Organic base catalysed synthesis of benzimidazole

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Abstract: A mild and effective protocol for benzimidazole synthesis from o-phenylenediamine and aromatic aldehydes catalysed by DBU is described. The synthesized compounds find application in the pharmaceutical, dye and material science fields. Mild reaction conditions, low amount of chemicals and use of metal-free catalysts are the highlights of the reaction.

1. INTRODUCTION

Benzene ring when fused with an imidazole unit produces an important class of heterocyclic aromatic compound called as benzimidazoles. The ever-demanding increase of benzimidazole motifs owing to its wide spread applications in pharmaceuticals [1], photochemistry [2] and as organic solderability preservative (OSP) [3]. It was first prepared by Hoebrecker in 1872 from 2-nitro-4-methylacetanilide by reduction followed by dehydration [4]. Since then, various reports came out describing the synthesis of benzimidazole[5]. Among these, majority of them achieved the target molecule by the condensation followed by cyclisation between o-phenylenediamine and aldehydes and/or carboxylic acids [6]. And there are only a few reports on the use of organic catalysts for the synthesis of benzimidazoles [7].

1,8-Diazabicyclo[5.4.0]undec-7-ene, well known as DBU is a base and used as a catalyst in several transformations [8]. Because of its non-nucleophilicity, low cost, homogeneity and recyclability, it has been found importance in a wide array of reactions. As our ongoing research interests includes the synthesis of heterocycles [9] and construction of C-heteroatom bonds [10], we were quite curious to see whether DBU can be used as a green catalyst for benzimidazole synthesis. Our efforts towards this led to the facile synthesis of benzimidazoles from o-phenylenediamine and aldehydes and are described here.

2. RESULTS AND DISCUSSIONS

2.1. Synthesis of 2-phenyl-1H-benzimidazole 3a

As an initial experiment, o-phenylenediamine 1 was treated with benzaldehyde 2a and 50 mol% DBU at room temperature using dichloromethanesolvent. The reaction was found to be complete within 10 hours. The solvent was rotavapoured off and was then column chromatographed using silica gel and mixtures of hexane and ethyl acetate. The benzimidazole 3a was found as a yellow viscous liquid in 84% yield (Figure 1).
The formation of 3a was established by spectral data. The $^1$H NMR spectrum showed a singlet at $\delta$ 5.36 corresponding to NH proton (Figure 2). The aromatic protons were observed between $\delta$ 7.02 – 7.80 as multiplets. The $^{13}$C NMR spectrum displayed a peak at $\delta$ 153.69 and was assigned to the carbon between two nitrogen atoms of the imidazole ring (Figure 3). The mass spectral data showed an m/z value as 193 which also matched with the calculated value (Figure 4). From these spectral evidences, the compound 3a was proved to be 2-phenyl-1H-benzimidazole.
2.2. Mechanistic postulate for the formation of 3a
Mechanistic pathway for the formation of 3a can be invoked along the following lines (Figure 5). Benzaldehyde 2a initially forms an electrophilic imine species III by reaction with one of the amine group of 1, followed by the intra-molecular attack by the other NH₂ group ortho to the former to get IV. The abstraction of H⁺ ion from the NH₂⁺ group of IV by DBU gives substituted benzimidazole 3a.

![Mechanistic rationale](image)

**Figure 5. Mechanistic rationale**

2.3. Generality of the reaction
The generality of the above reaction was tested with 1 and various aromatic aldehydes and in all cases, the corresponding benzimidazole derivatives were formed in good yields (Table 1). Electron-withdrawing or electron-donating substituents present on the aromatic ring makes no difference to the product yield.

| Entry | Aldehyde | Product | Yield (%) |
|-------|----------|---------|-----------|
| 1     | ![2b](image) | ![3b](image) | 82 |
| 2     | ![2e](image) | ![3e](image) | 84 |
3. EXPERIMENTAL SECTION

3.1. General methodology for the synthesis and isolation of benzimidazoles 3a – 3e
To a solution of o-phenylenediamine 1 (1 mmol) and aldehydes 2a – 2e (1.5 mmol) dissolved in 10 mL of DCM solvent, 50 mol% of DBU was added at room temperature and stirring was continued for 10 hours. Reaction progress was monitored using TLC on alumina sheets using 1:9 ethyl acetate-hexane mixture and the compounds were identified using UV light. The solvent was rotavapoured off after the completion of the reaction and the remainder was then column chromatographed using silica gel (100-200 mesh) and mixtures of EtOAc-hexane to yield 3a – 3e.

