Copper-catalyzed one-pot synthesis of benzimidazole derivatives

Hashem Sharghi, Mona Hosseini-Sarvari, and Fatemeh Moeini

Abstract: A simple, efficient, and environmentally benign method has been developed for the synthesis of 2-substituted benzimidazoles through a one-pot reaction of phenylenediamines with aryl aldehydes in excellent isolated yields under mild conditions using Cu(II) complex as the selective, recyclable, and heterogeneous catalyst at ambient temperature. The Cu(II) complex as a heterogeneous catalyst can be reused in further catalytic reactions, and it was found that its activity remained largely unchanged for eight successive runs. No metal-complex leaching was observed after the consecutive catalytic reactions. The salient features of this method include mild conditions, high yields, simple procedure, and good recovery and reusability of the heterogeneous catalyst.

Key words: benzimidazole, *o*-phenylenediamine, arylaldehydes, heterogeneous catalyst, *N*,*N*-bis (2-hydroxyphenyl)pyridine-2,6-dicarboxamide.

Résumé : On a développé une méthode simple, efficace et respectueuse de l'environnement pour la synthèse de benzimidazoles substitués en position 2; elle est réalisée avec d'excellents rendements en produits isolés et elle implique une réaction monotope de phénylènediamines avec des aldéhydes aromatiques, à la température ambiante et elle utilise un complexe de Cu(II) comme catalyseur sélectif, recyclable et hétérogène. Le catalyseur de Cu(II) utilisé comme catalyseur hétérogène peut être réutilisé pour d'autres réactions catalytiques et on a trouvé que son activité demeure pratiquement inchangée après huit réutilisations. On n'a observé aucun lixiviation du complexe métallique après des réactions catalytiques consécutives. Les principales caractéristiques de cette méthode incluent des conditions douces, des rendements élevés, une procédure simple et une bonne récupération et possibilité de réutilisation du catalyseur hétérogène.

Mots-clés : benzimidazole, *o*-phénylènediamine, aldéhydes aromatiques, catalyseur hétérogène, *N,N*-bis(2-hydroxyphényl)pyridine-2,6-dicarboxamide.

[Traduit par la Rédaction]

Introduction

Benzimidazoles are very useful intermediates for the development of molecules of pharmaceutical or biological interest. The benzimidazole ring is an important pharmacophore in modern drug discovery (1). Benzimidazole derivatives exhibit significant activity against several viruses such as HIV (2), herpes (HSV-1) (3), RNA (4), influenza (5), and human cytomegalovirus (HCMV) (2*a*). Substituted benzimidazole derivatives have found commercial applications in veterinarian medicine as anthelmintic agents and in diverse human therapeutic areas such as treatment of ulcers and as antihistaminics (6). Because of their importance, the synthesis of substituted benzimidazoles has become a focus of synthetic organic chemistry. The most commonly used synthetic approaches typically entail the condensation of an arylenediamine with a carbonyl equivalent (7, 8). Likewise, esters, lactones, and anhydrides could produce benzimidazoles through the cyclization of amide. However, 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 other synthetic approach involves a two-step procedure including the oxidative cyclodehydrogenation of aniline Schiff bases, which are often generated in situ from the condensation of phenylenediamines and aldehydes. Various oxidative and catalytic reagents, such as $TiCl_4$ (9*a*), H_2O_2/CAN (9*b*), $ZrOCl_2$ (10), $In(OTf)_3$ (11), $Sc(OTf)_3$ (12), $Yb(OTf)_3$ (13), I_2 in aqueous THF (14), BF_3–OEt_2 (15), H_2NSO_3H (16*a*), TsOH or *N,N*-dimethylaniline/graphite (16*b*), polyaniline – sulfate salt (17), and NH_4OAc (18), have been employed. The direct condensation of *o*-aryldiamines and aldehydes at room temperature is less developed, because it leads to the formation of a complex mixture of products containing 1,2-disubstituted benzimidazoles, the corresponding bis-anils, and dihydrobenzimidazoles as main byproducts (19). Unfortunately, some of these methods suffer from one or more limitations, such as high reaction temperature, prolonged reaction time, and toxic solvents. In addition, some of the catalysts are expensive, air sensitive, and homogeneous. The homogeneous catalysts cannot be separated from the reaction media and, subsequently, cannot be reused in further catalytic reactions.

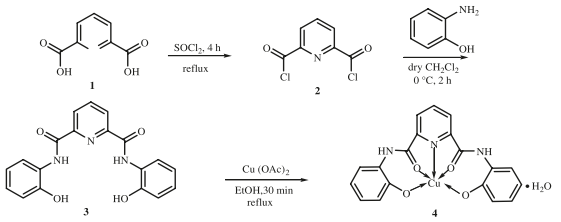
Received 13 July 2008. Accepted 15 September 2008. Published on the NRC Research Press Web site at canjchem.nrc.ca on 24 October 2008.

H. Sharghi,[1] M. Hosseini-Sarvari, and F. Moeini. Department of Chemistry, College of Sciences, Shiraz University, Shiraz 71454, Iran.

[1]Corresponding author (e-mail: shashem@chem.susc.ac.ir).

 doi:10.1139/V08-153

Scheme 1.



Recently, the development of heterogeneous catalysts (20) for fine chemicals synthesis has become a major area of research, since the potential advantages of these materials (i.e., simple recovery, reusability, and potential for incorporation in continuous reactors and microreactors) over homogeneous systems can have a major impact on the environmental performance of a synthesis (21). Considering the above issues, there is still a need to search for new catalysts superior to the existing ones with regards to toxicity, handling, operational simplicity, and heterogenicity. In continuation of our work (22) on the development of useful synthetic methodologies, herein, we wish to report a new Cu(II) complex as an excellent recoverable and heterogeneous catalyst for the synthesis of benzimidazole derivatives.

