Heterocyclic Letters
Vol. 15| No.3|523-530|May-July|2025
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

AN EFFICIENT CERIUM SULPHATE PROMOTED SYNTHESIS OF BIOACTIVE BENZIMIDAZOLES

A.V. Nakhate[a] , S. V. Shinde[b]* , R. D. Suryawanshi[c] , J. S. Godse[d] , R. P. Pawar[c]*

[a]Department of Chemistry, Maharashtra Institute of Technology, Aurangabad – 431010 (Maharashtra), India.
[b]Department of Chemistry, Pratibha Niketan College, Nanded – 431604 (Maharashtra), India.
[c]Department of Chemistry, Shiv Chhatrapati College, Aurangabad – 431003 (Maharashtra), India.
[d]Department of Engineering Science, Hi-Tech Institute of Technology, MIDC Waluj, Aurangabad-431136 (Maharashtra), India.
Corresponding author E-mail: rppawar@yahoo.com, balashinde09@gmail.com.

ABSTRACT:
A new group of modified benzimidazoles were made from o-phenylenediamine and aromatic aldehyde in ethanol at high heat with cerium sulphate ($Ce(SO_4)_2$) acting as a helper. It provides several advantages over existing approaches. Medicine uses benzimidazoles due to their antituberculosis, antimalarial, antihistamine, antibacterial, antiviral, antidiabetic, anticancer, antifungal, anti-inflammatory, analgesic, and anti-HIV effects. Benzimidazole molecules may have medicinal uses. Because of its pharmacophore relevance and numerous biological functions, benzimidazole synthesis must be efficient. Effective synthesis is required to create novel medications that are resistant to existing chemotherapies. Modern benzimidazole synthesis uses nano-sized metal catalysts to combine o-phenylene diamines with aldehydes without using any solvents. Cerium (III) salts improve heterocyclic structure synthesis, which fascinates chemists. It was these salts that helped make nitrogen heterocycle bonds, oxygen analogues, seven-membered rings, and mixed heterocyclic features.

KEYWORDS: Aldehydes; antibacterial; benzimidazole; cerium sulphate; o-phenylenediamine.

INTRODUCTION

Benzimidazole and its derivatives have sparked widespread attention in medicinal chemistry[i]. The benzimidazole structure has sparked tremendous research during the past two decades. The discovery of this class of medicines emphasises a noteworthy case study in modern drug development, demonstrating the unpredictability of pharmacological effects caused by structural alterations to a prototype therapeutic molecule. Benzimidazoles containing organic moieties offer a wide range of practical uses. Finding that 5,6-dimethyl benzimidazole is a

part of vitamin B12 has sparked new interest in studying benzimidazole and imidazole structures[ii]. Nimodazole and its derivatives can have a lot of different pharmacological and chemical effects. For example, thiabendazole can kill parasites, albendazole can treat measles, and omeprazole can help with ulcers. Benzimidazole derivatives with different substituents, like CH_3, F, Cl, NO_2, OH, and NH_2 in ortho, meta, or para positions, have been linked to many biological and pharmaceutical activities, such as fighting cancer, viruses, bacteria, fungi, parasites, inflammation, histamine, blocking the proton pump, antioxidants, lowering blood pressure, stopping blood clots, and killing cells. Researchers test specific imidazole derivatives against coronaviruses (HCoV-NL63) using the 5epw protein as a chemical instrument[iii]. Different isoxazoline heterocycles, such as benzimidazole derivatives, showed better antibacterial and radical-scavenging abilities while lowering haemolysis. Certain benzimidazole compounds were thought to have strong antifungal properties, possibly acting as a basis for suppressing microorganisms[iv-v]. Researchers are testing substituted benzimidazole derivatives for their ability to block gastric H+/K+ ATPase by preventing acid secretion[vi]. Similar to cefotaxime, indol-steroid-cyclobuta-imidazole derivatives inhibit the growth of Staphylococcus aureus, Escherichia coli, and Streptococcus pneumoniae. Some other studies suggested that this chemical might interact with a number of amino acid residues on the surface of 5f1g, such as Ser 61, Leu 116, Gln 117, Asp 120, Tyr 147, Asn 149, Ser 209, Tyr 218, Thr 318, and Asn 342. This could make it a new type of antibacterial agent[vii]. Recently, benzimidazoles have been used as ligands for asymmetric catalysis to show catalytic activity in a lot of different chemical compounds[viii].