3.2. Spectral data of compounds 3a – 3e
2-Phenyl-1H-benzimidazole 3a: \(^1^H\) NMR (500MHz, CDCl\(_3\)): δ 5.36, 7.01, 7.11, 7.17, 7.25, 7.36, 7.38, 7.61, 7.78, 7.80.; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): δ119.4, 122.2, 122.5, 125.4, 127.3, 128.2, 128.5, 128.7, 129.5, 135.5, 135.9, 142.6, 153.9.; LC-MS: m/z [M-H]\(^+\) Calculated for C\(_{13}\)H\(_{10}\)N\(_2\): 193, found: 193.

2-(4-Methoxy-phenyl)-1H-benzimidazole 3b: \(^1^H\) NMR (500MHz, CDCl\(_3\)): δ 3.78, 5.23, 6.80, 6.83, 6.85, 6.93, 6.95, 7.43, 7.65, 7.78, 7.96, 8.05.; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): δ54.4, 113.2, 120.3, 127.9, 128.5, 130.2, 130.9, 131.1, 162.8, 164.0.; HRMS: m/z [M-H]\(^+\) Calculated for C\(_{14}\)H\(_{12}\)N\(_2\)O: 223, found: 223.

2-(4-Nitro-phenyl)-1H-benzimidazole 3c: \(^1^H\) NMR (500 MHz, CDCl\(_3\)): δ 5.31, 8.07, 8.09, 8.38, 8.40.; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): δ123.8, 130.0, 139.5, 150.6.; HRMS: m/z [M-H]\(^+\) Calculated for C\(_{13}\)H\(_9\)N\(_3\)O\(_2\): 238, found: 238.

2-(4-Vinyl-phenyl)-1H-benzimidazole 3d: \(^1^H\) NMR (500 MHz, CDCl\(_3\)): δ 5.16, 6.98, 7.02, 7.12, 7.14, 7.15, 7.17, 7.19, 7.22, 7.24, 7.26, 7.28.; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): δ 118.2, 121.6, 122.0, 125.3, 126.1, 126.9, 127.4, 127.6, 127.9, 131.2, 134.1, 134.5, 134.7, 136.4, 141.9, 149.7.; HRMS: m/z [M+H]\(^+\) Calculated for C\(_{15}\)H\(_{12}\)N\(_2\): 220, found: 220.

2-(Pyridin-4-yl)-1H-benzimidazole 3e: \(^1^H\) NMR (500 MHz, CDCl\(_3\)): δ 5.31, 7.22, 7.25, 7.32, 7.37, 7.79, 8.12, 8.14, 8.79.; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): δ121.5, 122.4, 123.6, 128.9, 130.9, 136.2, 140.9, 143.7, 145.4, 149.5, 149.8, 150.2.; HRMS: m/z [M+H]\(^+\) Calculated for C\(_{12}\)H\(_9\)N\(_3\): 196, found: 196.

4. CONCLUSION
A mild, novel and modified way designed for the construction of substituted benzimidazole molecules from o-phenylenediamine and different aromatic aldehydes using DBU as an organic base have been reported here. The products were obtained in good yields in simple experimental conditions. Further studies towards their medicinal and material properties are underway in our laboratory.
REFERENCES

[1]. For some selected examples, see: (a) Garudachari B, Satyanarayana M N, Thippeswamy B, Shivakumar C K, Shivananda K N, Hegde G and Isloor A M 2012 *Eur. J. Med. Chem.* **54** 900 (b) Mukhopadhyay C, Ghosh S, Sengupta S and De S 2011 *RSC Adv.* **1** 1033 (c) Bhattacharya Sand Chaudhuri P 2008 *Curr. Med. Chem.* **15** 1762 (d) Aghatabay N M, Somer M, Senel M, DulgerB and Gucin F 2007 *Eur. J. Med. Chem.* **42** 1069

[2]. Manna S K, Das T and Samanta S 2019 *ChemistrySelect* **4** 8781

[3]. Tong K H, Ku M T, Hsu K L, Tang Q, Chan C Y and Yee K W 2013 *Int. Microsystems, Packaging, Assembly and Circuits Technology Conf.* (IMPACT) **8th** 22-25 October Taipei

[4]. Hoebrecker F 1872 *Ber. Dtsch. Chem. Ges.* **5** 920

[5]. Wright J B 1951 *Chem. Rev.* **48** 397

[6]. Alaqeel S I 2017 *J. Saudi Chem. Soc.* **21** 229

[7]. (a) Niwadange S N, Mahurkar S S and Kagne R P 2019 *Int. J. Res. Anal. Rev.* **6** 485 (b) Varala R, Nasreen A, Enugala R and Adapa S R 2007 *Tetrahedron Lett.* **48** 69

[8]. Nand B, Khanna G, Chaudhary A, Lumb A and Khurana J M 2015 *Curr. Org. Chem.* **19** 790 and references sited therein

[9]. Sivan A, Deepthi A and Nandialath V 2011 *Synthesis* **15** 2466

[10]. Sivan A and Deepthi A 2014 *Tetrahedron Lett.* **55** 1890