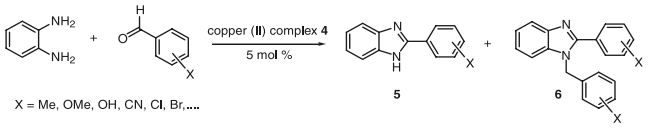
Results and discussion

The reaction pathway for the preparation of the catalyst is shown in Scheme 1. 2,6-Pyridinedicarboxylic acid (**1**) was boiled under reflux in $SOCl_2$ for 4 h. Excess of $SOCl_2$ was removed under reduced pressure to leave 2,6-pyridinedicarbonyldichloride (**2**). Then, a mixture of 2-aminophenol and triethylamine were dissolved in dry methylene chloride, temperature was adjusted to 0 °C, 2,6-pyridinedicarbonyldichloride was added dropwise, and the reaction mixture was stirred for 2 h. The resulting precipitate was filtered, washed with a saturated solution of $NaHCO_3$. Recrystallization of crude residue from an aqueous ethanol (50%) afforded 95% yield of yellowish solid of *N*,*N*-bis (2-hydroxyphenyl) pyridine-2,6-dicarboxamide (BHPPDAH) (**3**). In the next step, a mixture of BHPPDAH and cupric acetate was boiled under reflux in ethanol for 30 min. Finally, the reaction mixture was filtered, washed with H_2O, and air dried, which afforded 98% of brown solid of [Cu(BHPPDAH)H_2O] (**4**). This copper complex has already been synthesized by Gudasi and co-workers with different procedures and fully characterized (23).

In the presence of a catalytic amount of **4**, the reaction of *o*-phenylenediamine (*o*-PD) (1 mmol) was first examined with benzaldehyde (1 mmol) at room temperature in ethanol using atmospheric air as a green oxidant. Under optimized reaction conditions, we obtained exclusively the 2-substituted product, **5a** (x = H), and no N-alkylated product **6** was obtained (Scheme 2).

Control experiments without complex **4** under the same reaction conditions showed that no reaction occurred, thus confirming the effectiveness of Cu(II) complex as an effective heterogeneous catalyst (Table 1, entry 1). A catalytic amount of Cu(II) complex (5 mol%) is sufficient to obtain the desired product in high yield. A decrease in the amount of catalyst resulted in a significant reduction of the yield

Scheme 2.



while an increased amount of catalyst revealed negligible effect on the efficiency of the reaction (Table 1, entries 14 and 15). During the optimization studies, various solvents were examined, and it was found that solvent effect has an important role in terms of reaction rate, isolated yields, and selectivity (Table 1). *o*-Phenylenediamine and benzaldehyde were chosen as representative substrates. Among various solvents tested, acetonitrile, ethylene glycol, and 1,2-dichloroethane gave moderate yields of the expected product (Table 1, entries 8, 9, and 11). Methanol afforded the product in good yield (Table 1, entry 7). Obviously, ethanol was the solvent of choice owing to its fast reaction rate, high yield, good selectivity, cost effectiveness, and environmental acceptability (Table 1, entry 2). A trace benzimidazole was obtained when the reaction was operated in nitrogen atmosphere (Table 1, entry 5), supporting the fact that O_2 plays an important role in this reaction. Further bubbling of O_2 through the reaction mixture resulted in negligible change in the rate of reaction showing that the dissolved O_2 in solvent that is adsorbed by surface adsorption is sufficient for the efficient reaction completion.

To access the feasibility of applying this method in a preparative scale, we carried out the coupling of *o*-PD with benzaldehyde in 30 mmol scale in the presence of Cu(II) complex **4**. As expected, the reaction proceeded similar to the case in a smaller scale (Table 1, entry 2), and the desired 2-phenylbenzimidazole was obtained in 95% isolated yield in 2 h. The continuous bubbling of O_2 through the reaction mixture, instead of static atmosphere of air, did not accelerate the reaction rate, same as that mentioned in smaller scale reaction. $Cu(OAc)_2$ and Cu(II) salen were also examined as catalysts for this reaction; however, they were less effective compared with **4** and afforded banzimidazole **5** in 35% and 40% yields, respectively, (Table 1, entries 3 and 4).

From an environmental point of view, it is desirable to minimize the amount of waste for each organic transformation. In this context, the catalyst was recycled for subsequent runs. The recyclability of the catalyst was investigated using a model reaction between benzaldehyde and *o*-phenylendiamine in the presence of 5 mol% of the catalyst in ethanol as solvent. After the completion of the reaction, the mixture was filtered to separate the catalyst. The recycled catalyst was used for further runs, and it was found that its activity does not show any significant decrease even after 8 runs (Table 2).

Leaching experiment showed that the catalytic activity of Cu(II) complex **4** remained largely unchanged for 8 successive runs. To test the generality and versatility of this procedure in the synthesis of substituted benzimidazoles, we examined a number of differently substituted arylaldehydes and phenylendiamine using the optimized experimental conditions. As shown in Table 3, the aromatic aldehydes, having different substituents, such as methoxy, methyl, halogen, hydroxyl, nitrile, and nitro, were converted to the

Table 1. Copper(II)-catalyzed reaction of *o*-PD (1 mmol) and benzaldehyde (1 mmol) at room temperature.

