

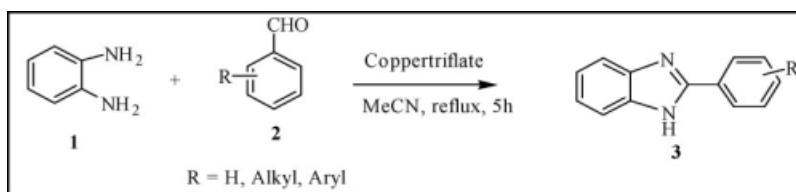
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Received April 2, 2009

DOI 10.1002/jhet.287

Published online 5 January 2010 in Wiley InterScience (www.interscience.wiley.com).



Copper triflate has been found to be an efficient catalyst for the synthesis of benzimidazoles from *o*-phenylenediamine and aldehydes at reflux temperature under acetonitrile solvent. This new method consistently has the advantage of excellent yields (74–95%) at reflux temperature.

J. Heterocyclic Chem., **47**, 153 (2010).

INTRODUCTION

Benzimidazoles are highly biologically active compounds and exhibit antiviral, antinulcer, antihypertension, and anticancer properties [1]. Because of wide biological significance, the synthesis of these compounds has received a great deal of attention. The synthesis of benzimidazoles involves treatment of 1,2-phenylenediamines with carboxylic acids or various derivatives under strongly acidic conditions or with aldehydes followed by oxidation [2,3] for which various oxidative reagents have been used [4,5]. Many of these processes suffer from one or more limitations, such as long reaction times, occurrence of several side reactions, drastic reaction conditions, low yields, and tedious work-up procedure. Therefore, the search continues for a better catalyst for the synthesis of benzimidazoles in terms of mild reaction conditions.

Recently, the use of copper triflate catalyst [6,7] has received considerable importance in organic synthesis because of their ease of handling, enhanced reaction rates, greater selectivity, simple workup. Among the various catalysts, particularly, copper triflate has advantages of low cost and ease of preparation. In view of

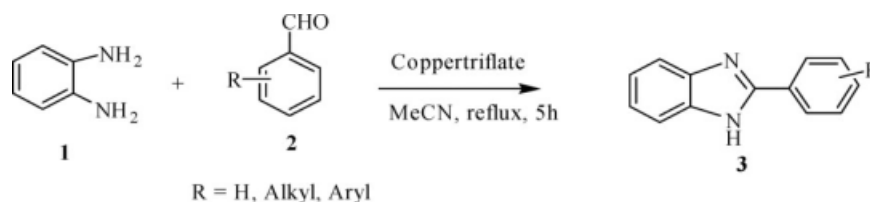
this, we have used copper triflate as an efficient catalyst for the benzimidazole synthesis in our laboratory.

RESULTS AND DISCUSSION

Initially, we have studied the condensation reaction of aldehyde (1.0 mmol) with 1,2-phenylenediamine (1.2 mmol) using copper triflate (1.0 mmol) under reflux temperature under acetonitrile solvent (Scheme 1). Copper triflate catalyst is acting as Lewis acid and the formation of benzimidazole may be through the following mechanism. (Scheme 2).

Encouraged by these results, we examined several aromatic aldehydes under the optimized conditions. This condensation proceeded smoothly in refluxing acetonitrile and also complete with in 5 h of reaction time. Several aldehydes (aromatic, heteroaromatic, and aliphatic) underwent the above conversion to form a series of benzimidazoles (Table 1). Aromatic aldehydes containing both electron-donating and electron-withdrawing groups worked well. The method is suitable for the preparation of benzimidazoles from an acid sensitive aldehyde such as furfuraldehyde (**3k**) and the sterically

Scheme 1



Scheme 2. Proposed mechanism for synthesis of benzimidazoles.

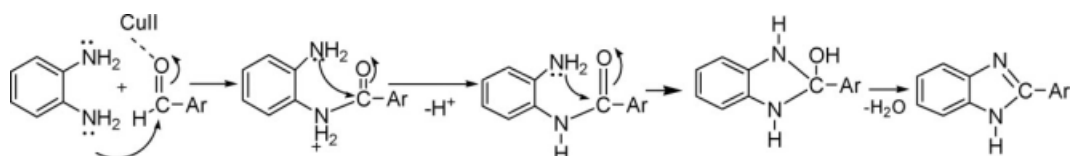


Table 1

Copper triflate catalyzed synthesis of benzimidazoles.

Entry	Aldehyde	Product	Time (h)	Isolated yield (%)
3a			3.5	95
3b			4.0	93
3c			4.0	93
3d			4.5	90
3e			4.5	88
3f			5.0	85
3g			4.5	88
3h			5.0	88
3i			5.0	85
3j			5.0	78
3k			5.0	75
3l			5.0	74

hindered aldehyde 2-naphthaldehyde (**3i**). Substituted aldehydes have been used with similar success to provide the corresponding benzimidazoles in high yields, which are also of much interest with regard to biological activity. The reaction conditions are mild and the experimental procedure is simple. The products were formed in high yields (74–95%). The structures of the products were determined from their spectral (¹H NMR, IR, and MS) data. Several examples illustrating this novel and general method for the synthesis of benzimidazoles are summarized in Table 1.

CONCLUSIONS

In summary, we have developed a new methodology for the synthesis of various benzimidazoles by using 1,2-phenylenediamines and substituted aldehydes in the presence of copper triflate catalyst at reflux temperature. Thus, this method is a simple, high yielding, time saving, and the utility of copper triflate catalyst for synthesis of benzimidazoles would be precious addition to available methods.

EXPERIMENTAL

General procedure for the synthesis of benzimidazoles. To a mixture of an aldehyde (0.5 mmol) and 1,2-phenylenediamine (0.6 mmol) in acetonitrile (5 mL) under a nitrogen atmosphere, coppertriflate (0.5 mmol) was added. The mixture was stirred at reflux temperature, and the reaction was monitored by TLC. After completion, the solvent was evaporated and the mixture was extracted with EtOAc (3 × 10 mL). The extract was concentrated, and the crude product was purified by silica gel column chromatography using ethyl acetate–*n*-hexane (1:9) as eluent to afford the desired product **3**. The residue was subjected to column chromatography (silica gel, hexane–EtOAc) to obtain the pure benzimidazole. The spectral (¹H NMR, IR, and MS) data of some representative benzimidazoles are given below.

Compound (3e). IR (KBr): ν 3189, 2980, 1625 cm⁻¹; ¹H NMR (CDCl₃ + DMSO-*d*₆): δ 12.70 (1H, br s), 8.07 (2H, d, J = 8.0 Hz), 7.57 (1H, m), 7.26–7.22 (3H, m), 7.19–7.06 (2H, m); FABMS: m/z 231 (³⁷Cl [M+H]⁺), 229 (³⁵Cl [M+H]⁺); Anal. Calcd for C₁₃H₉N₂Cl: C, 68.27; H, 3.94; N, 12.25. Found: C, 68.42; H, 3.86; N, 12.38.

Compound (3l). IR (KBr): ν 3055, 2925, 2853, 1624 cm⁻¹; ¹H NMR (CDCl₃ + DMSO-*d*₆): δ 11.86 (1H, br s), 8.75 (1H, br s), 8.39 (1H, dd, J = 8.0, 2.0 Hz), 8.02–7.90 (3H, m), 7.69–7.52 (4H, m), 7.26–7.18 (2H, m); FABMS: m/z 245 [M+H]⁺; Anal. Calcd for C₁₇H₁₂N₂: C, 83.61; H, 4.92; N, 11.47. Found: C, 83.87; H, 4.88; N, 11.61.

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