IRANIAN JOURNAL OF CATALYSIS

Urea-hydrogen peroxide/silica phosphoric acid-catalyzed oxidation-condensation Tandem reaction: One-pot synthesis of 2-substituted benzimidazoles from alcohols

Ahmad Reza Momeni*, Heshmat Allah Samimi, Reyhaneh Jahanian

Faculty of Sciences, Shahrekord University, 115-381, Shahrekord, Iran.

Received 23 October 2012; received in revised form 14 November 2012; accepted 15 November 2012.

ABSTRACT

An efficient one-pot oxidation/condensation tandem process has been developed for the synthesis of 2-substituted benzimidazole derivatives from benzylic alcohols and 1,2-phenylenediamine with use of urea-hydrogen peroxide/silica phosphoric acid as a bifunctional catalyst. This method provides a rapid and efficient access to 2-substituted benzimidazoles.

***Keywords**: Urea-hydrogen peroxide, Silica phosphoric acid, Benzimidazoles, Alcohols.*

1. Introduction

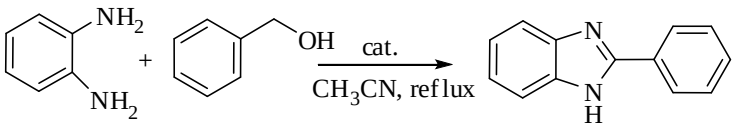
Benzimidazole and its derivatives are a kind of compounds which exerts a wide range of biological activities, such as anti-inflammatory [1–3] histamine-H3 antagonist [4, 5] anticancer [6, 7] and antimetabolite [8]. For their varied biological activities, benzimidazole derivatives have attracted continuing interest over the years and were widely applied as an important pharmacophore or building block in drug discovery [9–11].

The widespread interest in benzimidazole-containing structures has prompted extensive studies for their synthesis. There are two general methods for the synthesis of 2-substituted benzimidazoles. One is the coupling of phenylenediamines and carboxylic acids or their derivatives (nitriles, imidates, or orthoesters), under harsh dehydrating conditions [12-14]. The other way for the synthesis of these compounds is the reaction of 1,2-phenylenediamine (OPD) with aldehydes in the presence of acidic catalysts under various reaction conditions [15-23]. However, many of these methods have several drawbacks such as low yields, use of expensive reagents, long reaction times, tedious work-up procedures, co-occurrence of several side reactions and poor selectivity. Therefore, the search continues for a better catalyst for the synthesis of benzimidazoles in terms of operational simplicity, economic viability and in particular, with greater selectivity.

* Corresponding author: E-mail: momeni-a@sci.sku.ac.ir.
Tel: +98 381 4424419, Fax: +98 381 4424419

Oxidation and condensation are two major reactions of organic chemistry. More powerful and useful transformations are possible when these two classes of reactions are combined in a one-pot procedure. Benzylic alcohols oxidation and subsequent condensation-aromatization are good examples of such transformations.

There is a few reports of the direct preparation of 2-substituted benzimidazoles from alcohols; Watanabe *et al* prepared 2-substituted benzimidazoles by the ruthenium-catalyzed reaction of 1,2-phenylenediamines with alcohols which presumably proceed by way of the corresponding aldehyde generated *'in situ'* [24], that very high temperatures (200˚C) and autoclave conditions were required. Corma and co-workers prepared 2-substituted benzimidazoles by reaction of benzyl alcohol and 1,2-phenylenediamine in the presence of Au/CeO_2 and Pd/MgO as bifunctional catalyst [25]. Although this methodology shows utilization of bifunctional catalyst to couple both the steps of oxidation and cyclization, there is enough scope to improve this route as it suffers from drawbacks such as use of oxidant (O_2) under pressure conditions, long reaction time, use of expensive Au or Pd based catalyst and complex reaction procedure. Paraghi *et al* [26] have reported a route for synthesis of benzimidazole wherein the starting reactant alcohol is oxidized to generate aldehyde and then the diamine is added to yield the corresponding benzimidazoles using a mixture of H_2O_2 and MoO_3-SiO_2 as bifunctional catalyst. However the unstable nature of liquid hydrogen peroxide limits its applications in practical oxidation reactions.



cat.: UHP/SiO_2-OPO_3H_2 or MnO_2/SiO_2-OPO_3H_2

Scheme 1.