Entry	Catalyst (5 mol%)	Solvent	Time (h)	Yield of product **5a**[a] (%)	Yield of by product **6a**[b] (%)
1	–	EtOH	24	—	—
2	**4**	EtOH	2	95	—
3	$Cu(OAc)_2$	EtOH	2	35	10
4	Cu(II)salen	EtOH	2	40	—
5	**4**[c]	EtOH	2.5	5	—
6	**4**	DMF	4	10	—
7	**4**	MeOH	3	85	2
8	**4**	Acetonitrile	10	50	5
9	**4**	Ethylene glycol	4	50	45
10	**4**	Chloroform	6	30	5
11	**4**	1,2-Dichloroethane	4	50	5
12	**4**	THF	6	10	2
13	**4**	EtOAc	6	20	—
14	**4**[d]	EtOH	4	60	—
15	**4**[e]	EtOH	2	96	—
16	**4**	—	4	10	40

[a,b]Isolated yields.
[c]Operated in nitrogen atmosphere.
[d]Using 2.5 mol% of **4**.
[e]Using 10 mol% of **4**.

Table 2. Re-use of catalyst.

Number of uses	Yield[a] (%)	Recovery of catalyst
1	95	98
2	95	97
3	93	97
4	92	97
5	90	95
6	90	95
7	89	93
8	89	93

[a]All yields refer to isolated product.

corresponding benzimidazoles in high yields (Table 3, entries 2–11). Heteroaryl aldehydes, such as 2-thiophene and pyridinyl, also gave acceptable yields (Table 3, entries 13 and 14). The reactions of 3,4-diaminobenzoic acid, 3,4-diaminotoluene, and 3,4-diaminobenzophenon with benzaldehyde were also studied. As mentioned above, all the substrates consistently afforded the reaction selectively to the corresponding benzimidazoles in high yields (Table 3, entries 17, 18, and 19). The presented method is suitable for the preparation of benzimidazoles from an acid-sensitive aldehyde such as furfuraldehyde (Table 3, entry 12) and sterically hindered aldehyde such as 2-naphthaldehyde (Table 3, entry 15). The structures of the products were determined from their spectral (^{1}H NMR, ^{13}C NMR, IR, and MS) analysis.

The proposed mechanism for the Cu(II) complex-catalyzed synthesis of benzimidazole derivatives may tentatively be visualized to occur via a tandem sequence of reactions as depicted in Scheme 3.

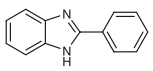
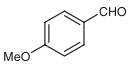
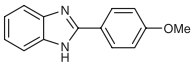
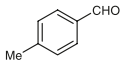
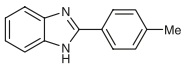
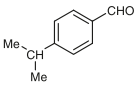
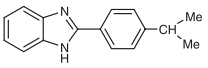
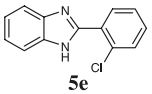
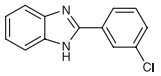
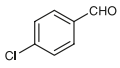
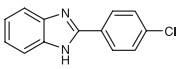
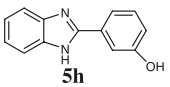
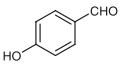
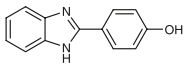
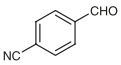
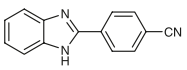
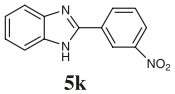
Mechanistically, a plausible pathway for this reaction involves the formation of intermediate Schiff base **A** very rapidly, as monitored by GC analysis. So, the rate-determining step (RDS) was found to be the oxidative-cyclization step. The compound **B** was formed as a result of an intermolecular reaction between the aniline amine and the intermediate imine moiety in **A**. We propose that reaction of **B** with Cu(II) complex **4** is accompanied by the reduction of Cu(II) to Cu(I), the utilization of O_2, and the concomitant generation of H_2O_2, as depicted in Scheme 3 (24–26).

H_2O_2 as efficient oxidant has been shown to catalyze the oxidation of some organic reactions (27, 28). We thought that, in the presence of H_2O_2, the rate of this reaction might increase. As we expected, in the presence of H_2O_2 (1 mmol), (*o*-PD) (1 mmol), benzaldehyde (1 mmol), and 5 mol% of **4** in 5 mL ethanol, the reaction time decreases. The mechanism for the increase in the rate of this reaction in the presence of H_2O_2 can be described as follows (25, 26): In the presence of H_2O_2, oxidation of **B** by Cu(II) is enhanced because of the regeneration of Cu(II) by H_2O_2 oxidizing Cu(I). The redox cycling between Cu(I)/Cu(II) H_2O_2 also produces a highly reactive OH radical, which can then attack to **C**, as shown in Scheme 3.

Conclusion

In summary, we have presented the first example of copper(II) complex-catalyzed synthesis of benzimidazoles in benign condition. This new and efficient catalytic method is amenable to a parallel-synthesis approach, as demonstrated by the synthesis of a library of benzimidazoles substituted at various positions on the ring. The advantage of this method is the use of atmospheric air as oxidant. No toxic reagents or byproducts were involved, and no laborious purifications were necessary. These conditions are also environment-friendly, cost-effective, and possess high generality to make our methodology industrialized as a valid contribution to the existing methodologies in the field of benzimidazole synthesis.

Table 3. Selective synthesis of benzimidazoles from various aryl aldehydes (1 mmol) and diamines (1 mmol) in the presence of Cu(II) complex **4** (5 mol%) in ethanol at room temperature.

