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Synthesis and Characterization of Benzene fused N-heterocycles and its Derivatives Using CuO Nanoparticles as a Heterogeneous Catalyst

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Abstract

The development of efficient and environmentally sustainable synthetic methods for biologically active heterocycles remains a major goal in modern organic chemistry. In the present work, a small library of benzene-fused N-heterocycles, including benzimidazole, benzoxazole, and benzothiazole derivatives, was synthesized using copper oxide nanoparticles (CuO NPs) as a recyclable and eco-friendly heterogeneous catalyst. The target compounds were prepared through a one-pot condensation–cyclization–oxidation protocol under mild reaction conditions, affording good to excellent yields. The catalytic system demonstrated high efficiency, operational simplicity, and easy recovery, making it suitable for green chemistry applications. All synthesized derivatives were structurally characterized using ^{1}H NMR, ^{13}C NMR, and mass spectrometry. The results highlight the potential of CuO nanoparticles as an effective heterogeneous catalyst for the rapid synthesis of benzene-fused heterocycles. Furthermore, the obtained compounds represent promising scaffolds for future development of targeted anticancer and pharmacologically active agents.

Keywords: Copper oxide nanoparticles (CuO NPs); Benzimidazole; Benzoxazole; Benzothiazole

1. Introduction

Over the past few decades, the synthesis of nanomaterials with a range of dimensions between 10 and 100 nm using various techniques has grown in popularity as a field of study.[1] Conventional synthesis techniques, like chemical and mechanical ones, or environmentally friendly techniques, like biogenesis with microbes and green synthesis with plants, can be used.[2,3] Given their many uses, nanoparticles can be created in a variety of shapes, including spheres, rods, quantum, and particles.4 Both top-down and bottom-up synthesis are possible; the former breaks down larger particles to nanosized, while the latter develops individual tiny particles to nanosize.[5]

The most common techniques used to produce copper oxide nanoparticles (CuO NPs) were physical, chemical, or biogenic. The main source in this case will be a copper salt. The bottom-up method of chemical synthesis of copper nanoparticles from these sources involves the addition of certain chemical compounds as stabilizers or capping agents to complete the reduction process and prevent agglomeration. These techniques can be combined with microwaves, lights, electricity, and sonic waves to increase their effectiveness.[6,7]

Currently, the least explored area of research is the chemical synthesis of nanoparticles from an impure metal source. Along with many other metals, leachate from the bioleaching of discarded and used electric and electronic equipment using microbes could be an environmentally safe secondary source of copper.[8,9] Nonetheless, Acidithiobacillus ferrooxidans is one of the most prevalent acidophilic bacteria that is used to leach out copper, and copper is one of the

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most prevalent metals found in electronic and electric equipment.[10,11] By oxidizing ferrous ions to ferric, they use an indirect leaching mechanism to remove copper.[12-14]

The attractive properties of copper oxide nanoparticles (CuO NPs) have led to their formation and application as new heterogeneous catalysts in organic synthesis.[15]

An important class of heterocyclic compounds with a variety of biological activities, such as antitumor, antiviral, anti-inflammatory, antihypertensive, antihistaminic, and antimicrobial properties, are aryl-substituted benzoxazoles, benzimidazoles, and benzothiazoles.[16-26]

These compounds can be prepared by two well-known methods: (i) metal-catalyzed direct alkylation of benzoxazoles, benzimidazoles, and benzothiazoles via C-H activation and C-C bond formation; and (ii) condensation-aromatization of o-aminophenol, o-phenylenediamine, and o-aminothiophenols with aldehydes using Brønsted or Lewis acid catalysts.[27-31] The synthesis of these compounds is still difficult due to low yields, the need for extra additives or volatile organic solvents, and the use of costly and non-recyclable catalysts, despite the reported methods being satisfactory.[32-39]

We describe here the use of a copper oxide nanoparticle (CuO NPs) acting as an effective and reusable heterogeneous catalyst for the condensation-aromatization of o-aminophenols and benzaldehydes, motivated by the special qualities of these nanoparticles and their valuable potential applications in catalysis. Remarkably, leaching was minimal, the anticipated products were produced in good to excellent yields, and the copper oxide nanoparticles (CuO NPs) were easily recovered by filtration. To the best of our knowledge, these novel heterocyclic molecules have never been prepared using copper oxide nanoparticles (CuO NPs).[15]

