

An Efficient and Green Protocol for The Synthesis Of 2-Arylbenzimidazoles Using Malic Acid as a Homogeneous and Reusable Catalyst

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ABSTRACT

A straightforward convenient and eco-friendly methodology is developed for the synthesis of substituted 2-arylbenzimidazoles by using malic acid as a catalyst in aqueous medium. O-phenylenediamines and aromatic aldehydes condense together to give benzimidazole derivatives. This methodology uses easily available non-toxic naturally occurring malic acid as a catalyst. The reaction is very simple, convenient and straightforward and gives moderate to high yields of 2-arylbenzimidazoles.

Keywords: O-Phenylenediamine, Benzimidazole, Aldehyde, Malic Acid.

I. INTRODUCTION

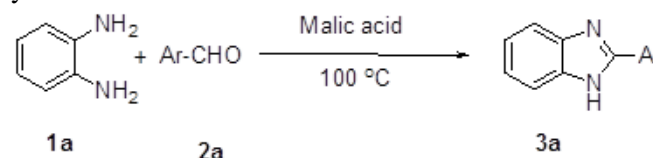
Benzimidazole and benzthiazole are important structural motifs of biologically important compounds. These heterocycles are well known to exhibit range of pharmacological activities such as antibacterial, antiulcers, antihypertensives, antivirals, antifungals, anticancers and antihistaminics [1]. Therefore their synthesis is an important part of heterocyclic chemistry.

There are many methods reported in literature for the synthesis of benzimidazole derivatives. The condensation of 1,2-phenylenediamines with carboxylic acids or their derivatives is a most common method, but it needs harsh conditions like polyphosphoric acid [2] at 170-180 °C, use of different catalysts Indion 190 resin [3], BF₃.OEt₂ [4], Ceric ammonium nitrate [5], iodine, [6] Silica sulfuric acid [7], In(OTf)₃ [8], SiO₂/ZnCl₂ [9], silica supported sodium hydrogen sulphate [10], PEG [11], H₂O₂/ Fe(NO₃)₃ [12]. In recent years, Solvent-free synthesis of benzimidazoles under microwave irradiation using Yb(OTf)₃ [13], KSF clay [14], metal halide supported alumina [15] and solid support [16,17] has been reported. However most of the methods suffer from drawbacks like use of harsh reaction conditions, strong acidic conditions, toxic reagents, catalyst or solvents etc. Therefore, highly efficient and

environmentally benign methodology is still a hot topic of interest for the synthesis of benzimidazole derivatives.

II. RESULTS AND DISCUSSION

We started our work with optimization of reaction conditions. We selected O-phenylenediamine 1a and benzaldehyde 2a as starting compounds. Firstly the reaction was performed at room temperature without catalyst in water (5 mL) under stirring condition for one hour but desired product was not obtained under this condition. Then reaction was carried out in presence of malic acid (1%) as a catalyst at room temperature for one hour but only trace quantity of product was formed under these conditions as indicated by TLC. In order to improve the results catalyst percentage and temperature were varied; we found that 10 mol % of catalyst at 100 °C for two hours gave desired product 3a in 90% yield (Table 1).



Scheme 1. Synthesis of benzimidazoles.

Table 1. Optimization studies using *O*-phenyldiammine **1a** and aldehyde **2a** in water and under conventional heating condition.

Entry	Catalyst (mol%)	Temp.(°c)	Time hr	Yield ^a (%)
1	0	R.T.	1	-
2	1	R.T.	1	Trace
3	2	50	1	10
4	5	70	1	20
5	5	70	2	30
6	10	100	2	90

^aIsolated yield.

In order to evaluate the scope and limitations of malic acid catalysis, the protocol was extended to other examples, under the optimized reaction conditions in water. Firstly, various aromatic aldehydes were treated with *O*-phenyldiammine under optimized reaction conditions to give the corresponding benzimidazole

derivatives in good to excellent yields (Figure 1). Results are summarized in Table 2. Aqueous solution of the catalyst can be successfully used for the next cycles without any pretreatment. It shows the high reusability of malic acid catalyst in synthesis.

Table 2. Synthesis of 2-substituted benzimidazoles from *O*-phenylenediamine and aldehydes.

Sr. No.	Ar	Product	Yield %	Nature	Observed M.P. °C	Reported ¹⁸ M.P. °C
1	Phenyl	3a	90	Off white solid	287-289	289-291
2	2-Chlorophenyl	3b	80	Pinkish red solid	230-232	231-233
3	3-Chlorophenyl	3c	78	Colorless solid	232-234	234-236
4	4-Chlorophenyl	3d	70	Colorless solid	286-298	289-291
5	2-Methylphenyl	3e	75	Colorless solid	220-222	220-222
6	4-Methylphenyl	3f	76	Colorless solid	264-266	265-267
7	2-Methoxyphenyl	3g	67	Colorless solid	174-176	175-176
8	4-Methoxyphenyl	3h	60	Colorless solid	218-220	220-221

III. EXPERIMENTAL SECTION

Materials and method

All the reagents were used as received from commercial source without further purification. Thin-layer chromatography (TLC) was performed on silica gel 60F₂₅₄ (0.25 mm thickness) plates and were visualized under short (254 nm) and long (365 nm) UV light. Column chromatography was performed using silica gel 200-400 mesh. Melting points (m.p.) were determined in open capillary tubes using paraffin oil bath and are uncorrected. ¹H and ¹³C NMR spectra were recorded on a 400 and 100 MHz NMR spectrometer using CDCl₃ and DMSO-*d*₆ as solvent. Chemical shifts δ are reported in ppm relative to Me₄Si internal standard. The multiplicity of signals is designated by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet).

General procedure for synthesis of benzimidazoles.

A mixture of *O*-Phenylenediamine **1a** (1.0 mmol), aldehyde **2a** (0.5 mmol), and malic acid (10mol %), in H₂O (5 mL) was refluxed at 100 °C for 2h. After the completion of reaction (TLC check), reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 × 5 mL), organic layer was dried over Na₂SO₄ and concentrated under vacuum. The crude residue was purified by column chromatography on silica gel using ethyl acetate: hexane as eluent. All compounds are reported in the literature. Melting points were recorded in an open capillary and are uncorrected. All melting points and spectral data match with the reported values given in the literature.

¹H data of selected compounds:

- 1) 2-Phenylbenzimidazole (**3a**): Off white solid; m.p: 287-289 °C; (lit.¹⁸. 289-291°C).
¹H NMR (DMSO-d₆): δ 12.02 (br s, 1H), 7.80 (d, *J* = 7.6 Hz, 2H), 7.57-7.65 (m, 1H), 7.60- 7.49 (m, 4H), 7.20-7.18 (m, 2H).
- 2) 2-(3-Chlorophenyl) benzimidazole (**3c**): Colorless solid; m.p: 232-234 °C; (lit.¹⁸. 234-236 °C) ¹H NMR (DMSO-d₆): δ 12.60. (br s, 1H), 8.50 (s, 1H), 8.33 (d, *J* = 6.8 Hz, 1H), 7.70-7.60 (m, 4H), 7.40-7.32 (m, 2H).

IV. CONCLUSION

In conclusion, we have developed an efficient and green protocol for the synthesis of 2-aryl benzimidazoles by using malic acid as a reusable catalyst which is non toxic naturally occurring and inexpensive. The operational simplicity, cleaner reaction condition use of water as a green solvent, moderate to high yields, and avoids use of hazardous mineral acids or Lewis acids makes this protocol superior to many other existing methods.

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