Entry	Aldehyde	Diamine	Product	Time (h)	Yield[a] (%)
1			 **5a**	2	95
2			 **5b**	3.5	90
3			 **5c**	3	90
4			 **5d**	3.3	87
5			 **5e**	4	87
6			 **5f**	4.3	87
7			 **5g**	8	85
8			 **5h**	4	85
9			 **5i**	4.3	90
10			 **5j**	8	85
11			 **5k**	10	80

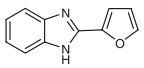
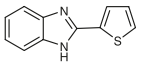
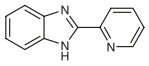
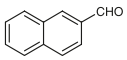
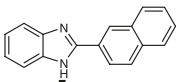
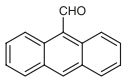
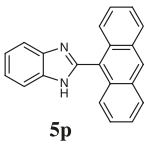
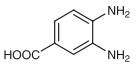
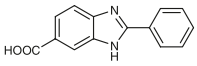
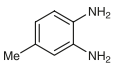
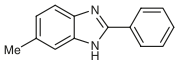
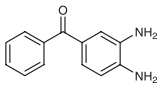
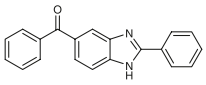
Experimental

Starting materials were obtained from Fluka, Sigma-Aldrich, and Merk companies. Progress of the reactions was followed by TLC using silica-gel polygrams SIL G/UV 254 plates or by GC using a Shimadzu gas chromatograph GC-14A, equipped with a flame-ionization detector and a 3 m long glass column packed with DC-200 stationary phase using nitrogen as the carrier gas. The NMR spectra were recorded on a Bruker Avance DPX-250 (^{1}H NMR 250 and ^{13}C NMR 62.9 MHz) in pure duterated solvents with tetramethylsilane (TMS) as internal standard. Melting points were determined in open capillary tubes in a Buchi-545 circulating-oil melting-point apparatus.

Preparation of BHPPDAH

2,6-Pyridinedicarboxylic acid (3.34 g, 20 mmol) was boiled under reflux in $SOCl_2$ (40 mL) for 4 h. Excess of $SOCl_2$ was removed under reduced pressure to leave 2,6-pyridinedicarbonyldichloride. Then 2-aminophenol (4.36 g, 40 mmol) was dissolved in dry methylene chloride (100 mL) followed by triethylamine (5.5 mL, 40 mmol). After that, 2,6-pyridinedicarbonyldichloride (4.08 g, 20 mmol) was added dropwise to the above-mentioned solution at 0 °C,

Table 3 (*concluded*).

Entry	Aldehyde	Diamine	Product	Time (h)	Yield[a] (%)
12			 **5l**	4.5	87
13			 **5m**	5	85
14			 **5n**	3	85
15			 **5o**	6	90
16			 **5p**	5	90
17			 **5q**	8	80
18			 **5r**	3.2	87
19			 **5s**	7.5	85

[a]Isolated yields.

and the reaction mixture was stirred for 2 h. Then, the precipitate was washed with a saturated solution of $NaHCO_3$. Recrystallization from aqueous ethanol (50%) afforded a yellowish solid of BHPPDAH in 95% yield. Mp 223 °C (Lit. 220–222 °C (23)). ^{1}H NMR (DMSO-d_6) δ_H: 6.82–7.06 (6H, m), 7.99 (2H, d, J = 7.9 Hz), 8.26–8.39 (3H, m), 10.02 (2H, s), 10.41(2H, s). ^{13}C NMR (DMSO-d_6) δ_C: 115.3, 119.1, 122.2, 124.9, 125.3, 125.4, 140.2, 148.5, 148.8, 160.9.

Prepration of [Cu (BHPPDA) H_2O] complex

A mixture of BHPPDAH (1.74 g, 5 mmol) and cupric acetate (2 g, 10 mmol) was boiled under reflux with ethanol (100 mL) for 30 min. Then, the reaction mixture was filtered, washed with H_2O, and dried in air to give a 98% yield of brown solid of [Cu(BHPPDAH)H_2O]. The copper(II) complex decomposes in two stages. The first step is 150–220 °C, and the second step is 220–470 °C ranges (23).

General method for the preparation of benzimidazole derivatives

A mixture of *o*-phenylendiamine (1 mmol), aldehyde (1 mmol), and catalyst (5 mol%) in 5 mL ethanol was stirred at room temperature for appropriate time. When the reaction was finished (monitored by TLC), the catalyst was filtered out, the filtrate was evaporated, and the residue was purified by short column chromatography over silica gel using *n*-hexane/ethyl acetate (7:1) or recrystallized from EtOH/H_2O (2:1) to afford the corresponding benzimidazole.

All produced benzimidazoles were characterized in detailed structural data by ^{1}H NMR and ^{13}C NMR, as given below.

