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Effect of different solvents on synthesis of 2-phenyl benzimidazole and its derivatives

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ABSTRACT : In the initial catalytic activity experiments, different solvents were screened for the reaction. Herein the reaction of benzaldehyde and orthophenylene diamine was selected as the model reaction.

Solubility experiments showed that the cobalt (II) acetylacetone is miscible with methanol and relatively readily soluble in polar solvents such as ethanol, and they are partially immiscible with no-polar solvents such as ethyl acetate, and tetrahydrofuran.

As shown in Table 1, the reactions could proceed effectively in polar organic solvents, such as methanol and ethanol (entries 1, 2), and cobalt (II) acetylacetone/CH_3OH was found to be the most effective catalyst/solvent system and gave the highest yield of 97% (entry 1) among the solvents selected.

KEYWORDS: Cobalt (II) acetylacetone, methyl alcohol, 2-phenylbenzimidazole, ethyl acetate, tetrahydrofuran.

I. INTRODUCTION

Organic molecules bearing different heterocyclic ring systems have attracted a great deal of attention in now a day, both in chemical and medicinal research that could be attributed to their different pharmacological applications. Benzimidazoles represent a class of nitrogen heterocyclic which possesses biological and pharmacological activities.

Among these potential heterocyclic drugs, benzimidazole scaffolds are considerably prevalent. Due to their isostructural pharmacophore of naturally occurring active biomolecules, benzimidazole derivatives have significant importance as chemotherapeutic agents in diverse clinical conditions. Synthetically produced heterocycles designed by organic chemists are used as pharmaceuticals, dyestuff, agrochemicals and are of increasing importance in many other areas including adhesives, molecular engineering, polymers etc. In biological processes naturally occurring heterocyclic moieties played a vital role.

They are broadly found in naturally in plant alkaloids, nucleic acids, and anthocyanins and flavones as well as in chlorophyll. Additionally, several proteins, hormones, vitamin's contain aromatic heterocyclic ring system [1-3]. Heterocycles act as drugs because they have specific chemical reactivity and they provide convenient building blocks to which pharmacologically active substituent can be attached.

Thus, we needed the development of innovative methodology for bioactive heterocyclic in synthetic organic and medicinal chemistry with some advantages including its simplicity of operation, greener approach, easy workup procedure, selectivity, higher yields, and high-atom economic [4]. Nitrogen heterocyclic compounds are among the most privileged and significant structural components of pharmaceuticals [5,6]. A recent analysis of the nitrogen heterocyclic composition of U.S. FDA (Food and Drug Administration) approved drugs has revealed the relative frequency by which various nitrogen heterocyclic compounds have been incorporated into approved drugs architecture [7]. Benzimidazole is an aromatic N-heterocyclic formed by the fusion of benzene and imidazole ring.

Nitrogen containing heterocycles, are present in vitamins, proteins and nucleic acids. Benzimidazole is a heterocyclic aromatic organic compound. The most prominent compound available in the nature containing benzimidazole skeleton is Nribosyl dimethyl benzimidazole, which serves as axial ligands for cobalt in vitamin B_{12} [8].

Benzimidazole moieties are very important class of heterocyclic compounds that have many applications in pharmaceutical industry. Benzimidazole derivatives have attracted a significant attention in recent years because of their

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medicinal applications as antiviral, antifungal [9], antihypertensive [10], and anticancer [11], compounds.

Apart from therapeutic applications, benzimidazoles formed as intermediates in different organic reactions. In addition to this benzimidazoles are used as fluorescent whitening agent, dyes, organic ligands and functional materials [12-14].

Pharmacologically active molecules such as albendazole / mebendazole / thiabendazole (antihelmentic), omeprazole (antiulcer), astimizole (antihistaminic) etc. contains the substituted benzimidazoles and display a broad spectrum of potential pharmacological activities. Benzimidazole derivatives also show cytotoxic activity.

Substituted benzimidazole derivatives is evaluated by their ability to inhibit gastric H^+/K^+ ATPase and by blocking the gastric acid secretion [15]. Some of the benzimidazole derivatives such as Albendazole, Mebendazole were widely used in treatment of parasitic worm infestations.

It has been reported that many molecules containing benzimidazole moiety exhibit a wide range of different biological activities as a result of changing the groups on the core structure, as shown in Fig. 2. These biological activities include anti-cancer (1) [16], bactericidal (2), [17], fungicidal (3) [18] and [19], analgesic (4) [20] and anti-viral properties (5) [21]. Some have cardiovascular applications (6) [22] while some derivatives have been synthesized and evaluated for inhibition of HIV-1 infectivity [23].

II. EXPERIMENTAL SECTION

All melting points were determined in open capillary tube and were uncorrected. IR spectra were recorded with potassium bromide pellets technique, ^{1}H NMR spectra were recorded on AVANCE 300 MHz Spectrometer in DMSO using TMS as internal standard. Mass spectra were recorded on a FT VG-7070 H Mass Spectrometer using EI technique at 70 eV. All the reactions were monitored by thin layer chromatography.

III. MATERIAL AND METHODS

In the initial catalytic activity experiments, different solvents were screened for the reaction. Herein the reaction of benzaldehyde and o-phenylenediamine was selected as the model reaction.

1) Effect of solvents on synthesis of benzimidazole derivatives :

a) One-pot synthesis of 2-phenyl benzimidazole derivatives by oxidative condensation reaction with o-phenylenediamine (1.05 mmol), substituted benzaldehyde (1 mmol), catalyst cobalt (II) acetylacetone (0.05 mmol) and solvent CH_3OH stirring at room temperature for 4 hours.

