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An efficient synthesis of Benzimidazole derivatives by using Metaltriflate catalyst in an aqueous media

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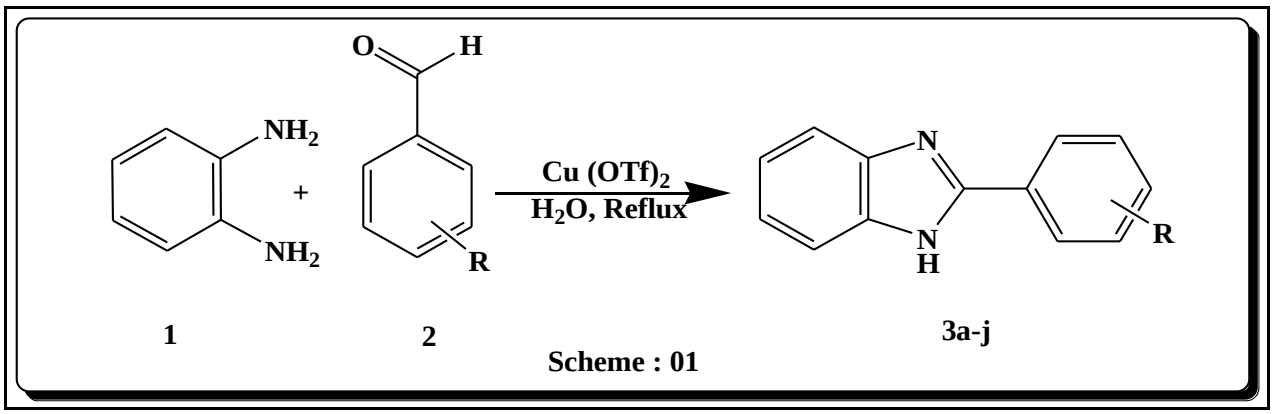
Abstract : Copper (II) Trifluro-methane-sulfonate efficiently catalysed the synthesis of benzimidazoles and derivatives form o-phenyldiamine and substituted aldehydes in an aqueous media as a green solvent at reflux condition. This method provides a novel and efficient route for the synthesis of benzimidazole and benzthiazole derivatives in good to excellent yields with catalytic amount of $Cu(OTf)_2$.
Keywords : Metal Triflate, o-phenyldiamine, benzaldehyde, reflux.

Introduction:

Organic chemists synthesize hundreds of new heterocyclic compounds every week. In most cases the chemist has specific reasons for synthesizing a particular compound, usually based on theoretical considerations, medicinal chemistry, biological mechanisms or a combination of all three. The heterocyclic compounds are very widely distributed in nature and are very essential to living organisms. They play a vital role in the metabolism of all the living cells. Among large number of heterocycles found in nature, nitrogen heterocycles are the most abundant specially those containing oxygen or sulphur due to their wide distribution in nucleic acid illustration and their involvement in almost every physiological process of plants and animals [1]. Benzimidazole is a group of substances have found practical applications in organic synthesis1 and a significant structural element in medicinal chemistry owing to its diverse biological activities [2]. Benzimidazoles are also being developed as DNA minor groove binding agents with antitumor activity. These act as ligand to transition-metal for modeling biological systems [3].

A wide range of methods are available for the synthesis of benzimidazole derivatives including condensation of either o-phenylenediamine, o-aminobenzenethiol, and/or o-aminophenol with aldehydes, acid chloride, esters, carboxylic acids, and orthoesters in the presence of various acid catalysts [4-9]. Also, syntheses of these compounds have been reported using ILs [10-12]. In recent years, solvent-free synthesis of benzimidazole under microwave irradiation using $Yb(OTf)_3$ [13], KSF clay [14], Metal halide supported alumina [15] and solid support[16-17] has been reported. Although these procedures provide improvement, many of these catalysts or activators suffer from disadvantages such as the use of organic solvents or toxic reagents, harsh reaction conditions, long reaction time, need excess amounts of the reagents, and non-recoverability of the catalyst.

Taking in view of the applicability of heterocyclic compounds, the present work was undertaken to synthesize heterocycle like benzimidazole derivatives by using the $Cu(OTf)_2$ as a catalyst in an aqueous media as a green solvent (**Scheme 01**).



Scheme 01: Synthesis of Benzimidazole derivatives by using $Cu(OTf)_2$ in an aqueous media.

