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Beetroot extract: A green catalytic medium for streamlined one-pot synthesis of benzimidazole derivatives

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Abstract
A one-pot multicomponent reaction was established for the synthesis of benzimidazole derivatives through the interaction of o-phenylenediamine and aromatic aldehydes, utilizing beetroot extract as a catalytic medium. Beetroot extract, sourced from *Beta vulgaris* L., exhibited noteworthy catalytic activity in the production of the target compounds. This method is characterized by mild reaction conditions, straightforward product separation, yielding moderate to high product quantities, and short reaction durations. These attributes render this approach significantly more appealing than previously reported methods for synthesizing benzimidazole derivatives.

Keywords: Beet root extract, benzimidazoles, o-phenylenediamine, aldehydes

Introduction
In contemporary times, there has been a growing emphasis on the advancement of environmentally sustainable synthetic pathways and processes [1]. Multicomponent reactions (MCRs) stand as pivotal tools in the field of synthetic organic chemistry, offering advantages such as atom economy, reduced time requirements, one-pot methodologies, energy conservation, ecological compatibility, and the facilitation of targeted and diversely oriented synthesis [2, 3] Notably, there is a recent surge in the exploration of catalytic activities of substances like fruit extracts, vegetable extracts, and industrial as well as agricultural byproducts [4]. Consequently, the development of novel MCRs within the framework of green chemistry has garnered significant attention, particularly in domains such as organic synthesis, pharmaceutical manufacturing, and material science.

Benzimidazole, a significant nitrogen-containing heterocyclic moiety, is a compound comprising an imidazole ring fused to a benzene nucleus [5]. The biological properties of benzimidazoles can be attributed to their structural resemblance to purines. Numerous benzimidazole derivatives have been identified, exhibiting diverse biological activities, including antimicrobial, antiviral, antifungal, antimalarial, antitumor, anticancer, antihypertensive, anti-inflammatory, and antioxidant properties [6-11] Various synthetic methodologies are available for the preparation of benzimidazole derivatives. A commonly employed approach involves the condensation reaction of 1,2-phenylenediamine with carboxaldehydes, carboxylic acids, or their derivatives, such as chlorides, nitriles, and orthoesters. This synthesis typically necessitates strong acidic conditions and high temperatures [12].

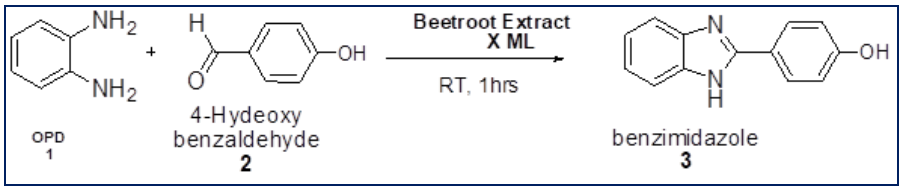
In recent years, a substantial body of literature has documented various methods for synthesizing benzimidazole and related compounds [13]. Despite their potential, some of these methods exhibit shortcomings, including heavy reliance on transition metal-based catalysts, the use of organic solvents, extended reaction times, laborious workup procedures, costly reagents, suboptimal yields, and limited atom economy [5] Consequently, there remains a demand for the development of more straightforward routes to benzimidazole derivatives, with a preference for environmentally friendly synthetic methods that employ low-cost, unprocessed natural feedstock extracts [14] Continuing our investigations into the synthesis of heterocyclic compounds, we present a simple, mild, and environmentally benign approach for the synthesis of benzimidazole and its analogues using beetroot extract, which serves as a

natural catalyst or provides an advantageous catalytic medium for the reactions. This method aligns with the principles of green chemistry. Beetroot (*Beta vulgaris* L.) is commonly consumed in various forms, including juice, powder, oven-dried, and jam-processed, in different food cultures. It contains water-soluble nitrogen-containing pigments known as betalains, which are particularly abundant in red beet (*Beta vulgaris*).

Our analysis revealed that the pH of our fruit extract is 4.6, indicative of the presence of acidic components that may facilitate the reaction in the desired direction. Currently, fruit juices are increasingly used in organic synthesis as homogeneous catalysts due to their high selectivity in producing the desired products. With the biological significance of the benzimidazole nucleus in mind, this research was conducted to synthesize substituted benzimidazoles in the presence of beetroot at room temperature.

Results and Discussion

In the initial phase of our study, a model reaction involving o-phenylenediamine (1) and 4-Hydroxy benzaldehyde (2) was conducted with varying quantities of beetroot fruit extract (2 mL, 4 mL, and 6 mL), as depicted in Scheme I. Continuous monitoring of the reaction progress was carried out using thin-layer chromatography (TLC). To optimize the reaction conditions, we systematically investigated the impact of different amounts of fruit extract on both reaction time and the percentage yield of the product, as outlined in Table 1 (entries 1-3). The catalytic efficacy of these fruit extracts in yielding benzimidazole derivatives was evident. Notably, the use of 4 mL of beetroot extract (Table 1, entry 2) demonstrated superior efficiency in facilitating the desired conversion. Consequently, 4 mL of beetroot extract was chosen as the optimal catalyst or catalytic medium for the synthesis of benzimidazole derivatives, as elucidated in Table 2.