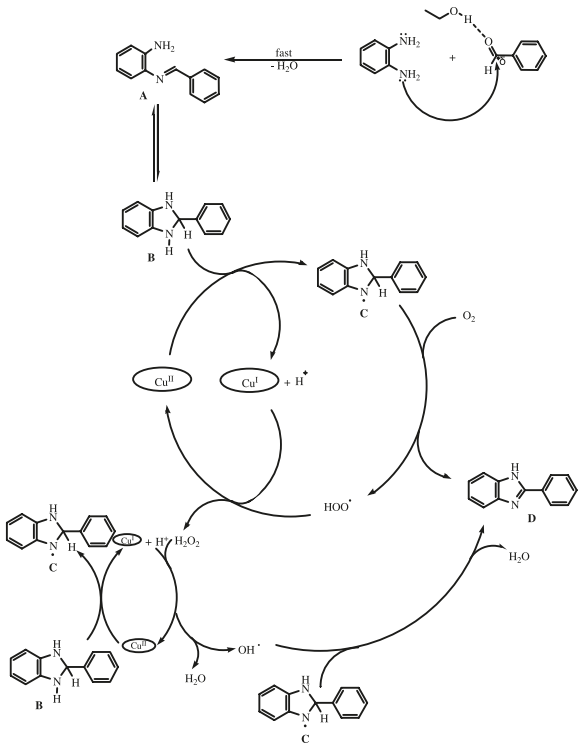
*2-Phenyl-1*H*-benzimidazole (5a)*

Purification by flash column chromatography, eluted with *n*-hexane/ethyl acetate (7:1), gave compound **5a** as a colourless powder in 95% yield. Mp 290–292 °C (Lit. 292 °C (29)). ^{1}H NMR (DMSO-d_6) δ_H: 7.14–7.25 (2H, m), 7.44–7.61 (5H, m), 8.20 (2H, d, J = 7.2 Hz), 12.94 (1H, s). ^{13}C NMR (DMSO-d_6) δ_C: 122.1, 126.4, 128.4, 128.9, 129.2, 129.8, 130.1, 151.2.

*2-(4-Methoxyphenyl)-1*H*-benzimidazole (5b)*

Purification by flash column chromatography, eluted with *n*-hexane/ethyl acetate (7:1), gave compound **5b** as a colourless powder in 90% yield. Mp 226 °C (Lit. 226–227 °C (31)). ^{1}H NMR (DMSO-d_6) δ_H: 3.78 (3H, s), 7.10 (2 H, d, J = 8.8 Hz), 7.16 (2H, q, J = 3.0 Hz), 7.50 (2H, m), 8.12 (2H, d, J = 8.8 Hz), 12.76 (1H, s). ^{13}C NMR (DMSO-d_6) δ_C:

Scheme 3.



55.2, 111.0, 114.3, 118.4, 121.5, 122.0, 122.6, 128.0, 151.3, 160.5.

*2-(4-Methylphenyl)-1*H*-benzimidazole (5c)*

Purification by flash column chromatography, eluted with *n*-hexane/ethyl acetate (7:1), gave compound **5c** as a colourless powder in 90% yield. Mp 270–272 °C (Lit. 270–272 °C (30)). ^{1}H NMR (DMSO-d_6) δ_H: 2.35 (3H, s), 7.15–7.20 (2H, m), 7.33 (2H, d, J = 8.1 Hz), 7.46–7.56 (2H, m), 8.07 (2H, d, J = 8.1 Hz), 12.84 (1H, s). ^{13}C NMR (DMSO-d_6) δ_C: 20.9, 121.9, 126.3, 127.4, 128.9, 129.4, 139.5, 151.3.

*2-(4-Isopropylphenyl)-1*H*-benzimidazole (5d)*

Purification by flash column chromatography, eluted with *n*-hexane/ethyl acetate (7:1), gave compound **5d** as a colourless powder in 87% yield. Mp 250–251 °C (Lit. 250–251 °C (20)). ^{1}H NMR (DMSO-d_6) δ_H: 1.22 (6H, d, J = 6.9 Hz), 2.93 (1H, m), 7.17 (2H, m), 7.40 (2H, d, J = 8.1 Hz), 7.51–7.62 (2H m), 8.10 (2H, d J = 8.2 Hz), 12.83 (1H, s). ^{13}C NMR (DMSO-d_6) δ_C: 23.6, 33.3, 111.2, 118.6, 121.5, 122.3, 126.4, 127.7, 150.3, 151.3.

*2-(2-Chlorophenyl)-1*H*-benzimidazole (5e)*

Purification by flash column chromatography, eluted with *n*-hexane/ethyl acetate (7:1), gave compound **5e** as a colourless powder in 87% yield. Mp 233–234 °C (Lit. 234 °C (29)). ^{1}H NMR (DMSO-d_6) δ_H: 7.20–7.24 (2H, m), 7.48–7.51 (2H, m), 7.54–7.68 (3H, m), 7.89–7.93 (1H, m), 12.74 (1H, s) ^{13}C NMR (DMSO-d_6) δ_C: 111.7, 119.0, 121.7, 122.7, 127.3, 129.9, 130.3, 131.1, 131.6, 132.0, 134.6, 143.1, 149.1.

*2-(3-Chlorophenyl)-1*H*-benzimidazole (5f)*

Purification by flash column chromatography, eluted with *n*-hexane/ethyl acetate (7:1), gave compound **5f** as a colourless powder in 87% yield. Mp 230–232 °C (Lit. 234.7–235.3 °C (36)). ^{1}H NMR (DMSO-d_6) δ_H: 7.21 (2H, m), 7.49–7.64 (4H, m), 8.13 (1H, dd, J_1 = 6.6, J_2 = 1.8 Hz), 8.21 (1H, s), 13.04 (1H, s). ^{13}C NMR (DMSO-d_6) δ_C: 111.5, 119.0, 122.0, 122.9, 125, 126, 129.5, 130.9, 132.1, 133.7, 143.5, 149.7.

*2-(4-Chlorophenyl)-1*H*-benzimidazole (5g)*

Purification by flash column chromatography, eluted with *n*-hexane/ethyl acetate (7:1), gave compound **5g** as a colourless powder in 85% yield. Mp 292–293 °C (Lit. 292 °C (29)). ^{1}H NMR (DMSO-d_6) δ_H: 7.18–7.21 (2H, m), 7.60 (4H, m), 8.17 (2H, d, J = 8.6 Hz), 12.99 (1H, s). ^{13}C NMR (DMSO-d_6) δ_C: 111.4, 118.9, 121.9, 122.7, 128.1, 129, 134.5 150.1.

