Chiang Mai J. Sci. 2013; 40(4) : 618-624
http://it.science.cmu.ac.th/ejournal/
Contributed Paper

Simple and Efficient Synthesis of Benzimidazole Derivatives Using Cobalt (II) Acetylacetone at Room Temperature

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Received: 28 May 2012
Accepted: 4 November 2012

ABSTRACT

A very simple, mild and highly efficient green catalyst has been developed for the synthesis of 2-substituted benzimidazoles by treatment of substituted ortho-phenylenediamines and aldehydes at room temperature in the presence of cobalt (II) acetylacetone ($Co(acac)_2$). The products were directly recrystallized from hot methanol in good yields.

Keywords: aldehydes, o-Phenylenediamines, benzimidazoles, cobalt (II) acetylacetone

1. INTRODUCTION

The benzimidazole ring system is an important pharmacophore in medicinal chemistry and modern drug discovery [1-4]. Substituted benzimidazole derivatives have found applications in diverse therapeutic areas including antiulcer agents, antihypertensives, antivirals, antifungals, anticancers and antihistaminics [5-8]. The widespread interest in the benzimidazole-containing structures has led to extensive studies of their synthesis. The commonly used synthetic approaches typically entail the condensation of an arylenediamine with a carbonyl equivalent [9, 10]. Likewise, esters, lactones, and anhydrides could produce benzimidazoles through the cyclization of amide. This might have a limited scope, since the necessary reaction conditions are harsh and result in a meager assortment of final products. For example, the reaction of arylenediamines with aliphatic esters and lactones, which uses strong mineral acids at high temperatures, necessitates conditions that would not allow for a wide range of functional groups and attractive substrates. The most important methodology toward the synthesis of benzimidazoles is the oxidative cyclo-dehydrogenation of aniline Schiff bases, which are often generated in situ from the coupling reaction between o-phenylenediamines and aldehydes [11]. Various oxidative and catalytic reagents such as sulfamic acid [12], I_2 [13], DDQ [14], air [15], oxone [16], $FeCl_3 \cdot 6H_2O$ [17], $In(OTf)_3$ [18], $Yb(OTf)_3$ [19], $Sc(OTf)_3$ [20], $KHSO_4$ [21], ionic liquid [22-24] have been employed. However, they often suffer from a variety of disadvantages, such as drastic reaction conditions, poor yields, severe side reactions, high reaction temperature, prolonged reaction time and requirement of expensive reagents. Therefore, the discovery of mild and practical routes for synthesis of derivatives of

benzimidazole continues to attract the attention of researchers.

Herein, we developed a facile and efficient protocol for preparation of benzimidazoles compounds using cobalt (II) acetylacetone at room temperature (Figure 1). The reactions proceeded efficiently under mild conditions and products were isolated with ease compared to many previously reported catalysts. The results showed that the cobalt (II) acetylacetone had a wide range of application for different substrates and products could be obtained conveniently in excellent yields.

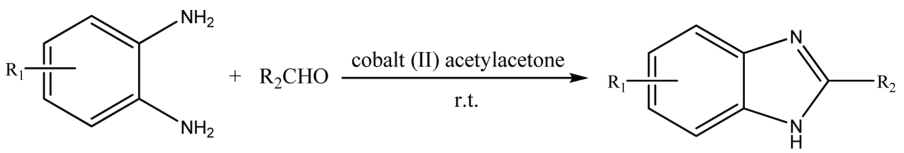


Figure 1. Synthesis of benzimidazole derivatives catalyzed by cobalt (II) acetylacetone.

2. MATERIALS AND METHODS

Melting points were determined on a Thomas Hoover capillary apparatus and were uncorrected. NMR spectra were obtained from a Bruker DPX 400 spectrometer. The IR spectra were recorded with a Bomem Michelson model 102 FTIR. Products were identified using a Shimadzu high performance liquid chromatograph (HPLC). Analytical TLC was performed on precoated silica gel 60 F254 plates. All starting chemicals (AR grade) were purchased from commercial suppliers and used without further purification.

2.1 General Procedure for the Synthesis of Benzimidazoles

The aldehyde (1 mmol), substituted ortho-phenylenediamine (1.05 mmol) and methanol (5 mL) were added to a 25 mL round-bottom flask equipped with magnetic stirrer. To this solution, cobalt (II) acetylacetone (0.05 mmol) was added and stirred for the appropriate time at room temperature. Then the reaction mixture was extracted with ethyl acetate (3×20 ml). The organic phase was washed with water and dried Na_2SO_4. The solvent was removed *in vacuo* to give the crude product which was recrystallized from hot methanol to obtain the pure benzimidazoles.