In continuation of our work [27-29] on the development of useful synthetic methodologies, we present here, a one-pot multistep process for the synthesis of benzimidazoles starting from alcohols (Scheme 1). Urea–hydrogen peroxide (UHP)/silica phosphoric acid (SiO_2-OPO_3H_2) used as green bifunctional oxidative and acidic catalyst for this purpose. The catalyst presented here allows starting the reaction from the alcohols that will be oxidized to the corresponding aldehyde and then condense with diamine 'in situ'.

2. Experimental

All products are known compounds and their structures were characterized by comparing their physical and spectral data with those of reported compounds in the literature [22, 30-32]. Silica Phosphoric acid [33] and activated manganese dioxide [34] were prepared according to previous reported procedures.

2.1. General procedure for synthesis of 2-arylbenz imidazoles catalyzed by UHP/SiO_2-OPO_3H_2

A mixture of benzyl alcohol (1 mmol), 1,2-phenylenediamine (1 mmol) and $MgBr_2$ (0.2 mmol) were dissolved in CH_3CN (5 mL) in a round-bottomed flask. A mechanically premixed combination of UHP (8 mmol) and SiO_2-OPO_3H= (100 mg) was added. After 60 min stirring at reflux, the catalyst was removed by filtration and washed by additional hot methanol. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel preparative thin layer chromatography (20% ethyl acetate in hexane).

2.2. General procedure for synthesis of 2-arylbenz imidazoles catalyzed by MnO_2/ SiO_2-OPO_3H_2

For the synthesis of the benzimidazoles, using MnO_2/SiO_2-OPO_3H_2, to a mixture of benzyl alcohol (1 mmol) and 1,2-phenylenediamine (1 mmol) in CH_3CN (5 mL), a mechanically premixed combination of active MnO_2 (6 mmol) and SiO_2-OPO_3H_2 (100 mg) was added. The mixture was stirred at reflux for 120 min, the catalyst was removed by filtration and washed by additional hot methanol. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel preparative thin layer chromatography (20% ethyl acetate in hexane).

Selected Spectral Data

2-(4-Methoxyphenyl)-1H-benzimidazole (6): mp = 226–228ºC. ^{1}H NMR (DMSO-d_6, ppm) δ: 3.82 (s, 3H, OCH_3), 7.25–7.73 (m, 8H, aromatic), 12.99 (bs, NH).

Table 1. Effect of UHP and SiO_2-OPO_3H_2 on the synthesis of 2-phenyl-1H-benzimidazole.

Entry	Catalyst amount	Yield (%)
Effect of UHP ratio (mmol)[a]		
1	4	32
2	6	52
3	8	70
4	10	66
Effect of SiO_2-OPO_3H_2 (g)[b]		
5	0	-
6	0.05	70
7	0.1	74
8	0.2	74

[a]Reaction conditions: benzyl alcohol (1 mmol), OPD (1mmol), $MgBr_2$ (0.2 mmol), CH_3CN (5 ml), 1 h at reflux conditions. SiO_2-OPO_3H_2 (0.05 g).
[b]UHP (8 mmol).

2-(3-Nitrophenyl)-1H-benzimidazole (3): m.p = 309–310ºC. ^{1}H NMR (DMSO-d_6, ppm) δ: 7.31–8.62 (m, 8H, aromatic), 12.20 (bs, NH).

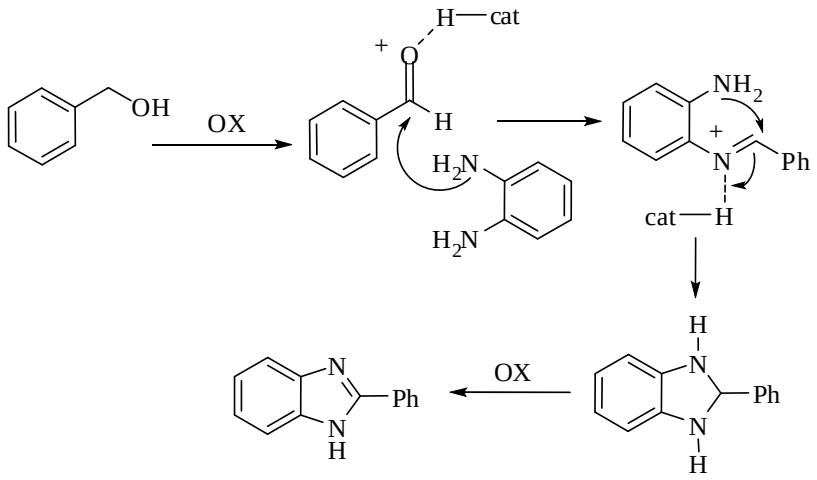
2-(4-Chlorophenyl)-1H-benzimidazole (7), m.p: 290-292 ºC. ^{1}H NMR (DMSO-d_6, ppm) δ: 7.18-8.08 (m, 8H, aromatic), 12.70 (bs, NH).