*3-(1*H*-Benzimidazol-2-yl)phenol (5h)*

Purification by flash column chromatography, eluted with *n*-hexane/ethyl acetate (7:1), gave compound **5h** as a colourless powder in 85% yield. Mp 182–183 °C (Lit. 181–184 °C (34)). ^{1}H NMR (DMSO-d_6) δ_H: 6.86–6.89 (1H, m), 7.16–7.19 (2H, m), 7.32 (1H, t, J = 8.1 Hz), 7.55–7.58 (4H, m), 9.81 (1H, s). ^{13}C NMR (DMSO-d_6) δ_C: 112.6, 117.0, 117.2, 122.1, 129.6, 131.2, 151.4, 157.7.

*4-(1*H*-Benzimidazol-2-yl)phenol (5i)*

Purification by flash column chromatography, eluted with *n*-hexane/ethyl acetate (7:1), gave compound **5i** as a pale yellow powder in 90% yield. Mp 254–255 °C (Lit. 254.1–256.6 °C (35)). ^{1}H NMR (DMSO-d_6) δ_H: 6.93 (2H, dd, J_1 = 8.5, J_2 = 1.2 Hz), 7.10–7.22 (2H, m), 7.52–7.53 (2H, m), 8.02 (2H, d, J = 8.6 Hz), 10.07 (1H, s), 12.65 (1H, s). ^{13}C NMR (DMSO-d_6) δ_C: 115.7, 121.0, 121.6, 128.1, 151.8, 159.1.

*4-(1*H*-Benzimidazol-2-yl)benzonitrile (5j)*

Purification by flash column chromatography, eluted with *n*-hexane/ethyl acetate (7:1), gave compound **5j** as a colourless powder in 85% yield. Mp 262 °C (Lit. 261–262 °C (30)). ^{1}H NMR (DMSO-d_6) δ_H: 7.22–7.24 (2H, m), 7.50–7.70 (2H, m) 7.97 (2H, d, J = 8.3 Hz), 8.31 (2H, d, J = 8.3 Hz), 13.17 (1H, s) ^{13}C NMR (DMSO-d_6) δ_C: 111.8, 118.5, 119.3, 122.2, 123.2, 126.4, 631 126.9, 132.9, 134.2, 149.3.

*2-(3-Nitrophenyl)-1*H*-benzimidazole (5k)*

Purification by flash column chromatography, eluted with *n*-hexane/ethyl acetate (7:1), gave compound **5k** as a pale yellow powder in 80% yield. Mp 206–207 °C (Lit. 207–208 °C (32)). ^{1}H NMR (DMSO-d_6) δ_H: 7.21 (2H m), 7.61 (2H m), 7.74–7.84 (1H m), 8.23–8.32 (1H m), 8.52–8.57 (1H m), 8.95 (1H s), 13.24 (1H s). ^{13}C NMR (DMSO-d_6) δ_C: 116.0, 120.8, 122.7, 124.2, 130.6, 131.6, 132.4, 136.9, 148.3, 149.0.

*2-(2-Furyl)-1*H*-benzimidazole (5l)*

Purification by flash column chromatography, eluted with *n*-hexane/ethyl acetate (7:1), gave compound **5l** as a colourless powder in 80% yield. Mp 287–288 °C (Lit. 288 °C (29)). ^{1}H NMR (DMSO-d_6) δ_H: 6.69 (1H, dd, J_1 = 3.4, J_2 =

1.7 Hz), 7.16–7.20 (4H, m), 7.53 726 (1H, d, J = 3.1 Hz), 7.56 (1H, d, J = 3.1 Hz), 7.89 (1H, s). ^{13}C NMR (DMSO-d_6) δ_C: 110.6, 112.3, 115.0, 122.3, 138.8, 143.6, 144.6, 145.3.

2-(2-Thienyl)-1H-benzimidazole (5m)

Purification by flash column chromatography, eluted with *n*-hexane/ethyl acetate (7:1), gave compound **5m** as a yellow powder in 87% yield. Mp 329–331 °C (Lit. 330 °C (33)). ^{1}H NMR (DMSO-d_6) δ_H: 7.16–7.22 (3 H, m), 7.48–7.58 (2H, m), 7.73 (1H, d, J = 3.1 Hz), 7.82 (1H, d, J = 2.7 Hz), 12.96 (1H, s). ^{13}C NMR (DMSO-d_6) δ_C: 111.0, 118.4, 121.7, 122.6, 126.6, 128.2, 128.7, 133.6, 134.6, 147.0.

2-(2-Pyridyl)-1H-benzimidazole (5n)

Purification by flash column chromatography, eluted with *n*-hexane/ethyl acetate (7:1), gave compound **5n** as a colourless powder in 85% yield. Mp 218 °C (Lit. 218 °C (29)). ^{1}H NMR (DMSO-d_6) δ_H: 7.16–7.24 (2H, m), 7.47–7.71 (3H, m), 7.98 (1H, dd, J_1 = 7.7, J_2 = 1.7 Hz), 8.30–8.34 (1H, m), 8.71 (1H, d, J = 6.9 Hz), 13.01 (1H, s). ^{13}C NMR (DMSO-d_6) δ_C: 112.0, 119.2, 121.4, 121.9, 123.1, 124.6, 134.8, 137.5, 143.7, 148.4, 149.3, 150.7.