Experimental:

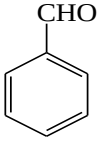
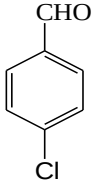
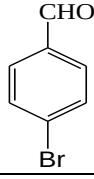
Materials and Methods

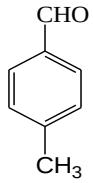
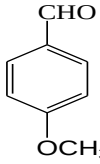
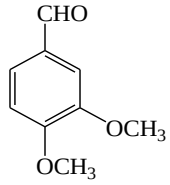
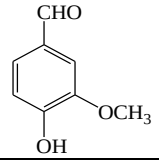
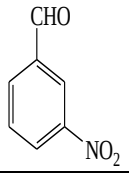
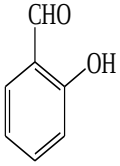
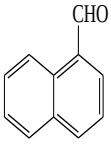
Melting points were measured in open glass capillaries on melting-point apparatus and were uncorrected. ^{1}H NMR was recorded at room temperature on a Bruker Avance II 400MHz Spectrometer (SAIF, Punjab University, Chandigarh) in $CDCl_3$ using TMS as internal standard. IR spectra (using KBr pellets) were obtained with a Perkin Elmer Spectrum RX FTIR (SAIF, Punjab University, Chandigarh) instrument. The reactions were monitored on TLC using pre-coated plates (silica gel on aluminum, Merck). All reagents were obtained from commercial sources and used without further purification. Solvents for chromatography were distilled before use. Compounds were characterized by IR and ^{1}H NMR spectroscopy.

General procedure for synthesis of substituted benzimidazole derivatives.

In a 50 ml round bottom flask, a mixture of o-phenyldiamine (1 mmol) and aldehydes (1 mmol) in water (5 ml) were mixed and refluxed on water bath in the presence of Copper trifluromethane sulfonate (5 mol %) for appropriate time given in a **table 1**. The progress of the reaction was monitored by using TLC. After completion of the reaction mixture was cooled and filtered. Precipitate is washed with distilled water (5 X 5ml) to recover the catalyst and dried it over vacuum. Crude product is recrystallized in ethanol to obtain the pure product. To enhance purity the product was purified by silica gel column chromatography using ethyl acetate: pet-ether (2:8) as an eluent.

Table 1: Synthesis of substituted benzimidazole derivatives by using $Cu(OTf)_2$ at reflux condition in an aqueous media.

Entry	Aldehydes	Products	Time (Hr)	[a]Yield (%)
1		**3a**	05	94
2		**3b**	3.5	88
3		**3c**	04	90

4		**3d**	07	90
5		**3e**	06	87
6		**3f**	07	85
7		**3g**	05	85
8		**3h**	07	86
9		**3i**	04	87
10		**3j**	05	88

[a]Yields refer to the pure isolated product

Spectral data for selected compound

[1] **2-(4-Methoxyphenyl) benzimidazole** [Entry 5]**:** ^{1}H NMR (DMSO-d6): δ11.90 (br s, 1H), 8.01 (d, *J* = 8.1 Hz, 2H), 7.50 - 7.60 (m, 2H), 7.28 - 7.28 (m, 2H), 7.11 (d, *J* = 8.4Hz, 2H), 3.28 (s, 3H); (LC-MS) m/z: 225.07 $[M + H]^+$

[2] **2-(3-nitrophenyl) benzimidazole** [Entry 8]**:** ^{1}H NMR (DMSO-d6): δ12.2 (brs, 1H), 8.8 (s, 1H), 8.20 (d, *J* = 7.1 Hz, 1H), 8.23 (d, *J* =7.2 Hz, 1H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.5 - 7.62 (m, 2H),7.22 (t, *J* = 6.1 Hz, 2H); (LC-MS) m/z: 240.06 $[M + H]^+$

Results and discussion

In recent years, metal triflate catalysts have gained importance in several organic transformations due to their interesting reactivity as well as for economic and environmental reasons. Keeping in view environmentally benign conditions we tried to develop green and efficient routes for synthesis of biologically active heterocyclic compounds by using metal triflates in an aqueous media as green solvent. Thus, here we report the formation of substituted 2-arylbenzimidazole by a direct condensation reaction of aryl aldehyde with o-phenylenediamine in the presence of $Cu(OTf)_2$ under reflux condition in an aqueous media as a greener protocol.

In order to study the generality of this protocol, the applicability of the $Cu(OTf)_2$ in an aqueous media at reflux condition was then examined for the reaction of a series of substituted aromatic aldehydes with o-phenylenediamine under the optimized reaction conditions. As shown, a variety of substituted aromatic aldehydes, bearing either electron-donating or electron-withdrawing substituents, afforded the products in excellent yields and high purities. Products were confirmed by comparing with authentic sample (^{1}H NMR, IR and Mass).

Conclusions

In conclusion here we describe a highly efficient and environmentally benign process for the synthesis of substituted 2-arylbenzimidazole by a direct condensation reaction of aryl aldehyde with o-phenylenediamine in the presence of $Cu(OTf)_2$ under reflux condition in an aqueous media. The use of this inexpensive and easily available catalyst makes this protocol practical, environmentally friendly and economically attractive. This method offers several advantages such as high yield of product, simple work-up procedure and easy isolation.

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