3. 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 ortho-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 2-phenyl-1*H*-benzo[*d*]imidazole was first studied. The efficiency of the reaction was mainly affected by the amount of the catalyst. As can be seen from Table 2, the optimal amount of cobalt (II) acetylacetone was 0.05 mmol (entry 2). The isolated yield of 2-phenyl-1*H*-benzo[*d*]imidazole decreases with the increase of cobalt (II) acetylacetone from 0.05 mmol to 0.5 mmol.

Table 1. Effect of solvents on synthesis of benzimidazole derivatives [a].

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

[a] Reaction conditions: benzaldehyde (1 mmol), ortho-phenylenediamine (1.05 mmol), and cobalt (II) acetylacetone, (0.05 mmol) r.t., 4 h.

Table 2. Effect of amount of cobalt (II) acetylacetone on synthesis of benzimidazoles [a].

Entry	Catalyst (mmol)	Isolated yield (%)
1	0	65
2	0.05	97
3	0.2	86
4	0.5	79

[a] Reaction conditions: benzaldehyde (1 mmol), ortho-phenylenediamine (1.05 mmol), and methanol 5ml, r.t., 4 h.

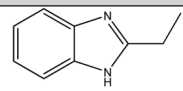
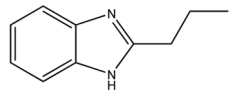
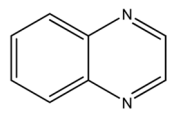
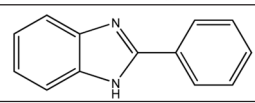
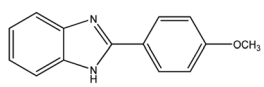
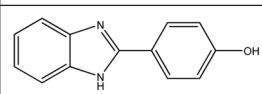
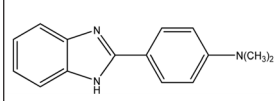
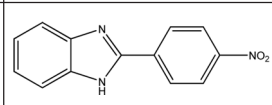
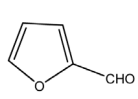
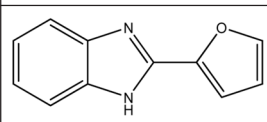
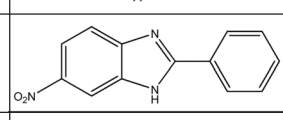
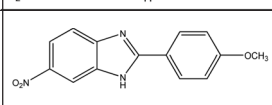
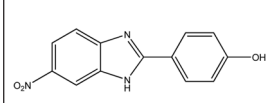
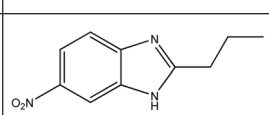
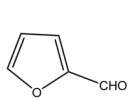
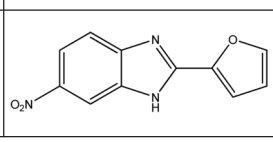
Then, the scope of the reaction with other aldehydes and substituted ortho-phenylenediamines was investigated catalyzed by cobalt (II) acetylacetone under the optimized reaction conditions (Table 3). In general, the reaction proceeded smoothly at room temperature to give the corresponding products in 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. For aromatic aldehydes carrying either electron-withdrawing or electron-donating substituents could facilitate the reaction, and gave almost the same yields (entries 5, 9). In the case of substituted ortho-phenylenediamines, it is noteworthy that both the electrondonating and weak electron-withdrawing substituents were advantageous to the reaction. Substrates bearing strong electron-withdrawing groups (Table 3, entries 10, 11, 13 and 14) render the less electrophilic to nucleophilic attack and exhibited slightly lower conversions. Unsubstituted ortho-phenylenediamines could be converted into the corresponding products in good yields at room temperature. It is interesting to note that increasing the electron-withdrawing ability of the substituted ortho-phenylenediamines decreases the rate of the reaction and the rate of conversion.

A proposed mechanism to account for the facile formation of benzimidazoles is depicted in Scheme 2. The reaction between an aldehyde and a substituted ortho-phenylenediamine leads to the formation of Schiff base (I). Intramolecular attack by the second amino group on C=N double bond facilitates the formation of hydrobenzimidazole (II) which undergoes subsequent air oxidation [15] to give the desired benzimidazole as the final product.

