One-pot synthesis of a new imidazole-5-carboxylic acid derivative via heterocyclization reaction

Abstract
In the current study, a new benzimidazole molecule 2-(3-bromo-4-hydroxy-5-methoxyphenyl)-1-methyl-1H-benzod|imidazole-5-carboxylic acid was synthesized via the hetero cyclization of ethyl 4-(methylamino)-3-nitrobenzoate with 5-bromo-4-hydroxy-3-methoxybenzaldehyde in the presence of sodium dithionite in DMSO followed by the base hydrolysis. The synthesised compound was characterized using IR, NMR (¹H and ¹³C) and Mass techniques.

Keywords: heterocyclization, benzimidazole, Na₂SO₄

Introduction
From few decades, fused heterocyclic chemistry has occupied a prominent place in Medicinal Chemistry. Moreover, fused imidazole systems have attracted the researcher’s interest due to their natural occurrence and significant medicinal applications.¹–³ Additionally, the benzimidazole derivatives are the bioisosters of natural nucleotides, which can interact easily with the macromolecules (proteins, enzymes and receptors) of the biological system, has made the benzimidazole and its derivatives as the privileged pharmacophore in drug discovery process.³ They are able to produce anti-inflammatory,⁴ antibacterial,⁴ anti cancer,⁴ analgesic,⁵ antiviral⁶ and anticonvulsant⁷ activity, etc.. Further benzimidazoles also can act as inhibitors for α-Glucosidase,⁸ Cyclooxygenase,⁹ Poly (ADP-ribose) polymerase¹⁰ and lysophosphatidic acid acyltransferase-β.¹¹ Interestingly, benzimidazoles are also being incorporated into various commercially available drugs.¹²–¹⁴ This vast applicability and usefulness of the fused imidazole nucleus inspired us to design and develop the target molecule.

Further, harsh and vigorous reaction conditions as well as tedious work up procedures¹⁵–²⁰ of the classical methods which are available so far for the synthesis of benzimidazole derivatives necessitate the simple one-pot reductive cyclization method. Furthermore, several new one-pot methods which were reported in recent years utilises either the costly reagents or hazardous reaction conditions.²¹–²³ Moreover, Sodium dithionite (Na₂SO₄) a protein reducing agent was able to reduce several functional groups like aldehydes, ketones, conjugated ketones and nitro group. It was also been reported as an agent during one-pot synthesis of the benzimidazole and its derivatives.²⁴–²⁶ Thus, advantage of one-pot synthesis to conduct the reaction in more sustainable way by minimizing the use of reagents and solvents as well as with the reduction in reaction time has motivated us to utilize the same in our research.

Results and discussion
Synthetic strategy for the title compound is as depicted in the Figure 1. A new benzimidazole derivative (2) was synthesized by reacting ethyl 4-(methylamino)-3-nitrobenzoate (1) with 3-bromo-4-hydroxy-5-methoxybenzaldehyde in the presence of three equivalence of Na₂SO₄ in DMSO at 90°C.¹¹ Base hydrolysis of the compound 2 yielded the title compound (3). The synthesis of ethyl 4-(methylamino)-3-nitrobenzoate (1) was explained in our earlier report.¹⁹

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Formation of the target molecule was confirmed by the IR (ATR) data. A broad band near 3394cm⁻¹ justified the presence of -OH group. A characteristic stretching for acid carbonyl was observed at 1701cm⁻¹. Further, the stretching frequencies for the aromatic and aliphatic hydrogen were observed at 3065, 2906 and 2870cm⁻¹ respectively. An absorption band at 1624cm⁻¹ confirms the presence of a bromine atom in the molecule (Supplementary Figure 1).

The ¹H NMR spectrum also evidenced the formation of the title compound. A characteristic singlet at δ3.88ppm was assigned to the –N-methyl protons. Additionally, the spectrum exhibited a doublet for C₂-H of 3-Br-4-Oh-5-OMe-C₆H₅ at δ7.40ppm (J=1.6Hz) and a proton on the 6° carbon of the 3-Br-4-Oh-5-OMe-C₆H₅ ring.
exhibited a doublet at δ7.56ppm with coupling constant 1.6Hz, due to meta coupling. The protons on the 7th and 4th carbon atom of the benzimidazole ring displayed two doublets at δ7.66 (J=8.2Hz) and 8.21ppm (J=1.2Hz) correspondingly. A doublet of doublet at δ7.89ppm (J=8.8 and 1.6Hz) was accredited to the proton on the 6th carbon atom of the benzimidazole ring. A characteristic broad singlet was appeared at δ10.12ppm for the hydroxyl group on the 4th position of the 3-Br-4-OH-5-OMe-C₆H₂ ring. An acid proton has resonated to give a broad singlet at δ12.79ppm (Supplementary Figure 2).

The target molecule is also confirmed by its ¹³C NMR, which has given a characteristic carbonyl signal at δ168.3ppm. Further, spectrum also exhibited signal at δ154.4ppm, which corresponds to -C=N- of the benzimidazole ring. The 4th carbon of the 3-Br-4-OH-5-OMe-C₆H₂ ring resonated at δ148.7ppm and the 5th carbon of the same, which is having methoxy substitution, was assigned at δ146.1ppm. The signals at δ142.2 and 140.1ppm corresponds to the two =C-N- carbon of the benzimidazole ring. The peaks at δ125.8, 125.1, 124.0, 121.8, 121.1, 112.7, 111.8, 109.7ppm was assigned for the remaining aromatic carbons. A methoxy and -N-CH₃ carbons were resonated at δ56.9 and 32.4ppm, respectively. Molecular weight of the compound was in agreement with the data obtained from ESI-MS spectrum with peaks at (m/z) 376.95 (M⁺+H), 378.90 [(M⁺+H)+2]. Melting point of the compound was 260°C (Supplementary Figure 3).

**Materials and methods**

Laboratory grade chemicals were procured and desired molecules were synthesized with the aid of standard techniques. Melting point of the target molecule was determined using the open capillary method. The novel synthesized molecules were established and characterized with the help of Thin-layer chromatography (TLC), FTIR spectra were recorded on a Shimadzu ATR Spectrometer, ¹H and ¹³C NMR data from Bruker DRX-300 and 400MHz NMR spectrometer and Bruker DRX-75 and 100MHz NMR) in (DMSO)-d₆ respectively (Tetramethylsilane (TMS-an internal standard)) and ESI-MS spectra by Shimadzu LCMS 2010 spectrometer (Supplementary Figure 4).

**Synthesis of the title compound**

A reaction mixture containing ethyl 4-(methylamino)-3-nitrobenzoate (1) (0.006mol), 3-bromo-4-hydroxy-5-methoxybenzaldehyde (0.006 mol), sodium dithionate (0.024mol) in DMSO was refluxed with stirring at 90°C for 3h. The completion of reaction was monitored by Thin Layer Chromatography (TLC). After completion, the reaction mass was cool to room temperature and poured on crushed ice. The solid formed was collected, filtered and dried, which afforded the compound (2). The hydrolysis of compound (2) with 15mL (33%) NaOH in ethanol yielded the required molecule (3) (Figure 2).
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Conclusion

In this present research, a novel benzimidazole acid was easily synthesized with the help of “one-pot” method, followed by the base hydrolysis. The compound under interest was characterized and confirmed with the help of analytical and spectral techniques.

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Conflict of interest

All the authors declare that they have no Conflict of interest.

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