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Research Article

A MILD AND EFFICIENT SYNTHESIS OF BENZIMIDAZOLE BY USING ZINC SULPHATE SOLVENT FREE CONDITION

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ABSTRACT

The ring system in which a benzene ring is fused to the 4,5-positions of imidazole is designated as benzimidazoles. Benzimidazole derivatives have been synthesized using a catalytic amount of Zinc sulphate at room temperature by using mortar and pestle with excellent yields. The remarkable selectivity under mild, neutral and solvent free conditions, commercially available inexpensive catalyst is an attractive feature of this method.

Keywords: Benzimidazoles, Zinc Acetate, Solvent Free, Sonication.

INTRODUCTION

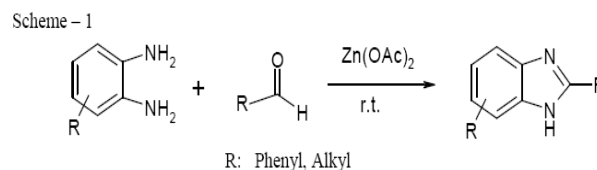
Various benzimidazole derivatives are well known to possess pharmacological activities such as human and veterinary anti-helminthic¹, anti-ulcer²⁻⁴, cardiotoxic⁵, antihypertensive⁶, etc. The literature precedence revealed that the substitutions at the 1, 2 and 5 positions of the benzimidazole moiety are crucial for exhibiting wide range of pharmacological activities. Specifically, 2-substituted analogs of benzimidazole are known to be potent biologically active compounds⁷⁻⁹. Introduction of acetylene groups (integral part of several pharmacophores) in the 2-substituted benzimidazole have shown interesting biological activities e.g. alkynyl benzimidazoles as modulators of metabotropic glutamate receptors¹⁰. Tazarotene¹¹ (tazorac® and zorac®) with a phenylacetylene substructure exhibits antiacne and antipsoriatic activities. Efavirenz¹² (stocrin®) possessing an acetylene substructure exhibits anti HIV activity.

Traditionally, the synthesis of benzimidazoles involves the condensation of *o*-phenylenediamine with aldehydes¹¹⁻¹³, and carboxylic acids or their derivatives (nitriles, amidates, orthoesters) under harsh dehydrating conditions.¹⁴ Benzimidazoles have also been prepared on a solid-phase to provide a combinatorial approach^{15,16}. The most popular strategies for their synthesis utilize *o*-nitroanilines as intermediates or resort to direct Nalkylation of an unsubstituted benzimidazol¹⁷. A number of synthetic methods that involve intermediate *o*-nitroanilines have evolved to include the synthesis of benzimidazoles on solid supports¹⁸. The condensation of *o*-phenylenediamine with carbonyl compounds in the presence of strong acids such as

polyphosphoric acid or mineral acids and other reagents such as I₂/KI/K₂CO₃, Nhalosuccinamide (X=Cl, Br, I), Yb(OTf)₃, PEG-100, (NH₄)H₂PW₁₂O₄₀ and palladium as well as microwave irradiation and solid phase reactions 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^{19,20}.

We report synthesis of benzimidazole in solvent free condition by using sonicator technique.

Reaction Scheme



MATERIALS AND METHODS

All reagents and solvents for syntheses were commercially available and used without further purifications. Melting points are uncorrected and were determined in open capillary tubes in a paraffin bath. TLC was performed on silica gel-G and visualization was done using iodine or UV-light. IR

spectra were recorded with a Perkin-Elmer 1000 instrument in the KBr phase. ¹H-NMR spectra were obtained on a VARIAN 200MHz instrument.

Procedure:

A mixture of o-phenyldiamine (2 m mol), p-nitrobenzaldehyde (2 m mol) and Zinc acetate (0.1m mol) was stirred in mortar and pestle and the progress of the reaction was monitored by

thin-layer chromatography (TLC). The reaction mixture was filtered and extracted with ether (3x30ml). The combined ethyl acetates extracts were dried with Na₂SO₄ and concentrated under reduced pressure. In all the cases, the product obtained after the usual work up gave satisfactory spectral data.

Result table

Entry I	Aldehyde	Time (min)	Yields	M.P. °C
1	Benzaldehyde	7	90	289
2	Anisaldehyde	9	95	234
3	4-methyl benzaldehyde	9	94	224
4	4-chlorobenzaldehyde	7	95	291
5	4-fluorobenzaldehyde	7	97	245
6	3-bromobenzaldehyde	7	96	265
7	Furan-2-carbaldehyde	7	95	285
8	Cinnamaldehyde	12g	95	199-201
9	3-nitrobenzaldehyde	10	90	309-310

RESULTS AND DISCUSSION

A wide variety of compounds were applied under optimal reaction conditions to prepare benzimidazoles. The results are summarized in **Table-1**. Variety of aldehydes, aliphatic, heterocyclic and aromatic having both electron- donating and electron withdrawing groups were employed for benzimidazole formation. Similar conditions gave considerable yields, the spectral data of products were confirmed by IR and NMR. This is better method for synthesis of benzimidazole derivatives in short time.

Spectral analysis

P-nitro bezaldehyde : IR (KBr): 840, 1342, 1525, 1619, 2987, 3474 cm⁻¹; ¹H1NMR (300MHz, CDCl₃): δ =6.9 (m, 2H, J=7.2Hz), 7.3 (d, 2H, J=7.2Hz) ; 8.2 (d, 2H, J=7.2Hz); 8.4((d, 2H, J=7.8Hz); 8.6 (s, br, 1H, NH);

Anisaldehyde Entry 4: IR (KBr): 833, 1035, 1125, 1342, 1536, 1628, 2988, 3478 cm⁻¹; ¹H1NMR (300MHz, DMSO): δ = 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).

CONCLUSION

In conclusion, this manuscript describes a method in which Zn(OAc) using pestle and mortar 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.

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