A mild and efficient synthesis of Benzimidazole by using lead peroxide under solvent free condition

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ABSTRACT

Benzimidazoles derivatives have been synthesized using a catalytic amount of Zinc acetate at room temperature with excellent yields. The remarkable selectivity under mild, neutral and solvent free conditions, commercially available inexpensive catalyst is an attractive feature of this method.

Key words: benzimidazoles, Zinc acetate, solvent free

INTRODUCTION

The development of simple, efficient, environmentally-benign and economically viable chemical processes or methodologies for widely used organic compounds is in great demand¹. Benzimidazole are present in various bioactive compounds possessing antiviral, antihypertension and anticancer properties²³. Compounds possessing the benzimidazole moiety express significant activity against several viruses such as HIV⁴, Herpes(HSV-1)⁵ and influenza⁶. Bis-benzimidazole is DNA-minor groove binding agents possessing anti-tumour activity⁷.

The condensation of o-phenylenediamine with carbonyl compounds in the presence of strong acids such as polyphosphoric acid or mineral acids⁸ and other reagents such as I₂/KI/K₂CO₃⁹, N-halosuccinamide (X=Cl, Br, I)¹⁰, Yb(OTf)₃¹¹, PEG-100¹², (NH₄)H₂PW₁₂O₄₀¹³ and palladium as well as microwave irradiation¹⁴ and solid phase reactions¹⁵ are reported in literature. However, many of the synthetic protocols reported so far suffer from disadvantages, such as a requirement for anhydrous conditions, use of organic solvents, harsh reaction conditions, prolonged reaction
times, expensive reagents and low to moderate yields. Almost all the reported methods make use of an acid catalyst, giving rise to tedious working procedures. Therefore, the development of a cost-effective, safe and environmentally friendly reagent is still needed.

Scheme – 1

In this communication, we report a simple and efficient method for synthesis of benzimidazole derivatives using zinc acetate as a catalyst under mild conditions.

MATERIALS AND METHODS

All reagents and solvents for synthesizes were commercially available and used without further purifications.

General Procedure
A mixture of o-phenyldiamine (2 m mol), p-nitrobenzaldehyde (2 m mol) and Zinc acetate (0.1m mol) was stirred magnetically at room temperature and the progress of the reaction was monitored by thin-layer chromatography (TLC). The reaction mixture was filtered and extracted with ethyl acetates (3x30ml). The combined ethyl acetates extracts were dried with Na$_2$SO$_4$ and concentrated under reduced pressure. In all the cases, the product obtained after the usual work up gave satisfactory spectral data.

RESULTS AND DISCUSSION

A wide variety of compounds were applied under optimal reaction conditions to prepare benzimidazoles. The results are summarized in Table-2. Variety of aldehydes, aliphatic, heterocyclic and aromatic having both electron- donating and electrone withdrawing groups were employed for benzimidazole formation. In all cases, the yields were excellent. (Table-2, entries 1-18). Four different types of o-phenylenediamines were employed and all of them reacted smoothly under the reaction conditions. The aliphatic aldehydes which were also reacted under similar conditions gave considerable yields (Table-2, entries 12-13). The spectral data of products were confirmed by IR and NMR.

**Entry 2:** IR (KBr): 840, 1342, 1525, 1619, 2987, 3474 cm$^{-1}$; H$^1$NMR (300MHz, CDCl$_3$): $\delta$ = 6.9 (m, 2H, J=7.2Hz), 7.3 (d, 2H, J=7.2Hz) ; 8.2 (d, 2H, J=7.6Hz); 8.4((d, 2H, J=7.8Hz); 8.6 (s, br, 1H, NH);

**Entry 4:** IR (KBr): 833, 1035, 1125, 1342, 1536, 1628, 2988, 3478 cm$^{-1}$; H$^1$NMR (300MHz, DMSO): $\delta$ = 3.25 (s, 3H), 7.52( s, broad, 2H), 7.68 (d, 2H, J=7.6Hz, 2H) ; 7.93 (m, 2H); 8.12(d, J=7.6Hz, 2H); 11.92 (s, 1H)
Entry 5: IR (KBr): 837, 925, 1045, 1109, 1355, 1544, 1629, 2988, 3479 cm⁻¹; H¹NMR (300MHz, DMSO): δ = 7.2 (m, 2H), 7.55 (d, broad, J=7.5Hz, 1H); 7.62 (d, broad, J=7.5Hz, 1H); 8.21(d, J=6.8Hz, 1H); 8.55(d, J=7.8Hz, 1H); 9.12 (s, 1H), 12.5 (s, 1H)

Entry 9: IR (KBr): 732, 815, 1036, 1537, 1627, 2929, 3329, 3478 cm⁻¹; H¹NMR (300MHz, DMSO): δ = 5.2 (s, 1H), 7.3 (s, broad, 2H), 7.5 (d, 2H, J=7.6Hz, 2H); 7.8 (m, 2H); 8.2 (d, J=7.6Hz, 2H); 12.1 (s, 1H)

