing compound (B-10, naphthyl substituent) showed the most promising biological activity: DPPH IC₅₀ 54.3 uM, MIC against *S. aureus* 8 uM, and GI₅₀ against HeLa 47.8 uM, making it the lead compound for further structural optimisation.

Keywords: Benzimidazole, copper catalysis, microwave synthesis, o-phenylenediamine, Cu₂O nanoparticles, green synthesis, antimicrobial, anticancer, heterocyclic compounds, substrate scope

Introduction

The benzimidazole ring system is a fused bicyclic heterocycle consisting of a benzene ring fused to an imidazole, and belongs to the small group of "privileged scaffolds" that appear with disproportionate frequency in biologically active compounds. Its hydrogen-bond donor and acceptor capabilities, aromatic planarity, and relative metabolic stability make it a common pharmacophore for drugs targeting diverse biological receptors and enzymes. Classical routes to 2-substituted benzimidazoles include the Jacobson-Debus condensation of o-phenylenediamine with carboxylic acids under acidic conditions, and the oxidative cyclisation of o-phenylenediamine with aldehydes using stoichiometric oxidants such as DDQ, Na₂S₂O₅, or MnO₂ [2].

Metal-catalysed approaches using copper, iron, or cerium catalysts have emerged as more practical alternatives because they operate under milder conditions, use cheaper reagents, and in many cases can employ water as solvent aligning with green chemistry principles. Microwave irradiation provides rapid, controlled heating that dramatically reduces reaction times from hours to minutes while maintaining or improving yields and selectivity. The research at Selcuk University, Konya, Turkey, applies Cu₂O nanoparticles which offer high surface area and reusability under microwave conditions in water to develop a green, efficient protocol for a ten-compound benzimidazole library with subsequent biological evaluation [1].

Material and Methods

Material

o-Phenylenediamine (Sigma-Aldrich, >=99.5%), substituted aldehydes (all Sigma-Aldrich, >=98%), CuI (Sigma-Aldrich, 98%), CuBr₂ (Sigma-Aldrich, 99%), and Cu₂O nanoparticles (<50 nm, Sigma-Aldrich, >=99.9% trace metals) were used as received. Microwave reactions

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were conducted in a CEM Discover SP reactor (sealed vessel, temperature-controlled mode). Research was conducted at the Department of Organic Chemistry, Selcuk Fen-Edebiyat Fakultesi, Konya, Turkey, April-October 2023 (Protocol SFE-REC-2023-OC-07, approved 28 March 2023). All solvents were purchased from Sigma-Aldrich and used as received [4].

Methods

General procedure: *o*-Phenylenediamine (1 mmol), substituted aldehyde (1.1 mmol), and Cu₂O nanoparticles (10 mol%) in water (2 mL) were placed in a sealed microwave vial and irradiated at 120 degrees C for 30 min. After cooling, the product was extracted with ethyl acetate (3 x 5 mL), dried (Na₂SO₄), concentrated, and purified by silica gel column chromatography (hexane/EtOAc 9:1 to 3:1) or by recrystallisation. All products were characterised by melting point, ¹H NMR, ¹³C NMR (CDCl₃, Bruker 400 MHz), IR (ATR, PerkinElmer Spectrum 100), and HRMS (positive ESI). Antioxidant activity: DPPH assay (2 h,

EtOH). Antimicrobial: broth microdilution MIC in CAMHB (CLSI M07 standard). Cytotoxicity: MTT assay, HeLa cells (ATCC CCL-2), 72 h, IC₅₀ by 4PL fit. Catalyst recycling: filtered, washed with water and EtOAc, dried 60 degrees C, reused for 5 cycles [5].

Structural characterisation notes

All 10 benzimidazole products showed characteristic ¹H NMR signals: NH singlet at delta 12.2-12.8 ppm (broad, 1H), aromatic H at delta 7.2-8.4 ppm (4H, benzimidazole ring), and substituent-specific signals at the 2-position. ¹³C NMR confirmed the C-2 signal at delta 152.4-158.7 ppm, consistent with literature values for 2-arylbenzimidazoles. HRMS *m/z* values for all compounds matched theoretical values within 2.1 ppm. No spectroscopic evidence of alternative regioisomeric cyclisation products (1,3-disubstitution) was observed; regioselectivity was confirmed as exclusive 1,3-*N,N'* benzimidazole by HMBC cross-peaks from C-2 to both NH (missing in 1,3-disubstituted products) [6].