Researchers have proposed several methods for the synthesis of these compounds and their derivatives. The most common preparation method includes the condensation of 1,2-diaminobenzene with carboxylic acids. Nonetheless, it requires severe reaction conditions, such as polyphosphoric acid[ix], and temperatures ranging from 170˚C to 180˚C. A suggested method involves combining aromatic aldehyde with 1,2-diaminobenzene using several catalysts, such as Indion 190 resin[x], $BF_3.OEt_2$[xi], ceric ammonium nitrate[xii], and iodine[xiii]. These chemicals are used to study silica sulphuric acid[xiv], $In(OTf)_3$[xv], $SiO_2/ZnCl_2$[xvi], sodium hydrogen sulphate on silica[xvii], PEG[xviii], and $H_2O_2/Fe(NO_3)_3$[xix]. Recently, microwave irradiation (MW) with $Yb(OTf)_3$[xx], KSF clay [xxi], metal halide-supported alumina[xxii], and solid support[xxiii] have been used to create benzimidazoles without the need for any solvents. Nonetheless, many of these methods have significant limitations, such as the need for a strongly acidic environment, long reaction times, limited yields, laborious workup procedures, high chemical utilisation, and the use of hazardous reagents, solvents, and catalysts. A The basic issue in organic synthesis is to create a simple, efficient, and universal synthetic technique for physiologically active molecules that utilises readily available catalysts. Cerium (IV) salts have recently gained popularity due to their ease of product separation, catalyst renewal, and environmental friendliness when compared to other inorganic salts. These chemicals have been used by researchers to selectively remove tetrahydropyranyl, methoxymethyl, and benzyloxymethyl ethers[xxiv], make acetamidophenols[xxv], and change oximes into aldehydes and ketones[xxvi-xxvii]. There is currently no known use of $Ce(SO_4)_2 \cdot 4H_2O$ as a catalyst in the manufacture of benzimidazole derivatives[xxviii]. We show how to make benzimidazoles using cerium (IV) sulphate as a good catalyst (Scheme 2).

EXPERIMENTAL

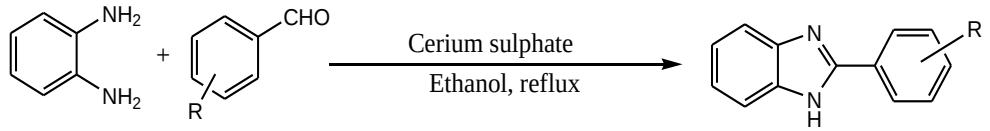
Materials and methods

The chemicals, reagents, and solvents were sourced from commercial suppliers including Aldrich, S.D. Fine Chemical, and Spectrochem, and were utilised without prior purification.

The 1H-NMR spectra were acquired using Varian FT-NMR spectrometers operating at 400 MHz, with tetramethyl silane (TMS) as the internal standard. Melting points of synthesised compounds were determined in open glass capillaries utilising the Melting Point Apparatus (Metler).

1.General Procedure for cerium sulphate catalyzed synthesis of substituted benzimidazole derivatives:

In a 50 mL round-bottom flask, o-phenylenediamine (1 mmol), aromatic aldehyde (1 mmol), and cerium sulphate (10 mol%) were combined in ethanol (5 mL) and subjected to reflux for the requisite duration. Thin-layer chromatography (TLC) utilising a solvent system of n-hexane and ethyl acetate at a ratio of 8:2 was employed to assess the reaction's progress. Upon completion of the reaction, the liquid was chilled, and 20 mL of ethyl acetate was added. The organic layer was rinsed with water and brine solution, desiccated over Na_2SO_4, and subsequently evaporated



1 2(a-q) 3(a-q)

1.1.Spectral Data

1.1.1. 2-(3-chlorophenyl)-1*H*-benzimidazole (3g).

^{1}H NMR (DMSO, δ in ppm): 7.18-7.22 (m, 2H, Ar), 7.52-7.59 (m, 4H), 8.11 (dd, 1H), 8.20 (s, 1H, Ar), 13.01 (s, 1H).

IR (KBr): 3458, 2917, 2850, 2659, 1698, 1573, 1470, 1393, 1317, 1212, 832, 746 cm^{-1}.

1.1.2.2-(4-methylphenyl)-1*H*-benzimidazole (3k).

^{1}H NMR (DMSO, δ in ppm):7.61 (m, 2H), 7.22 (dd, 2H), 7.19 (m, 2H), 6.95 (dd, 2H), 3.96 (brs, 1H), 2.37 (s, 3H).

IR (KBr):3144, 2946, 1661. 1571, 1466, 1396, 1310, 1213, 833, 748 cm^{-1}.

1.1.3.2-(4-methoxyphenyl)-1*H*-benzimidazole (3m).

^{1}H NMR (DMSO, δ in ppm):7.60 (m, 2H), 7.16 (dd, 2H), 7.07 (m, 2H), 6.72 (dd, 2H), 4.13 (brs, 1H), 3.55 (s, 3H).