Scheme 1: Synthesis of benzimidazoles from OPD and 4-hydroxybenzaldehyde

In our endeavor to broaden the substrate scope and establish the applicability of a specific chemical protocol, we conducted an investigation involving various substituted aromatic aldehydes in conjunction with o-phenylenediamine (OPD) as the reagent. Our findings indicate that the chosen aromatic aldehydes, incorporating both electron-withdrawing and electron-donating functional groups, displayed a consistent reactivity profile under identical reaction conditions. This harmonious reactivity translated into the generation of products in moderate to high yields, as delineated in Table 2 (entries 1-16).

A distinctive observation emerged during our research, particularly concerning chloro-substituted aldehydes. These specific substrates exhibited a noticeably delayed reaction rate, leading to a consequential reduction in the overall chemical yield

Table 1: Effect of beetroot extract quantity on reaction yield

Entry	The volume of Extract X mL	Time	Yield
1	2	110	45
2	4	40	92
3	6	40	85

The observed phenomenon can be ascribed to the inherent electron-withdrawing attributes of chlorine atoms. The electron-withdrawing nature of chlorine tends to reduce the electron density within the aromatic ring, thereby impeding the progress of the chemical transformation. This is exemplified by entries 3b, 3c, 3f, 3g, and 3j in Scheme I.

In contrast, aldehydes equipped with electron-donating substituents, such as hydroxyl, methoxy, and dimethylamino groups, exhibited accelerated reaction kinetics, ultimately resulting in relatively substantial product yields. This heightened reactivity can be attributed to the electron-donating characteristics of these specific functional groups, which enhance the electron density within the aromatic ring. Consequently, this electron-rich environment promotes a more favorable reaction pathway, facilitating the formation of the desired product, as illustrated by entries 3d, 3e, 3h, and 3i in Scheme 1.

Table 2: Effect of aromatic substitution on reaction yield

Entry	Ar	Reaction time (h)	Yields (%)	M.P. (C)
3a	Ph-4-OCH_3	4	90	214-216
3b.	Ph-2-OH	6	92	270-272
3c	Ph-3-NO_2	4	89	298-300
3d	Ph-(3,4-$OH)_2$	6	93	232-234
3e	Ph-(3,4-$OCH_3)_2$	10	78	232-234
3f	Ph-4-Cl	6	76	258-286
3g	Ph-4-CH_3	7	81	236-238
3h	Ph-3-OH	5	82	270-272

Materials and Methods

All the required chemicals were purchased from Sigma Aldrich and used without further purification with the exception of benzaldehyde which was distilled prior to use. The beet root were purchased from local market. The purity determination of the starting materials and reaction monitoring was accomplished by thin-layer chromatography (TLC) on Merck silica gel 60 F254 plates also by exposing to iodine chamber. Melting points were determined in open capillary tubes and is uncorrected. IR spectra were recorded on Perkin Elmer FT-IR spectrophotometer in KBr pellets and frequency is expressed in cm-1. The 1H NMR spectra were recorded on Brucker Ac 400 MHz nuclear magnetic resonance spectrophotometer in CDCl3 as a solvent using Tetramethyl Silan (TMS) as the internal standard. The chemical shifts have been expressed in δ-ppm scale, the melting points and other data were recorded in Table 2.

Preparation of beetroot extract

The fresh red beetroots were purchased from the local vegetable market and were washed thoroughly to remove the soil. Then peeled and chopped the beetroots into small slices using a knife, and weighed. About 100 g of red beet was mixed in a blender with 25 mL of distilled water to grind in a

mixer grinder. The ground mixture of beetroots was squeezed over the Whatman filter paper kept on the funnel, and the fresh extract in the beaker which appeared red color, aqueous liquid. This extract (pH=5.2) was used directly as a catalyst for the reaction.

General procedure for the synthesis of 2-aryl-1-arylmethyl-1H-benzimidazoles.

A mixture of o-phenylenediamine (10 mmol, 1.08 g), aromatic aldehyde (20 mmol, 2.12 g), and 4 mL beetroot extract 25 mL ethanol was stirred at room temperature for the appropriate time given in Table 2. After the given time (Table I) the reaction mixture turned into a 1precipitate, this precipitate was washed with water (3 × 5 mL), and again checked for TLC, and the single spot obtained in the Pet-Ether: ethyl acetate system (70:30). The product was dried under vacuum and further recrystallized from ethanol to afford the pure product.

Conclusion

In summary, we have effectively devised a straightforward, highly efficient, environmentally benign, and relatively more sustainable method for synthesizing benzimidazole derivatives. The use of beetroot extract as a natural catalyst has afforded an acidic catalytic environment conducive to the production of the desired compounds. The appealing aspects of this methodology include the ready accessibility of the catalyst, a relatively shorter reaction duration, and the ease of product separation, collectively underscoring its merits in the realm of benzimidazole derivative synthesis.

Acknowledgments

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