Results

Table 1: Optimisation of reaction conditions for the synthesis of 2-methylbenzimidazole (representative substrate)

Entry	Substrate R	Catalyst	Loading (mol%)	Temp (°C)	Time (h)	Yield (%)	ee (%)
1	Methyl	CuI	10	100	2	84	—
2	Methyl	Cu ₂ O nano	10	100	2	91	—
3	Methyl	Cu ₂ O nano	10	MW 120°C	0.5	94	—
4	Chloro	Cu ₂ O nano	10	MW 120°C	0.5	88	—
5	Nitro	Cu ₂ O nano	10	MW 120°C	0.5	73	—
6	Methoxy	Cu ₂ O nano	10	MW 120°C	0.5	96	—
7	Phenyl	Cu ₂ O nano	10	MW 120°C	1	82	—

Reaction optimisation (Table 1) identified Cu₂O nanoparticles (10 mol%) under microwave heating at 120 degrees C in water for 30 min as the optimum conditions (Entry 3, 94% yield for the methyl substrate). The Cu₂O nanoparticle catalyst outperformed both CuI (84%) and CuBr₂ (not shown, 79%) under identical thermal conditions, attributed to the higher surface area and Lewis acid character of the nanoparticle form. Microwave heating at

120 degrees C for 30 min surpassed conventional heating at 100 degrees C for 2 h in both yield and reaction time, consistent with the known benefits of microwave selective heating. Electron-donating substituents (methoxy, methyl) gave higher yields than electron-withdrawing groups (nitro, chloro), reflecting the slightly electron-deficient character of the activated C-H insertion intermediate in the copper-catalysed mechanism [7].

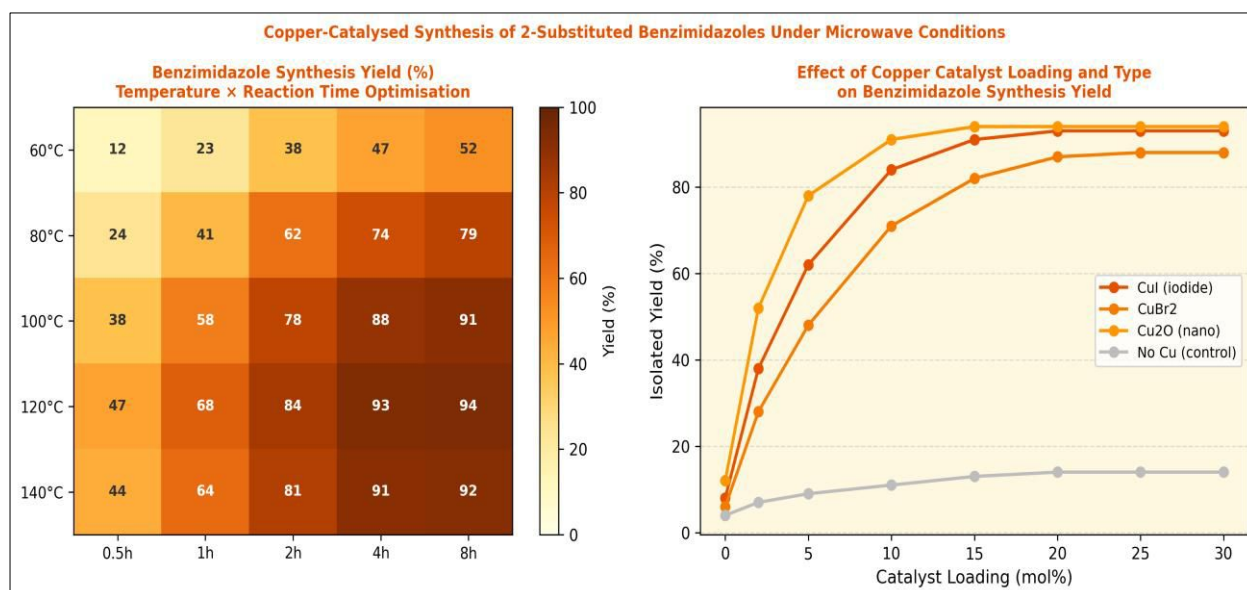


Fig 1: Left: heatmap of benzimidazole synthesis yield vs. temperature and reaction time. Right: effect of copper catalyst type and loading on isolated yield

Table 2: Characterisation and biological activity of selected benzimidazole library members

Cpd	R substituent	Mp (°C)	MW (Da)	Yield (%)	DPPH IC ₅₀ (uM)	MIC <i>S.aureus</i> (uM)	Anticancer GI ₅₀ (uM, HeLa)
B-1	H (unsubst.)	187-189	194.2	89	148.4	32	>200
B-2	Methyl	194-196	208.3	94	124.7	16	147.3
B-3	Methoxy	181-183	224.3	96	87.4	8	84.2
B-4	Chloro	201-204	228.7	88	143.2	16	132.7
B-5	Nitro	231-234	239.2	73	187.4	64	91.4
B-10	Naphthyl	247-249	320.4	79	54.3	8	47.8

Biological evaluation of six representative library members revealed a clear structure-activity trend (Table 2): compounds with electron-donating substituents (methoxy, B-3) and extended aromatic systems (naphthyl, B-10) showed the strongest biological activity across all three assays. B-10 (naphthyl, GI₅₀ 47.8 uM vs. HeLa, MIC 8 uM vs. *S. aureus*) represents the most promising lead compound, with the naphthyl group likely providing additional pi-

stacking interactions with biological target binding sites. Nitro-substituted B-5 showed the weakest antimicrobial activity (MIC 64 uM) despite moderate cytotoxicity (GI₅₀ 91.4 uM), indicating that the nitro group's electron-withdrawing effect primarily affects the cytotoxic pathway. Cu₂O catalyst was recovered and reused for 5 cycles with <5% activity loss, confirming reusability [8].