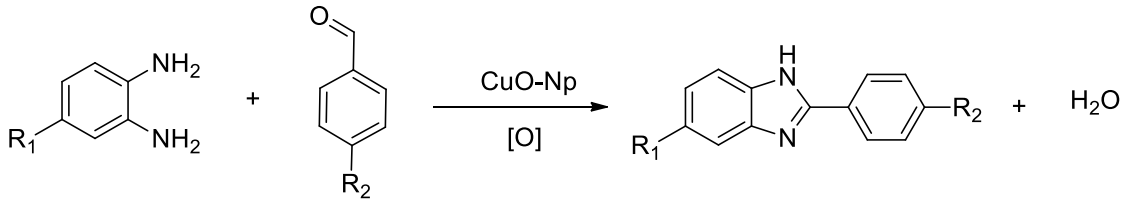
These sulfur and nitrogen-containing scaffolds are ideal for interacting with receptors and enzymes involved in the development of cancer because they are bioisosteric with purines and can mimic naturally occurring substrates. [40,41] Derivatives of benzimidazoles have been shown to impede cell proliferation by blocking microtubule polymerization, kinases, and topoisomerases.[42,43] Benzoxazoles and benzothiazoles, which often target angiogenesis signalling and mitochondrial pathways, exhibit DNA intercalation and apoptosis-inducing properties.[44-46] Their affinity for protein targets is increased by their structural planarity and capacity to form hydrogen bonding and π–π interactions.

In order to find possible anticancer agents, our study combines green chemistry through CuO NP-mediated synthesis and structure-based drug design.[47-51]

2. Results and discussion

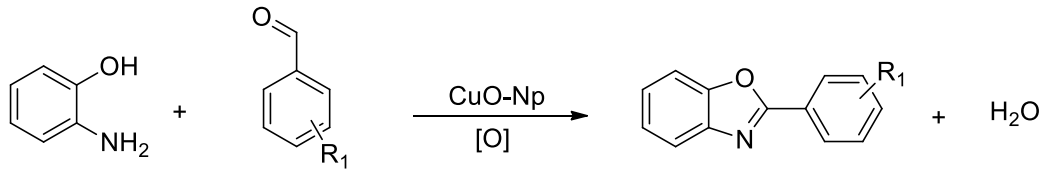
Chemistry: During the development of Benzene fused *N*-heterocycles and its Derivatives Using CuO Nanoparticles as a Heterogeneous Catalyst. We came across the formation of Benzimidazoles, Benzoxazoles, and Benzothiazoles derivatives.

Synthesis of Benzimidazole



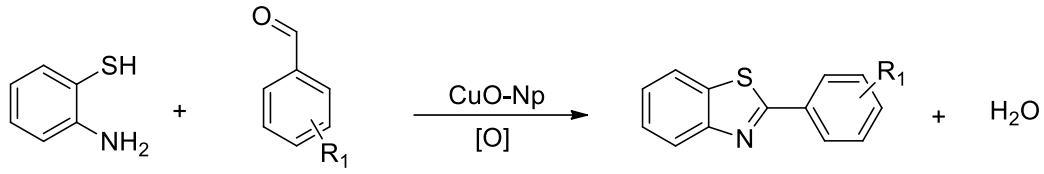
Scheme 2: Synthesis of Benzimidazole

Synthesis of Benzoxazoles



Scheme 3: Synthesis of Benzoxazoles

Synthesis of Benzothiazoles



Scheme 4: Synthesis of Benzothiazoles

3. Experimental method

All commercial chemicals and solvents are of reagent grade and were used without further purification. The thin layer chromatography was performed on Merck precoated silica gel 60 F254 plates, with visualization under UV light. Melting points were recorded (uncorrected) on Optimelt MPA 100 at a scan of 2°C/min. 1H NMR and 13C NMR spectra were recorded on Agilent NMR VNMRS 400 spectrometer using tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ), coupling constants (J-values) are reported in hertz (Hz), and spin multiplicities are indicated by the symbols as: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br. s (broad singlet). The experiments to determine the molecular mass were performed on a G6160 A infinity lab LC/MSD/IQ mass spectrophotometer from Agilent (Singapore) equipped with an electrospray ionization (ESI) source.

