Journal of Sciences, Islamic Republic of Iran 36(2): 143 - 149 (2025) http://jsciences.ut.ac.ir
University of Tehran, ISSN 1016-1104

NH4I-Catalyzed Selective Synthesis of 2-Substituted Benzimidazoles

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Received: 17 December 2025 / Revised: 20 June 2026 / Accepted: 14 July 2026

Abstract

By reacting 1,2-diamines with aromatic, aliphatic, and heteroaromatic nitroalkenes while using ammonium iodide (NH_4I) as a green catalyst, a simple and effective synthetic pathway was created. This method is environmentally friendly and allows for the highly regioselective synthesis of 2-substituted benzimidazole derivatives in good to excellent isolated yields (78-94%). A plausible reaction mechanism was proposed. The scope and limitations were further examined.

Keywords: Ammonium iodide (NH_4I); Green catalyst; 2-substituted benzimidazoles; 1,2-diamines; chemoselectivity.

Introduction

Heterocycles are abundant in the environment and are crucial to living organisms. These compounds benefit biological metabolic processes (1-6). Nitrogen heterocycles, especially those with oxygen and sulfur, are common in nature due to their key roles in nucleic acid structure and vital physiological processes (7-9). Benzimidazoles are important heterocyclic compounds, widely used as intermediates in developing various pharmaceutical agents and functional materials (Figure 1) (10-12).

Several effective methods have been devised to assemble these heterocycles due to their increasing significance and extensive utility. Benzimidazoles are typically synthesized using aryl-1,2-diamines to participate in the condensation process with acids, aldehydes, or alcohols (13-17). There is a genuine requirement for novel procedures that accommodate a variety of substitution patterns and structural diversity in the target library, despite the availability of a wide range of methods for benzimidazole synthesis. However, numerous of these methodologies are plagued by constraints, including costly catalysts, noxious solvents, and certain metal-based Lewis acids that pose environmental hazards. Furthermore, these methods generate a mélange of 1,2-disubstituted and 2-substituted benzimidazoles as a result of the non-regioselective amino groups of 1,2-phenylenediamine. Among these, 2-substituted benzimidazoles are found to be valuable

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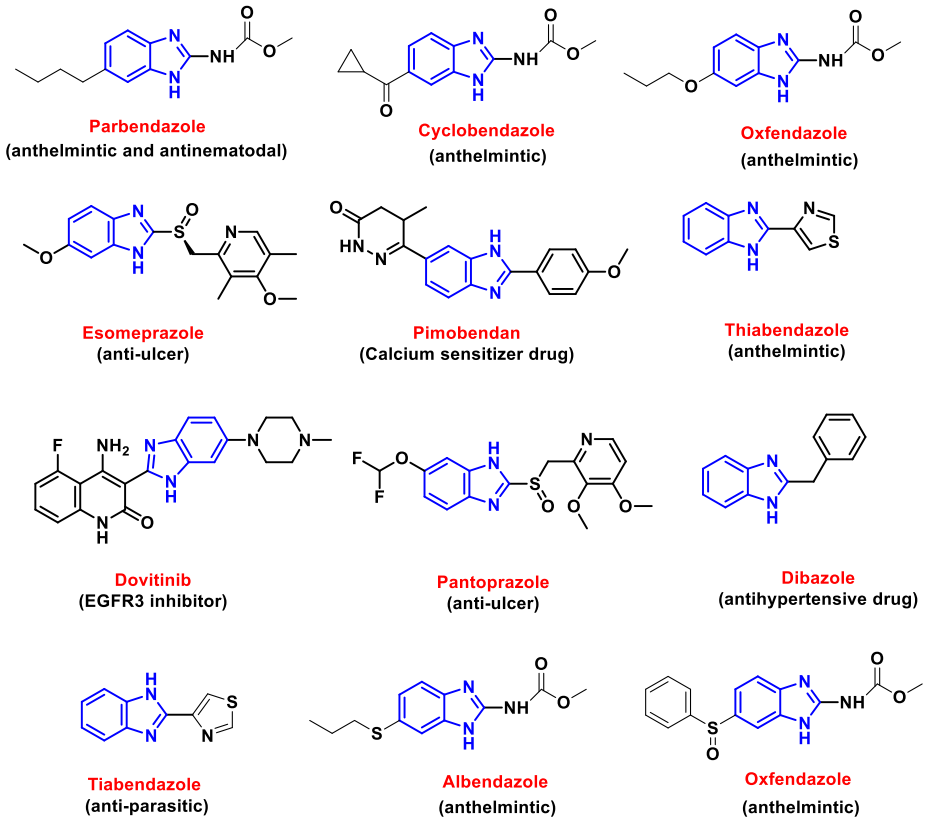


Figure 1. Biologically relevant 2-substituted benzimidazole moieties

building elements for a variety of pharmaceutical applications (18-31). Therefore, it is still necessary to develop a synthetic procedure that is highly discerning, mild, and environmentally benign in order to synthesize these significant classes of heterocyclic compounds.