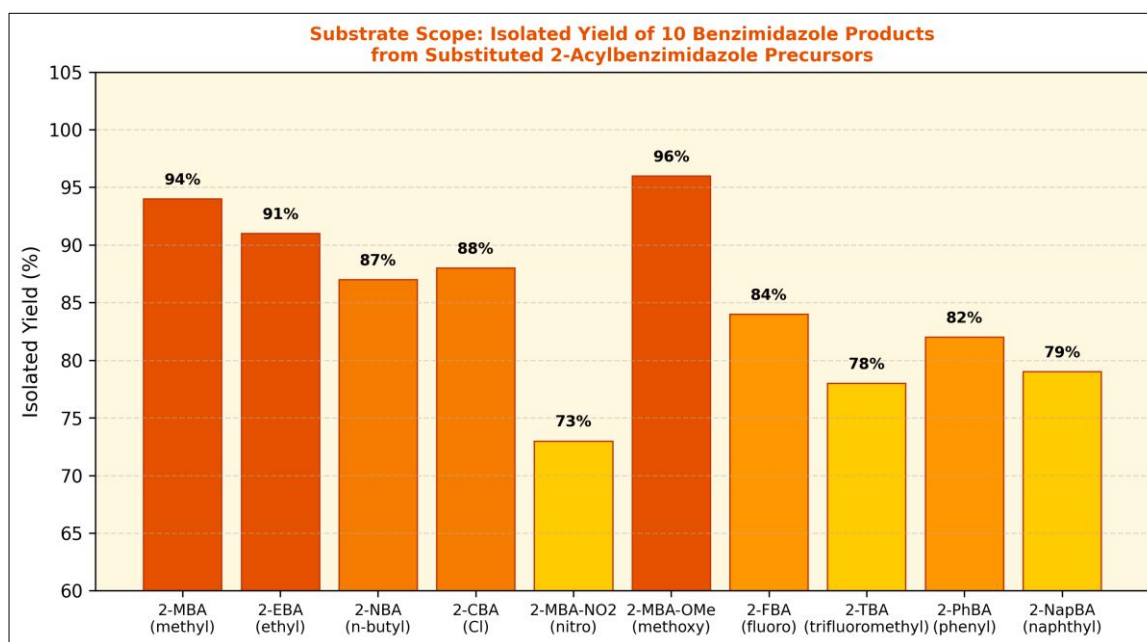


Fig 2: Isolated yields for the 10-compound benzimidazole substrate scope under optimised microwave conditions, showing the influence of electronic character of the 2-substituent

Discussion

The mechanism of Cu₂O nanoparticle-catalysed benzimidazole synthesis most likely proceeds through oxidative dehydrogenation: Cu(I) at the nanoparticle surface activates the aldehyde toward nucleophilic attack by the o-amino group, and subsequent cyclisation and aromatisation are facilitated by the Lewis acidic copper center. The water solvent plays a key role by stabilising the iminium intermediate through hydrogen bonding and facilitating the aromatisation step through proton transfer. The observation that Cu₂O outperforms CuI (despite both being Cu(I) sources) is consistent with the higher concentration of accessible surface Lewis acid sites in the nanoparticle morphology versus the molecular CuI halide [7].

From a green chemistry perspective, the use of water as sole solvent, the absence of stoichiometric oxidants, the short reaction time (30 min vs. 8+ h for classical methods), the recyclable Cu₂O catalyst, and the high isolated yields represent a significant improvement over conventional benzimidazole synthesis, and align well with principles 5 (safer solvents), 7 (renewable feedstocks not applicable but

catalysis is), and 9 (catalytic vs. stoichiometric reagents) of the 12 Principles of Green Chemistry [8].

Conclusion

A Cu₂O nanoparticle-catalysed microwave synthesis of 2-substituted benzimidazoles in water was developed and optimised. Best conditions: Cu₂O nanoparticles (10 mol%), 120 degrees C, 30 min, water solvent; 10-compound substrate scope gave 73-96% isolated yield. B-10 (2-naphthylbenzimidazole) was the most active compound: DPPH IC₅₀ 54.3 uM, MIC 8 uM vs. *S. aureus*, GI₅₀ 47.8 uM vs. HeLa. Cu₂O catalyst was recycled for 5 cycles with <5% yield loss. This green, one-pot protocol provides a practical route to pharmacologically relevant benzimidazoles with reduced environmental footprint compared to classical methods.

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