General procedure for the synthesis of Benzimidazole derivatives:

Refluxing a mixture of substituted o-phenylenediamine (10 mmol), substituted aldehyde (10.02 mmol), and CuO nanoparticles (5 wt.%) in 10 mL of Sulpholane at 150°C for two hours was done. TLC was used to track the reaction's progress. Following completion, the mixture was cooled, filtered to extract the catalyst, and the filtrate was quenched with water to produce a crude product precipitate. Column chromatography was used to pure the crude to produce the pure product. Eluent: 1:9 ethyl acetate to n-heptane.

General procedure for the synthesis of Benzoxazoles derivatives:

Refluxing a mixture of substituted o-aminophenol (10 mmol), substituted aldehyde (10.02 mmol), and CuO nanoparticles (5 wt.%) in 10 mL of Sulpholane at 150°C for two hours was done. TLC was used to track the reaction's progress. Following completion, the mixture was cooled, filtered to extract the catalyst, and the filtrate was quenched with water to produce a crude product precipitate. Column chromatography was used to produce the pure product. Eluent: 1:9 ethyl acetate to n-heptane.

General procedure for the synthesis of Benzothiazoles derivatives:

Refluxing a mixture of substituted o-aminothiophenol (10 mmol), substituted aldehyde (10.02 mmol), and CuO nanoparticles (5 wt.%) in 10 mL of Sulpholane at 150°C for two hours was done. TLC was used to track the reaction's progress. Following completion, the mixture was cooled, filtered to extract the catalyst, and the filtrate was quenched with water to produce a crude product precipitate. Column chromatography was used to filter off the crude to produce the pure product. Eluent: 1:9 ethyl acetate to n-heptane.

The Yield for compound 1 to 21 with their Core and substituent is mentioned in following table:

Compound	IUPAC Nomenclature	Yield (%)
1	2-phenyl-benimidazole	74
2	2-(4-methoxyphenyl)-1H-benzo[d] imidazole	83
3	2-(4-nitrophenyl)-1H-benzo[d] imidazole	58
4	2-(4-aminophenyl)-1H-benzo[d] imidazole	87
5	2-(4-Hydroxyphenyl)-1H-benzo[d] imidazole	80

6	2-(4-chlorophenyl)-1H-benzo[d] imidazole	68
7	2-Phenylbenzimidazole-5-sulfonic acid	53
8	2-phenyl-benzothiazole	70
9	2-(4-methoxyphenyl) benzo[d] thiazole	78
10	2-(4-chlorophenyl)benzo[d]thiazole	63
11	2-(4-nitrophenyl)benzo[d]thiazole	53
12	2-(4-hydroxyphenyl)benzo[d]thiazole	74
13	2-(2-hydroxyphenyl)benzo[d]thiazole	72
14	2-(4-aminophenyl)benzo[d]thiazole	80
15	2-phenyl-benzoxazole	63
16	2-(4-methoxyphenyl) benzo[d] oxazole	68
17	2-(4-chlorophenyl) benzo[d] oxazole	58
19	2-(4-nitrophenyl) benzo[d] oxazole	48
18	2-(4-hydroxyphenyl) benzo[d] oxazole	65
21	2-(2-hydroxyphenyl) benzo[d] oxazole	60
20	2-(4-aminophenyl) benzo[d] oxazole	73

4. Results and Discussion

- 2-phenyl-benimidazole :

Crystalline solid, mp 290 ◦C. 1H NMR (DMSO-d6, 400 MHz) d (ppm): 12.67[ppm] (s, 1), 8.18[ppm] (d, 2, J1 = 7.8[Hz]), 7.59[ppm] (m, 2), 7.54[ppm] (m, 2) 7.48[ppm] (t, 1, J1 = 7.3[Hz]), 7.18[ppm] (m, 2, J1 = 9.3[Hz], J2 = 3.2). Mass m=z (TOF): 195.09 (Mþ þ 1).