The formula for ammonium iodide is NH_4I, and it is an inorganic white ionic compound. Ammonium iodide is a dietary supplement that is used to treat iodine deficiency. This looks very promising for exploring cheap reagents such as NH_4I in various synthetic developments, eg., carbon-carbon, carbon-heteroatom, heteroatom-heteroatom bond formation reactions (32-36). It is extensively used in organic synthesis due to its low cost, easy availability, operational simplicity, and environmentally benign nature. NH_4I serves as a versatile source of nucleophilic iodide rather than being

Aspect	Iodine (I_2)	Ammonium Iodide (NH_4I)
Chemical nature	Element (halogen) CAS No: 7553-56-2 = I_2	Ionic salt ($NH_4^+ + I^-$) CAS No: 12027-06-4 = NH_4I
Physical form	Shiny dark violet/black solid	White crystalline solid
Odour	Strong, pungent	Odourless
Volatility	Sublimes easily (toxic vapors)	Non-volatile
Toxicity	More toxic – corrosive, harmful vapors, skin & eye burns	Less toxic – irritant, harmful if ingested in large amounts
Health hazards	Respiratory irritation, thyroid dysfunction,	Mild irritation, iodine overload on chronic exposure

intrinsically nucleophilic. The iodide anion (I^-) exhibits a Mayr–Patz nucleophilicity parameter of N ≈ 5.0–5.5 (s ≈ 1.0) in polar protic solvents, reflecting its high polarizability, strong S_N2 reactivity, and relatively low oxidation potential, which allows facile generation of electrophilic iodine species ($I^+/I^•$) under mild conditions. The ammonium cation, while non-nucleophilic, can participate in hydrogen bonding and act as a proton donor, stabilizing intermediates and facilitating reactions.

We report a highly regioselective synthesis of 2-substituted benzimidazoles as part of our work on green synthesis for bioactive heterocycles (37, 38). This method uses mild conditions and the green catalyst NH_4I.

Materials and Methods

Experimental

General

^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker (400 MHz) FT-NMR spectrometer using DMSO-d_6 or $CDCl_3$ as solvents, with TMS as an internal standard (δ ppm). Chemical shifts are given relative to TMS. FT-IR spectra were taken on a *JASCO FT-IR* 400 plus with KBr pellets. Uncorrected melting points were determined with a Guna Enterprises capillary melting point apparatus. TLC used 2.5×7.5 cm glass plates coated with 250 mμ Merck GF254 silica gel; spots were detected with iodine vapour or UV. Column chromatography used CDH silica gel (60-120 mesh).

General procedure for the synthesis of 2-substituted benzimidazole

To a stirred solution of 1,2-phenylenediamine 1 (1 mmol) in acetonitrile (3 mL) and NH_4I (20 mol%) at 80 °C, add nitroalkene 2 (1 mmol). Monitor the reaction by TLC. Cool to room temperature and pass through silica gel using ethyl acetate. Evaporate, then purify the residue by column chromatography (silica gel, petroleum ether/EtOAc = 4:1) to yield benzimidazole 3.

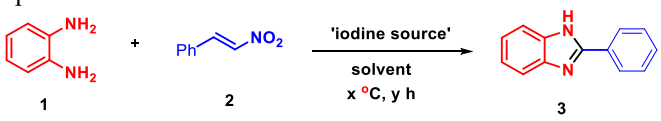
Spectral Data for representative compound

2-phenyl-1H-benzo[d]imidazole (3a): White solid; Mp: 283-284 °C (lit. Mp: 283- 285 °C); IR (KBr): 3046, 2623, 1677, 1546, 1405, 1310, 1271, 1113, 965, 738 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ: 12.91 (s, 1H), 8.19 (d, J = 7.6 Hz, 2H), 7.61–7.55 (m, 4H), 7.49–7.51 (m, 1H), 7.21–7.22 (m, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 151.2, 143.8, 135.0, 130.2, 129.8, 128.9, 126.4, 122.5, 121.6, 118.8, 111.3; MS (*m/z*): 195.0913 $[M+1]^+$.

Spectral data for other compounds is provided in 'Supporting Information' file.