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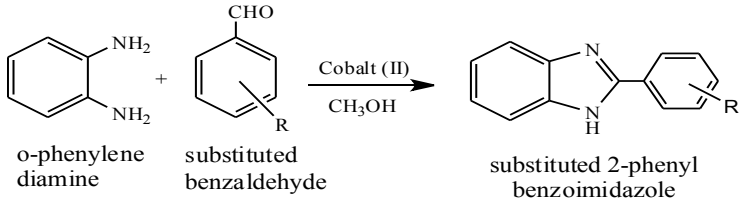
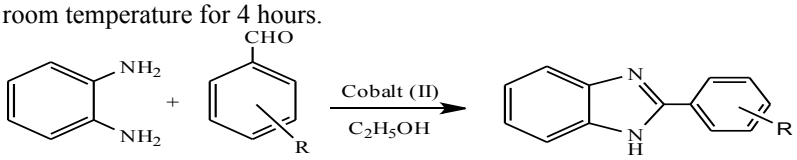


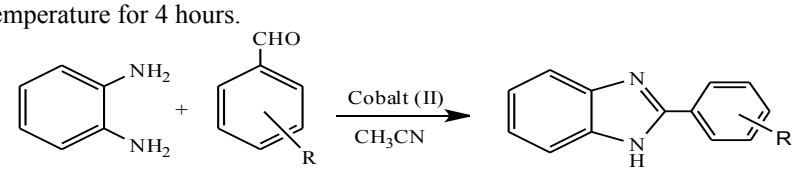
o-phenylene diamine | substituted benzaldehyde | substituted 2-phenyl benzoimidazole

b) One-pot synthesis of 2-phenyl benzimidazole derivatives by oxidative condensation reaction with o-phenylenediamine (1.05 mmol), substituted benzaldehyde (1 mmol), catalyst cobalt (II) acetylacetone (0.05 mmol) and solvent C_2H_5OHstirring at room temperature for 4 hours.



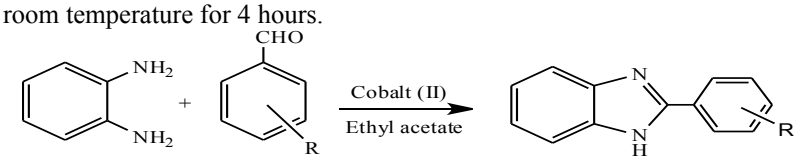
o-phenylene diamine | substituted benzaldehyde | substituted 2-phenyl benzoimidazole

c) One-pot synthesis of 2-phenyl benzimidazole derivatives by oxidative condensation reaction with o-phenylenediamine (1.05 mmol), substituted benzaldehyde (1 mmol), catalyst cobalt (II) acetylacetone (0.05 mmol) and solvent CH_3CN stirring at room temperature for 4 hours.



o-phenylene diamine | substituted benzaldehyde | substituted 2-phenyl benzoimidazole

d) One-pot synthesis of 2-phenyl benzimidazole derivatives by oxidative condensation reaction with o-phenylenediamine (1.05 mmol), substituted benzaldehyde (1 mmol), catalyst cobalt (II) acetylacetone (0.05 mmol) and solvent ethyl acetate stirring at room temperature for 4 hours.



o-phenylene diamine | substituted benzaldehyde | substituted 2-phenyl benzoimidazole

e) One-pot synthesis of 2-phenyl benzimidazole derivatives by oxidative condensation reaction with o-phenylenediamine (1.05 mmol), substituted benzaldehyde (1 mmol), catalyst cobalt (II) acetylacetone (0.05 mmol) and solvent THF stirring at room temperature for 4 hours.

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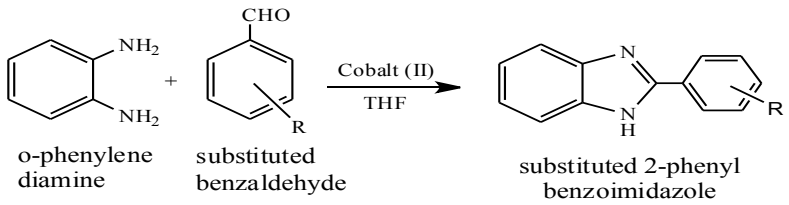

o-phenylene diamine | substituted benzaldehyde | substituted 2-phenyl benzoimidazole

IV.

V. RESULTS AND DISCUSSION

Solubility experiments showed that the cobalt (II) acetylacetone is miscible with methanol and relatively readily soluble in polar solvents such as ethanol, and they are partially immiscible with no-polar solvents such as ethyl acetate, and tetrahydrofuran.

In the initial catalytic activity experiments, different solvents were screened for the reaction. Herein the reaction of benzaldehyde and o-phenylenediamine was selected as the model reaction.

As shown in Table 1, the reactions could proceed effectively in polar organic solvents, such as methanol and ethanol (entries 1, 2), and cobalt (II) acetylacetone/CH_3OH was found to be the most effective catalyst/solvent system and gave the highest yield of 97% (entry 1) among the solvents selected. For establishing the best reaction conditions, synthesis of substituted 2-phenylbenzimidazole was first studied.

Table 1. Effect of solvents on synthesis of benzimidazole derivatives.

Entry	Solvents	Isolated Yield (%)
1	CH_3OH	97
2	C_2H_5OH	95
3	CH_3CN	54
4	$CH_3COOC_2H_5$	40
5	THF	32

In general, the reaction proceeded smoothly at room temperature to give the corresponding products in reasonable to good yields ranged from 80% to 97%. Compared with the other methods and catalysts, the separation procedure of products and catalyst from the reactor was easier.

VI. CONCLUSION

In conclusion we have developed a simple methodology for the preparation of substituted benzimidazoles derivatives. The advantage of this method are extremely mild reaction conditions, short reaction time, high yield, simple experimental technique and compliance with green chemistry protocols.

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