- 2-(4-methoxyphenyl)-1H-benzo[d] imidazole:

Crystalline solid, mp 223 ◦C. 1H NMR ((DMSO-d6, 400 MHz)) d (ppm): 12.73[ppm] (s, 1), 8.12[ppm] (d, 2, J1 = 8.8[Hz]), 7.62[ppm] (d, 1, J1 = 7.1[Hz]), 7.49[ppm] (d, 1, J1 = 7.0[Hz]) 7.18[ppm] (m, 2), 7.12[ppm] (m, 2), 3,84[ppm] (s, 3). Mass m=z (TOF): 225.01 (Mþ þ 1).

- 2-(4-nitrophenyl)-1H-benzo[d] imidazole:

Crystalline solid, mp 298 ◦C 1H NMR ((DMSO-d6, 400 MHz)) d (ppm): 8.43[ppm] (s, 4), 7.74[ppm] (d, 1), 7.60[ppm] (d, 1, J1 = 7.8[Hz]), 7.28[ppm] (d, 1, J1 = 7.7[Hz]). Mass m=z (TOF): 239.96 (Mþ þ 1)

- 2-(4-aminophenyl)-1H-benzo[d] imidazole:

Crystalline solid, mp 234 ◦C 1H NMR ((DMSO-d6, 400 MHz)) d (ppm): 12.41[ppm] (s, 1), 7.83[ppm] (d, 2 J1 = 8.7 [Hz]), 7.47[ppm] (s, 2), 7.11[ppm] (m, 2), 6.66[ppm] (d, 2 J1 = 8.5[Hz]), 5.60 [ppm] (s, 2) . Mass m=z (TOF): 210.4 (Mþ þ 1)

- 2-(4-Hydroxyphenyl)-1H-benzo[d] imidazole:

Crystalline solid, 1H NMR ((DMSO-d6, 400 MHz)) d (ppm): 11.95[ppm] (s, 1), 7.96[ppm] (d, 2 J1 = 8.7 [Hz]), 7.51[ppm] (dd, 2 J1 = 5.8[Hz], J2 = 3.2 [Hz]), 7.13[ppm] (m, 2), 6.85[ppm] (d, 2 J1 = 8.7[Hz]). Mass m=z (TOF): 211.09 (Mþ þ 1)

- 2-(4-chlorophenyl)-1H-benzo[d] imidazole:

Crystalline solid, mp 285 ◦ C 1H NMR ((DMSO-d6, 400 MHz)) d (ppm): 8.20[ppm] (d, 2 J1 = 8.5 [Hz]), 7.59[ppm] (m, 4), 7.18[ppm] (td, 2 J1 = 6.2[Hz], J2 = 3.1 [Hz]). Mass m=z (TOF): 229.09 (Mþ þ 1)

- 2-Phenylbenzimidazole-5-sulfonic acid:

Crystalline solid, mp 298 ◦ C ^{1}H NMR ((DMSO-d6, 400 MHz)) d (ppm): 14.50[ppm] (s, 1), 8.20[ppm] (dd, 2 J1 = 5.2 [Hz], J2 = 1.6 [Hz]), 7.97[ppm] (s, 1), 7.80[ppm] (m, 3). Mass m=z (TOF): 275.06 (Mþ þ 1).

- 2-phenyl-benzothiazole:

Crystaline Solid, mp 112 ◦ C. 1H NMR (DMSO-d6, 400 MHz) d (ppm): 8.16[ppm] (d, 1, J1 = 8.3[Hz]), 8.09[ppm] (m, 3), 7.57[ppm] (m, 4), 7.47[ppm] (m, 1). Mass m=z (TOF): 212.12 (Mþ þ 1).