Table- 2. Synthesis of benzimidazole in presence of Zn(OAc)₂ at room temperature

<table>
<thead>
<tr>
<th>Entry</th>
<th>1,2-Diamine</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Time(min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><img src="image1" alt="1,2-Diamine" /></td>
<td><img src="image2" alt="Aldehyde" /></td>
<td><img src="image3" alt="Product" /></td>
<td>10min</td>
<td>92</td>
</tr>
<tr>
<td>2.</td>
<td><img src="image4" alt="1,2-Diamine" /></td>
<td><img src="image5" alt="Aldehyde" /></td>
<td><img src="image6" alt="Product" /></td>
<td>10min</td>
<td>94</td>
</tr>
<tr>
<td>3.</td>
<td><img src="image7" alt="1,2-Diamine" /></td>
<td><img src="image8" alt="Aldehyde" /></td>
<td><img src="image9" alt="Product" /></td>
<td>10min</td>
<td>92</td>
</tr>
<tr>
<td>4.</td>
<td><img src="image10" alt="1,2-Diamine" /></td>
<td><img src="image11" alt="Aldehyde" /></td>
<td><img src="image12" alt="Product" /></td>
<td>15min</td>
<td>90</td>
</tr>
<tr>
<td>5.</td>
<td><img src="image13" alt="1,2-Diamine" /></td>
<td><img src="image14" alt="Aldehyde" /></td>
<td><img src="image15" alt="Product" /></td>
<td>20min</td>
<td>91</td>
</tr>
<tr>
<td>6.</td>
<td><img src="image16" alt="1,2-Diamine" /></td>
<td><img src="image17" alt="Aldehyde" /></td>
<td><img src="image18" alt="Product" /></td>
<td>15min</td>
<td>90</td>
</tr>
<tr>
<td>7.</td>
<td><img src="image19" alt="1,2-Diamine" /></td>
<td><img src="image20" alt="Aldehyde" /></td>
<td><img src="image21" alt="Product" /></td>
<td>10min</td>
<td>90</td>
</tr>
<tr>
<td>8.</td>
<td><img src="image22" alt="1,2-Diamine" /></td>
<td><img src="image23" alt="Aldehyde" /></td>
<td><img src="image24" alt="Product" /></td>
<td>20min</td>
<td>91</td>
</tr>
</tbody>
</table>
9. \(\text{NH}_2\text{NH}_2\) \(\text{O}\text{H} \quad \text{N} \quad \text{OH} \quad \text{NH}_2\text{NH}_2\) 25min 85

10. \(\text{NH}_2\text{NH}_2\) \(\text{O} \quad \text{H} \quad \text{OMe} \quad \text{OMe} \quad \text{NH}_2\text{NH}_2\) 40min 87

11. \(\text{NH}_2\text{NH}_2\) \(\text{O} \quad \text{H} \quad \text{NMe}_2 \quad \text{NMe}_2 \quad \text{NH}_2\text{NH}_2\) 40min 91

12. \(\text{NH}_2\text{NH}_2\) \(\text{O} \quad \text{H} \quad \text{N} \quad \text{N} \quad \text{NH}_2\text{NH}_2\) 40min 84

13. \(\text{NH}_2\text{NH}_2\) \(\text{O} \quad \text{H} \quad \text{N} \quad \text{N} \quad \text{NH}_2\text{NH}_2\) 50min 87

14. \(\text{NH}_2\text{NH}_2\) \(\text{O} \quad \text{H} \quad \text{N} \quad \text{N} \quad \text{NH}_2\text{NH}_2\) 50min 89

15. \(\text{NH}_2\text{NH}_2\) \(\text{O} \quad \text{H} \quad \text{N} \quad \text{N} \quad \text{NH}_2\text{NH}_2\) 10min 93

16. \(\text{NH}_2\text{NH}_2\) \(\text{O} \quad \text{H} \quad \text{N} \quad \text{N} \quad \text{NH}_2\text{NH}_2\) 10min 92

17. \(\text{NH}_2\text{NH}_2\) \(\text{O} \quad \text{H} \quad \text{N} \quad \text{N} \quad \text{NH}_2\text{NH}_2\) 10min 94

18. \(\text{NH}_2\text{NH}_2\) \(\text{O} \quad \text{H} \quad \text{N} \quad \text{N} \quad \text{NH}_2\text{NH}_2\) 20min 92

\(^a\) The substrate was treated with benzaldehyde (2 mmol) by using 0.1 mmol of \(\text{Zn(OAc)}_2\) in solvent free conditions and at room temperature.

\(^b\) All products were identified by their IR and \(^1\)H NMR spectra

\(^c\) Isolated yields.
CONCLUSIONS

In conclusion, this manuscript describes a method in which Zn(OAc)$_2$ is a highly efficient catalyst for the synthesis of benzimidazole derivatives. The advantages include low cost, ease of catalyst handling, mild reaction conditions and reactions carried out at room temperature with excellent yields.

REFERENCES

[12] Chhanda Mukhopadhyay ; Pradip Kumar Tapaswi.. *Tetrahedron lett.* **2008**, *49*, 6237