IR (KBr):3149, 2947, 1620. 1562, 1473, 1389, 1307, 1214, 833, 749 cm^{-1}.

RESULT AND DISCUSSION:

To determine the most effective reaction conditions, numerous solvents and mole ratios of cerium sulphate were evaluated. As indicated in Table 1, the study evaluated the model reaction of o-phenylenediamine and 4-chlorobenzaldehyde reacting with 10 mol% cerium sulphate. Different solvents provide varying yields of products. Ethanol was shown to be the best solvent for the condensation reaction, exceeding dichloromethane, methanol, tetrahydrofuran, and acetonitrile in respect to speed, yield, and toxicity. We adapted the cerium sulphate mole ratios in ethanol at reflux, as indicated in Table 2, to find the precise mol% necessary for the reaction. We produced the highest yields with 10 mol% cerium sulphate. Table 3 shows the electrostatic effects of several substituted aldehydes. It was discovered that aldehydes containing both electron-donating and electron-removing substituents produced high quantities of the required benzimidazoles. All of the products have been validated by comparing results to actual samples (1H-NMR, IR, and mass spectroscopy).

Table 1. Effect of Solvent in the synthesis of 2-(4-chlorophenyl) benzimidazole at reflux condition.

Entry	**Solvent**	**Time (min)**	**Yield (%)[a]**
1	CH_2Cl_2	120	49
2	CH_3OH	90	67
3	CH_3CH_2OH	60	94
4	THF	110	61
5	CH_3CN	90	79

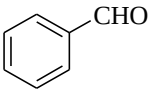
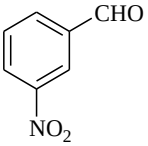
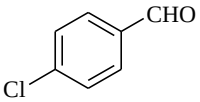
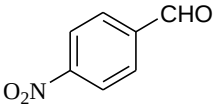
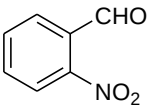
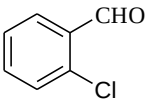
a -All are isolated yields

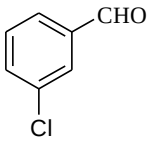
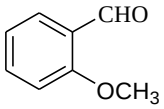
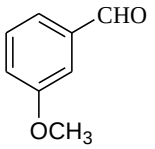
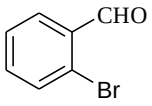
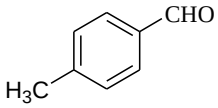
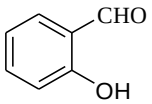
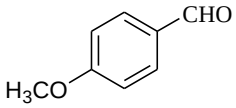
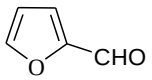
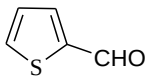
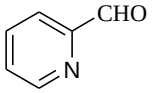
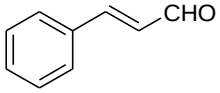
Table 2. Various mole ratios of cerium sulphate for the synthesis of 2-(4-chlorophenyl) benzimidazole.

Entry	**Cerium sulphate (mol%)**	**Time (min)**	**Yield (%)**
1	0	60	9
2	5	60	62
3	10	60	94
4	15	60	94
5	20	60	92

a - All are isolated yields.

Table 3. Synthesis of benzimidazoles from O-Phenylenediamine and aromatic aldehydes using cerium sulphate as catalyst in ethanol at reflux condition.

Compound	**Aldehyde**	**Time (min)**	**Yield (%)[a]**	**M.P. (°C)**
3a		70	89	292-293
3b		90	79	204-205
3c		60	94	288-289
3d		60	91	>300
3e		60	92	264-265
3f		75	93	234

3g		75	85	238
3h		55	90	179-180
3i		70	87	205-206
3j		60	86	246
3k		65	87	264-265
3l		70	81	239-240
3m		60	82	224-225
3n		60	78	284-285
3o		65	75	>300
3p		70	85	214-216
3q		75	84	199-201

[a]Yields refer to isolated products.

CONCLUSION

Finally, it was discovered that cerium sulphate works well as a catalyst to make benzimidazole derivatives from aromatic aldehydes and o-phenylenediamine. The use of cerium sulphate as an inexpensive, readily available catalyst makes this protocol practical, environmentally friendly, and economically attractive. The simple workup procedure, higher

product yields, and nontoxic nature of the catalyst are other advantages of the present method.

ACKNOWLEDGEMENT

We sincerely thank to the Principal of Maharashtra Institute of Technology, Aurangabad, Maharashtra, India, for their invaluable support and the use of their facilities, which enabled us to conduct this research work.

CONFLICT OF INTERESTS

The authors confirm no conflicts of interest.

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Received on March 30, 2025.