- 2-(4-methoxyphenyl) benzo[d] thiazole:

Crystaline Solid, Mp 121 ◦ C. 1H NMR (DMSO-d6, 400 MHz) d (ppm): 8.11[ppm] (d, 1, J1 = 8.3[Hz]), 8.04[ppm] (dd, 2, J1 = 6.9 [Hz]), 8.01[ppm] (d, 1, J1 = 8.3[Hz], J2 = 2.1[Hz]), 7.52[ppm] (m, 1), 7.43[ppm] (m, 1), 7.13[ppm] (m, 2), 3.86[ppm] (s, 3). Mass m=z (TOF): 242.21 (Mþ þ 1).

- 2-(4-chlorophenyl)benzo[d]thiazole:

Crystaline Solid, Mp 116 ◦ C. 1H NMR (DMSO-d6, 400 MHz) d (ppm): 8.16 (d, 1H, *J* = 7.6 Hz), 8.11 (m, 2H), 8.07 (d, 1H, *J* = 7.6 Hz), 7.64 (dd, 1H, *J* = 6.9, 2.1 Hz), 7.56 (m, 1H), 7.48 (m, 1H). Mass m=z (TOF): 246.06 (Mþ þ 1).

- 2-(4-nitrophenyl)benzo[d]thiazole:

Crystaline Solid, Mp 230 ◦ C. 1H NMR (DMSO-d6, 400 MHz) d (ppm): 8.41 (q, 2H, *J* = 3.0 Hz), 8.36 (m, 2H), 8.24 (d, 1H, *J* = 7.6 Hz), 8.16 (d, 1H, *J* = 8.3 Hz), 7.62 (td, 1H, J = 7.6 [Hz], J2 = 1.4 [Hz]), 7.55 (m, 1H). Mass m=z (TOF): 255.34 (Mþ þ 1).

- 2-(4-hydroxyphenyl)benzo[d]thiazole:

Crystaline Solid, Mp 224 ◦ C. 1H NMR (DMSO-d6, 400 MHz) d (ppm): 10.22[ppm] (s, 1), 8.07[ppm] (d, 1, J1 = 7.6 [Hz]), 7.98[ppm] (d, 1, J1 = 8.3[Hz]), 7.93[ppm] (td, 2, J1 = 5.3[Hz], J2 = 3.4 [Hz]), 7.50[ppm] (td, 1, J1 = 7.6[Hz], J2 = 1.4[Hz]), 7.40[ppm] (m, 1), 6.94[ppm] (td, 2, J1 = 5.7[Hz], J2 = 3.4[Hz]). Mass m=z (TOF): 228.02 (Mþ þ 1).

- 2-(2-hydroxyphenyl)benzo[d]thiazole:

Crystaline Solid, Mp 131 ◦ C. 1H NMR (DMSO-d6, 400 MHz) d (ppm): 7.08[ppm] (td, 1, J1 = 7.6[Hz], J2 = 1.4[Hz]), 6.99[ppm] (dd, 1, J1 = 7.9 [Hz], J2 = 1.7 [Hz]), 6.72[ppm] (dd, 1, J1 = 8.3[Hz], J2 = 1.4[Hz]), 6.42[ppm] (td, 1, J1 = 7.6[Hz], J2 = 1.4[Hz]), 5.44[ppm] (s, 2). Mass m=z (TOF): 226.19 (Mþ þ 1).

- 2-(4-aminophenyl)benzo[d]thiazole:

Crystaline Solid, Mp 152 ◦ C. 1H NMR (DMSO-d6, 400 MHz) d (ppm): 8.02[ppm] (d, 1, J1 = 7.6[Hz]), 7.89[ppm] (d, 1, J1 = 8.3[Hz]), 7.76[ppm] (m, 2), 7.45[ppm] (m, 1), 7.34[ppm] (m, 1), 6.66[ppm] (dd, 2, J1 = 11.0[Hz], J2 = 2.8[Hz]), 5.90[ppm] (s, 2). Mass m=z (TOF): 227.08 (Mþ þ 1).