2-(2-Naphthyl)-1H-1,3-benzimidazole (5o)

Purification by flash column chromatography, eluted with *n*-hexane/ethyl acetate (7:1), gave compound **5o** as a colourless powder in 90% yield. Mp 217 °C (Lit. 219 °C (37)). ^{1}H NMR (DMSO-d_6) δ_H: 7.19 (2H, dd, J_1 = 6.0, J_2 = 3.0 Hz), 7.37–7.40 (2H, m), 7.59–7.77 (5H, m), 8.11 (1H, dd, J_1 = 8.6, J_2 = 1.7 Hz), 8.49 (1H, s). ^{13}C NMR (DMSO-d_6) δ_C: 115.2, 123.2, 123.6, 126.5, 126.8, 127.2, 127.8, 128.5, 129.0, 134.2, 138.1, 145.9, 151.6.

2-(9-Anthryl)-1H-benzimidazole (5p)

Purification by flash column chromatography, eluted with *n*-hexane/ethyl acetate (7:1), gave compound **5p** as a yellow powder in 90% yield. Mp 301 °C (Lit. 302–303 °C (38)). ^{1}H NMR (DMSO-d_6) δ_H: 7.29 (2H, m), 7.46–7.72 (9H, m), 8.19 (2H, d, J = 8.1 Hz), 8.83 (1H, s). ^{13}C NMR (DMSO-d_6) δ_C: 115.6, 122.6, 125.9, 126.1, 127.3, 127.6, 128.9, 129.3, 131.1, 134.2, 139.4, 146.7, 150.0.

2-Phenyl-1H-benzimidazole-6-carboxylic acid (5q)

Purification by flash column chromatography, eluted with *n*-hexane/ethyl acetate (7:1), gave compound **5q** as a colourless powder in 80% yield. Mp 325 °C (Lit. 325 °C (20)). ^{1}H NMR (DMSO-d_6) δ_H: 7.47–7.66 (4H, m), 7.84 (1H, d, J = 8.4 Hz), 8.17–8.20 (3H, m), 12.79 (1H, s), 13.19 (1H, s). ^{13}C NMR (DMSO-d_6) δ_C: 122.7, 123.5, 124.0, 125.0, 126.7, 128.3, 129.2, 129.6, 130.3, 142.4, 153.7, 168.0.

5-Methyl-2-phenyl-1H-benzimidazole (5r)

Recrystallization from EtOH/H_2O (2:1) gave compound **5r** as a colourless powder in 87% yield. Mp 242–243 °C (Lit. 242–143 °C (30)). ^{1}H NMR (DMSO-d_6) δ_H: 2.35 (3H, S), 7.00 (1H, d, J = 8.1 Hz), 7.36–7.55 (5H, m), 8.14(2H, d, J = 7.6 Hz), 12.75 (1H, s). ^{13}C NMR (DMSO-d_6) δ_C: 21.3, 111.1, 118.4, 123.5, 126.2, 128.8, 129.2, 129.6, 130.3, 131.1, 150.9.

Phenyl(2-phenyl-1H-benzimidazol-5-yl)methanone (5s)

Recrystallization from EtOH/H_2O (2:1) gave compound **5s** as a pale yellow powder in 85% yield. Mp 221–222 °C (Lit. 221–221.5 °C (30)). ^{1}H NMR (DMSO-d_6) δ_H: 7.41–7.58 (11H, m), 8.19 (2H, d, J = 7.4 Hz), 13.28 (1H, s). ^{13}C NMR (DMSO-d_6) δ_C: δ 124.2, 126.7, 128.3, 129.0, 129.4, 129.5, 130.4, 131.0. 132.0, 138.7, 153.9.1, 195.5.

Acknowledgements

We gratefully acknowledge the support of this work by the Shiraz University Research Council. We are also grateful to Mr. H. Sajedian Fard and Mr. M.S. Darvish Tafvizi for helpful cooperation.