4. CONCLUSIONS

In summary, we devised an efficient, inexpensive protocol for the synthesis of benzimidazoles using cobalt (II) acetylacetone as the catalyst. The easy work-up procedure, lack of chromatographic separation and very good yields make this method a valid

Table 3. Preparation of benzimidazole derivatives using cobalt (II) acetylacetone as catalyst.

Entry	R_1	Aldehyde	Product	Time (h)	Yield (%) [a]
1	H	C_2H_5CHO		4	83
2	H	C_3H_7CHO		6	96
3	H			4	94
4	H	C_6H_5CHO		4	97
5	H	4-$MeOC_6H_4CHO$		4	91
6	H	4-OHC_6H_4CHO		4	81
7	H	4-$N(CH_3)_2C_6H_4CHO$		4	88
8	H	4-$NO_2C_6H_4CHO$		10	88
9	H			4	82
10	4-NO_2	C_6H_5CHO		4	84
11	4-NO_2	4-$MeOC_6H_4CHO$		4	80
12	4-NO_2	4-OHC_6H_4CHO		6	86
13	4-NO_2	C_3H_7CHO		10	87
14	4-NO_2			10	81

[a] Isolated yield.

contribution to the existing methodologies. These features make this process amenable for scale up purposes.

ACKNOWLEDGMENTS

This work was supported by the NSAF Foundation of National Natural Science Foundation of China and China Academy of Engineering Physics (Grant No: 11076017).

The spectral data for the compounds are given below:

Quinoxaline (Table 3, entry 3): Solid, m.p. 29°C-31°C (Lit. 30.5°C-31.5°C) [25], ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (d, 2H), 8.12 (d, 2H), 7.78 (t, 2H). Anal. calcd. for $C_8H_6N_2$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.95; H, 4.61; N, 21.63.

2-Phenyl-1H-benzimidazole (Table 3, entry 4): Solid, m.p. 296.5°C-297.5°C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.90 (br s, 1H), 8.19 (m, 2H), 7.57 (m, 2H), 7.50 (m, 3H), 7.19 (m, 2H). Anal. calcd. for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.42. Found: C, 80.50; H, 5.14; N, 14.50.

2-(4-Methoxyphenyl)-1H-benzo[d]imidazole (Table 3, entry 5): Solid, m.p. 226°C-227°C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.75 (s, 3H), 7.06 (d, 2H), 7.17 (q, 2H), 7.50 (m, 2H), 8.15 (d, 2H), 12.72 (s, 1H). Anal. calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 75.05; H, 5.43; N, 13.60.

2-(4-Hydroxyphenyl)benzimidazole (Table 3, entry 6): Solid, m.p. 256°C-257°C, ^{1}H NMR (400MHz, DMSO-d_6): δ 6.90 (d, 2 H), 7.14 (m, 2 H), 7.45 (d, 1 H), 7.59 (d, 1 H), 7.89 (d, 2 H), 9.90 (bs, 1 H), 12.59 (bs, 1 H). Anal. calcd. for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.33. Found: C, 74.19; H, 4.82; N, 13.49.

2-(4-Nitrophenyl)-1H-benzo[d]imidazole (Table 3, entry 8): Solid, m.p. 316°C-318°C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.20 (m, 2 H), 7.55 (m, 1 H), 7.66 (m, 1 H), 8.32 (d, 2 H), 8.36 (d, 2 H), 13.20 (bs, 1 H). Anal. calcd. for $C_{13}H_9N_3O_2$: C, 65.27; H, 3.79; N, 17.56. Found: C, 65.38; H, 3.84; N, 17.45.

2-(2-Furyl)-1H-benzimidazole (Table 3, entry 9): Solid, m.p. 286°C-287°C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.65 (dd, 1H), 7.18-7.23 (m, 4H), 7.51 (d, 1H), 7.56 (d, 1H), 7.89 (s, 1H). Anal. calcd. for $C_{11}H_8N_2O$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.83; H, 4.40; N, 15.12.

5-Nitro-2-phenyl-benzimidazole (Table 3, entry 10): Solid, m.p. 207°C-209°C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.51 (br s, 1H), 8.45 (d, 1H), 8.21-8.18 (m, 2H), 8.10 (dd, 1H), 7.75 (d, 1H), 7.59-7.55 (m, 3H). Anal. calcd. for $C_{13}H_9N_3O_2$: C, 65.27; H, 3.79; N, 17.56. Found: C, 65.36; H, 3.83; N, 17.48.

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