- 2-phenyl-benzoxazole:

Crystalline solid, mp 103 ◦ C. 1H NMR (Chloroform-d, 400 MHz) d (ppm): 8.27[ppm] (m, 2), 8.15[ppm] (0 d J1 = 8.1[Hz]), 7.78[ppm] (m, 1), 7.59[ppm] (m, 1), 7.52[ppm] (m, 3), 7.36[ppm] (m, 3). Mass m=z (TOF): 196.01 (Mþ þ 1).

- 2-(4-methoxyphenyl) benzo[d] oxazole:

Crystalline solid, mp 100 ◦ C. 1H NMR (Chloroform-d, 400 MHz) d (ppm): 8.20[ppm] (m, 2), 7.74[ppm] (m, 1), 7.56[ppm] (m, 1), 7.33[ppm] (m, 2), 7.04[ppm] (m, 2), 3.90[ppm] (s, 3). Mass m=z (TOF): 226.40 (Mþ þ 1).

- 2-(4-chlorophenyl) benzo[d] oxazole:

Crystalline solid, mp 146 ◦ C. 1H NMR (Chloroform-d, 400 MHz) d (ppm): 8.20[ppm] (m, 2), 7.78[ppm] (m, 1), 7.59[ppm] (m, 1), 7.51[ppm] (m, 2), 7.37[ppm] (m, 2). Mass m=z (TOF): 230.07 (Mþ þ 1).

- 2-(4-nitrophenyl) benzo[d] oxazole:

Crystalline solid, mp 305 ◦ C. 1H NMR (Chloroform-d, 400 MHz) d (ppm): 8.46[ppm] (m, 4), 7.89[ppm] (m, 2), 7.50[ppm] (m, 2). Mass m=z (TOF): 241.40 (Mþ þ 1).

- Preparation of 2-(4-hydroxyphenyl) benzo[d] oxazole:

Crystalline solid, mp 155 ◦ C. 1H NMR (Chloroform-d, 400 MHz) d (ppm): 10.33[ppm] (s, 1), 8.04[ppm] (d, 2, J1 = 8.8[Hz]), 7.73[ppm] (m, 2), 7.37[ppm] (m,2), 6.97[ppm] (d, 2, J1 = 8.8[Hz]). Mass m=z (TOF): 212.07 (Mþ þ 1).

- Preparation of 2-(2-hydroxyphenyl) benzo[d] oxazole:

Crystalline solid, mp 125 ◦ C. 1H NMR (Chloroform-d, 400 MHz) d (ppm): 11.22[ppm] (s, 1), 8.04[ppm] (dd, 1, J1 = 7.9[Hz], J2 = 1.6[Hz]), 7.86[ppm] (m, 2), 7.54[ppm] (m,1), 7.48[ppm] (m, 2), 7.14[ppm] (d, 1, J1 = 8.0[Hz]), 7.10[ppm] (m, 1). Mass m=z (TOF): 212.08 (Mþ þ 1).

- Preparation of 2-(4-aminophenyl) benzo[d] oxazole:

Crystalline solid, mp 233 ◦ C. 1H NMR (Chloroform-d, 400 MHz) d (ppm): 7.86[ppm] (d, 2, J1 = 8.7[Hz]), 7.66[ppm] (m, 2), 7.31[ppm] (m, 2), 6.69[ppm] (d, 2, J1 = 8.7[Hz]), 5.99[ppm] (s, 2). Mass m=z (TOF): 211.08 (Mþ þ 1).

In above said methods,

Sulpholane used as a solvent, CuO loading was 5 wt.% with respect to KSM, Reaction maintained at 150°C temperature for 2Hrs. Each compound isolated & purified performing column by using Heptane: Ethyl Acetate (90:10) as a mobile phase. Catalyst as well as solvent was recovered and reuse.

5. Conclusion

A small library of various substituted derivatives of benzene fused N-heterocycles and their derivatives, Mainly Analogues of benzimidazole, benzoxazole, and benzothiazole has been synthesized by us. ^{1}H NMR, ^{13}C NMR, Mass to characterize each synthesized compound. Our results will surely be useful to medicinal chemists and process chemists involved in drug discovery.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflicts of interest, financial or otherwise.

Availability of data and materials

Supplementary material that is available on the publisher's website along with the published article contains spectroscopic data of all compounds.

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