References

1. (*a*) M.J. Tebbe, W. A. Spitzer, F.Victor, S.C. Miller, C.C. Lee, T.R.E. Mckinney, and C.J. Tang. J. Med. Chem. **40**, 3937 (1997); (*b*) K.L. Brown. Chem. Rev. **105**, 2075 (2005).
2. (*a*) A.R. Porcari, R.V. Devivar, L.S. Kucera, J.C. Drach, and L.B. Townsend. J. Med. Chem. **41**, 1252 (1998); (*b*) M. Roth, M.L. Morningstar, P.L. Boyer, S.H. Hughes, R.W. Bukheit, and C.J. Michejda. J. Med. Chem. **40**, 4199 (1997).
3. M.T. Migawa, J.L. Giradet, J.A. Walke, G.W. Koszalka, S.D. Chamberlain, J.C. Drach, and L.B. Townsend. J. Med. Chem. **41**, 1242 (1998).
4. I. Tamm and P.B. Seghal. Adv. Virus Res. **22**, 187 (1978).
5. I. Tamm. Science (Washington, DC), **126**, 1235 (1957).
6. A.A. Spasov, I.N. Yozhitsa, L.I. Bugaeva, and V.A. Anisimova. Pharm. Chem. J. **33**, 232 (1999).
7. For comprehensive reviews on the chemistry of benzimidazoles, see: (*a*) J.B. Wright. Chem. Rev. **48**, 397 (1951); (*b*) P.N. Preston. Chem. Rev. **74**, 279 (1974).
8. K. Niknam and A. Fatehi-Raviz. J. Iran. Chem. Soc. **4**, 438 (2007); available from www.ics-ir.org/jics.
9. (*a*) R.R. Nagawade and D.B. Shinde. Indian. J. Chem. B, **46**, 349 (2007); (*b*) K. Bahrami, M.M. Khodaei, and F. Naali. J. Org. Chem. **73** (2008). In press.
10. R.R. Nagawade and D.B. Shinde. Russ. J. Org. Chem. **42**, 453 (2006).
11. R. Trivedi, S.K. De, and R.A. Gibbs. J. Mol. Catal A: Chem. **245**, 8 (2006).
12. T. Itoh, K. Nagata, H. Ishikawa, and A. Ohsawa. Heterocycles, **63**, 2769 (2004).
13. M. Curini, F. Epifano, F. Montanari, O. Rosati, and S. Taccone. Synlett, 1832 (2004).
14. P. Sun and Z. Hu. J. Heterocyclic Chem. **43**, 773 (2006).
15. R.R. Nagawade and D.B. Shinde. Chinese Chem. Lett. **17**, 453 (2006).
16. (*a*) M. Chakrabarty, S. Karmakar, A. Mukherji, S. Arima, and Y. Harigaya. Heterocycles, **68**, 967 (2006); (*b*) H. Sharghi, O. Asemani, and M.H. Tabaei. J. Heterocycl. Chem. **45**, 1 (2008).
17. U. Srinivas, Ch. Srinivas, P. Narender, V. Jayathirtha Rao, and S. Palaniappan. Catal. Commun. **8**, 107 (2007).
18. H. Sharghi, O. Asemani, and R. Khalifeh. Synth. Commun. **38**, 1128 (2008).
19. J.G. Smith and I. Ho. Tetrahedron Lett. **12**, 3541 (1971).
20. (*a*) H. Sharghi, M.H. Beyzavi, and M.M. Doroodmand. Eur. J. Org. Chem, 4126 (2008); (*b*) H. Sharghi, M. Aberi, and M.M. Doroodmand. Advan. Synth. Catal. In press.

21. (*a*) N. Mizuno and M. Misono. Chem. Rev. **98**, 199 (1998); (*b*) G. Sartori, R. Ballini, F. Bigi, G. Bosica, R. Maggi, and P. Righi. Chem. Rev. **104**, 199 (2004).
22. (*a*) H. Sharghi and M. Hosseini Sarvari. Synthesis, 243 (2003); (*b*) H. Sharghi and M. Hosseini Sarvari. J. Org. Chem. **69**, 6953 (2004); (*c*) H. Sharghi and M. Hosseini Sarvari. J. Iran. Chem. Soc. **1**, 28 (2004); available from www.ics-ir.org/jics/; (*d*) M. Hosseini Sarvari and H. Sharghi. Tetrahedron, **61**, 10903 (2005); (*e*) M. Hosseini Sarvari and H. Sharghi. J. Org. Chem. **71**, 6652 (2006); (*f*) H. Sharghi, A. Salimi Beni, and R. Khalifeh. Helv. Chim. Acta, **90**, 1373 (2007); (*g*) H. Sharghi, M. Hosseini Sarvari, and S. Ebrahimpourmoghaddam. Arkivoc, 255 (2007); (*h*) H. Sharghi and R. Khalifeh. Heterocycles, **71**, 1601 (2007); (*i*) H. Sharghi and M. Jokar. Heterocycles, **71**, 2721 (2007); (*j*) H. Sharghi and R. Khalifeh. Can. J. Chem. **86**, 426 (2008); (*k*) H. Sharghi and S. Ebrahimpourmoghaddam. Helv. Chim. Acta, **91**, 1363 (2008).
23. K.B. Gudasi, R.S. Vadavi, R.V. Shenoy, M.S. Patil, and S.A. Patil. Transition Met. Chem. **30**, 569 (2005).
24. Y. Li and M.A. Trush. Arch. Biochem. Biophys. **300**, 346 (1993).
25. R. Liu, B. Goodell, J. Jellison, and A. Amirbahman. Environ. Sci. Technol. **39**, 175 (2005).
26. Q. Liang and P.C. Dedon. Chem. Res. Toxicol. **14**, 416 (2001).
27. S. Velusamy, A.V. Kumar, R. Saini, and T. Punniyamurthy. Tetrahedron Lett. **46**, 3819 (2005).
28. S. Velusamy and T. Punniyamurthy. Eur. J. Org. Chem, 3913 (2003).
29. B.A. Abdelkrim. Tetrahedron Lett. **44**, 5935 (2003).
30. R.J. Perry and B.D. Wilson. J. Org. Chem. **58**, 7016 (1993).
31. B. George and E.P. Papadopoulos. J. Org. Chem. **42**, 441 (1977).
32. G. Holan, J.J. Evan, and M. Linton. J. Chem. Soc., Perkin Trans. 1, 1200 (1977).
33. P. Gogoi and D. Konwar. Tetrahedron Lett. **47**, 79 (2006).
34. M.N. Ibrahim. Asian J. Chem. **19**, 2419 (2007).
35. G. Navarrete-Vazquez, H. Moreno-Diaz, F. Aguirre-Crespo, I. Leon-Rivera, R. Villalobos-Molina, O. Munoz-Muniz, and S. Estrada-Soto. Bioorg. Med. Chem. Lett. **16**, 4169 (2006).
36. S. Jaroslav. Collect. Czech. Chem. Commun. **46**, 2703 (1981).
37. S. Robev. Dokl. Akad. Nauk, **34**, 663 (1981).
38. K. Niume, K. Toyofuku, F. Toda, K. Uno, M. Hasegawa, and Y. Iwakura. J. Polym. Sci. 663 (1982).