Results

Initially, we screened several ammonium salts and iodine sources as catalysts. The control reaction involved 1,2-phenylenediamine 1 (1 mmol) and β-nitrostyrene 2a (1 mmol) refluxing in acetonitrile (2 mL) for the specified time. As shown in Table 1, NH_4I was superior to the other selected ammonium salts (NH_4Cl, NH_4OAc, NH_4Br) in terms of isolated yield (91%, 3a). Hydroiodic acid (HI) is a potent, caustic liquid, so its use in this methodology is not recommended. Compared to ammonium iodide (NH_4I), molecular iodine (I_2), or *N*-iodosuccinimide (NIS), iodine is more expensive and hazardous. Thus, NH_4I is finalized as the best among the tested in terms of greenness, economic viability, and isolated product yields. After selecting the catalyst, its loading in the control reaction was tested. It was found that 20 mol% NH_4I was optimal for the regioselective synthesis of 2-substituted benzimidazole in a shorter reaction time. Several protic and aprotic solvents were tested (Table 2): DMF, DCE, DMSO, THF, NMP, toluene, solvent-free, and CH_3CN. Based on the results from Tables 1 and 2, 20 mol% NH_4I in acetonitrile under reflux conditions is optimal for the control reaction.



Discussion

The scope of the reaction for the synthesis of various 2-substituted benzimidazole derivatives 3a-o was subsequently investigated. This was achieved by modulating either the substituted 1,2-phenylenediamines 1 or the β-nitrostyrenes 2 using the optimized reaction conditions (Table 3). Table 3 shows that the required products were produced in excellent to exceptional isolated yields by a variety of substituted β-nitrostyrenes 2 that carried both electron-donating and electron-withdrawing groups (3b-3j). Divergent *o*-PDs were also investigated in a similar manner. The results are presented in Table 3. β-Nitrostyrenes derived from heteroaromatics also exhibited a high isolated yield of the product (3k-m, 78–87%). The formation of 1,2-disubstituted benzimidazoles has never been observed. The sole compounds produced by NH_4I catalysis are 2-substituted benzimidazoles. Alicyclic compounds, including cyclohexane carbaxaldehyde, are also susceptible to the optimised reaction parameters. Substituted *o*-PDs that contained -OMe, -Cl, and $-NO_2$ were also able to react and produce the corresponding products in high isolated yields (3o-3q, 84–90%). The title reaction was well received with aliphatic aldehydes,

Table 1. Optimization studies-Screening of catalysts (10 mol%)

Entry	Catalyst	Isolated yield (%)[a]
1	NH_4Cl	67
2	NH_4Br	56
3	NH_4OAc	12
4	NH_4NO_3	NA
5	NH_4I	91
6	HI	71
7	NaI	trace
8	I_2	85
9	NIS	78

[a]at 80 ºC, 12 h

Table 2. Optimization studies-Screening of solvents and catalyst loading in presence of NH_4I

Entry	Solvent	Isolated yield (%)[a]
1	DMF	42
2	DCE	21

including acetaldehyde and isovaleraldehyde (3r-3s, 87–88%).

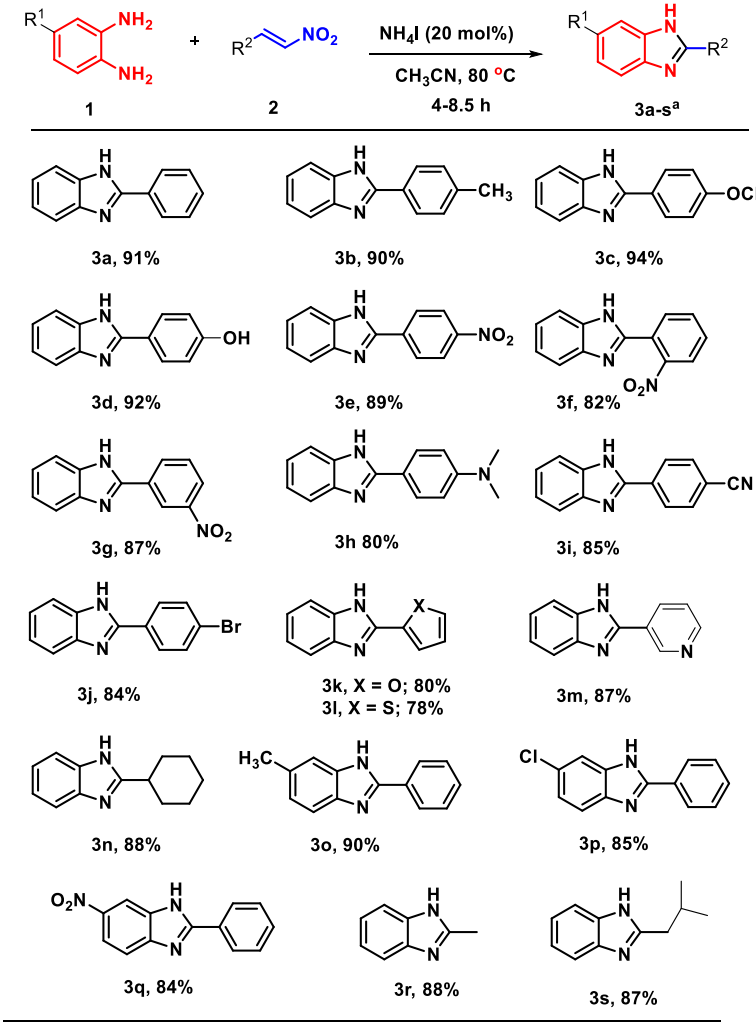
Physical and spectroscopic techniques, including IR, mass, ^{1}H, and ^{13}C NMR, were used to characterize all of the structures 3a-o. For instance, the ^{1}H NMR spectrum of compound 3a demonstrates two singlet signals at δ 12.91. These signals are attributed to the -NH group of the benzimidazole. The cyclized structure of 2-phenyl-1*H*-benzo[*d*]imidazole (3a) is represented by the total of 9H from the aromatic region, from 7.21 to 8.20. The cyclized aldehyde's 'C' (C2) is represented by 151.21 in the ^{13}C NMR spectrum. 3a's ESI spectrum confirms the formation, with a peak at $[M+H]^+$ at *m/z* 195. In general, selectivity claims require quantitative justification. No signals attributable to the 1,2-disubstituted product were observed by ^{1}H NMR or ^{13}C NMR. This indicates that any formation is below the detection limit. Related references for high regioselectivity with other catalysts are also provided (21-23, 27).

A plausible mechanism for this reaction was proposed and is illustrated in Figure 2, as evidenced by previous reports on NH_4I-catalyzed reactions and analogous mechanisms confirmed in the literature (34, 39-42). The Michael addition took place between 1,2-phenylenediamine 1 and β-nitrostyrene 2, which was activated by I_2. This reaction resulted in intermediate 4. This is rearranged to remove nitromethane (through the Retro-aza-Henry-type process) and produce the imine 5. The intramolecular attack of the electrophilic imine carbon by the resulting imine, activated by the catalyst and another -NH_2 group of *o*-phenylenediamine 1, resulted in the formation of the intermediate 6. This intermediate underwent aerial oxidation to produce the corresponding 2-substituted benzimidazole 3.

Conclusion

In conclusion, we have successfully executed a green, efficient, and straightforward procedure for the highly regioselective synthesis of 2-substituted benzimidazole derivatives **3a-s** from 1,2-diamines **1** and β-nitrostyrene **2** using an environmentally friendly NH_4I catalyst. As mentioned in the results and discussion, this protocol is far superior to typical iodine-catalysed reactions in both cost-effectiveness and toxicity. In Ref. 19, a mixture of benzimidazoles (2-substituted benzimidazole and *N*-alkylated 2-substituted benzimidazole) is formed when *o*-PD is treated with *aldehydes* in the presence of molecular iodine (2 mol%) in THF-H_2O at RT. Whereas in Ref. 20, selective synthesis of 2-substituted benzimidazoles was achieved by the condensation of *orthoesters* and 1,2-phenylenediamines using molecular iodine (10 mol%) in CH_3CN at RT. Our protocol is claimed to be the first example of employing NH_4I as a catalyst (source of '*in situ*' iodine) using *β-nitrostyrenes* and substituted *o*-PDs.

Table 3. Synthesis of 2-substituted benzimidazole derivatives



[a]Isolated yields

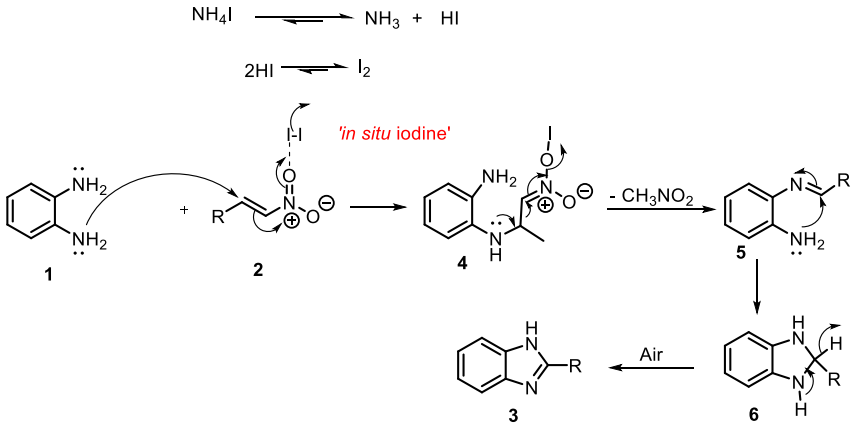


Figure 2. Proposed mechanism for the NH_4I-mediated synthesis of 2-substituted benzimidazoles

Acknowledgement

Dr.PRKV is thankful to the administration of Sasi Institute of Technology & Engineering, Tadepalligudem, West Godavari-534101, Andhra Pradesh, India.

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