3. Result and Discussion

3.1. Effect of the catalyst on the synthesis of 2-arylbenzimidazoles

In order to optimize the reaction parameters, initially we started our investigation by using UHP as the oxidant. The reaction of benzyl alcohol (BA) with UHP and UHP/SiO_2-OPO_3H_2 was performed in CH_3CN but no oxidation reactions were observed. Previously, various methods for the UHP promoted oxidation of benzylic alcohols have been reported. Representative examples include the oxidation of benzylic alcohols with UHP in combination with activators [35]. Then, we carried out the reaction again in presence of $MgBr_2$, benzyl alcohol successfully underwent oxidation reactions by this procedure.

The effect of various ratios of UHP and silica phosphoric acid on the catalytic activity in the synthesis of 2-phenyl-1H-benzimidazole was investigated, and the results are shown in Table 1. In the absence of silica phosphoric acid, the reaction did not yield any product. This result suggests



Scheme 2.

that acidic catalyst plays a critical role in this reaction. We kept SiO_2-OPO_3H_2 amount constant and used different ratio UHP/BA. As shown in the Table 1, with the increase in the amount of oxidant reagent (Entries 1-3) the yield of reaction increased. However, on further increasing the UHP ratio from 8 to 10, the yield of 2-phenyl-1H- benzimidazole decreased (Entry 4) with the formation of side products. Then, the reaction proceeded with different amount of SiO_2-OPO_3H_2. We found that increasing the amount of acidic catalyst from 0.05 to 0.1 g increased the yield of desired benzimidazole (Entries 6-7) but when the SiO_2-OPO_3H_2 increased to 0.2 g no change in yield was observed. Based on our results the best condition to prepare the 2-phenyl-1H-benzimidazole was achieved when UHP (8 mmol), silica phosphoric acid (0.1g), $MgBr_2$ (0.2 mmol), Benzyl alcohol (1 mmol) and OPD (1 mmol) were used, respectively.

3.2. Choice of reaction media

To check the influence of solvent on reaction outcome, we choose synthesis of 2-phenyl-1H-benzimidazole as model reaction. The model reaction was examined in various organic solvents, As Table 2 shows, all solvents, including low boiling point solvents such as dichloromethane (Entry 3), can be used in this reaction. Clearly, CH_3CN (Entry 2) stands out as the solvent of choice, with its fast conversion, and high yield.

3.3. Synthesis of 2-substituted benzimidazoles

To te.st the general scope and versatility of this procedure in the synthesis of 2- substituted benzimidazoles, we examined a number of differently substituted benzyl alcohols. As Table 3 shows, benzyl alcohols containing both electron-donating and electron- withdrawing groups worked well. α,β-unsaturated benzyl alcohols (Table 3, Entry 9) also afforded the desired products but in lower yields. Heteroaryl alcohol such as pyridine-3-methanol (Entry 8), gave desired benzimidazole in good yield under these conditions.

In continuation of this work, we decided to use the relatively

Table 2. Effect of solvent in the synthesis of 2-phenyl-1H-benzimidazole.[a]

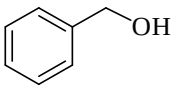
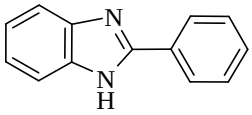
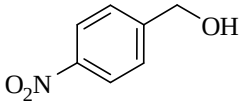
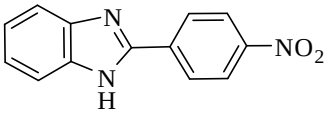
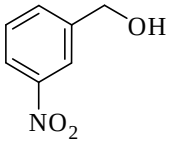
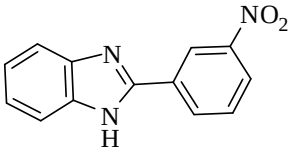
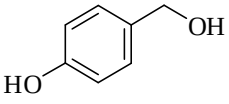
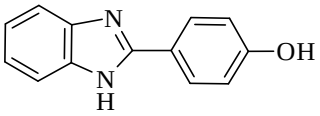
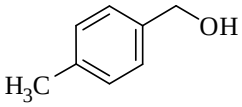
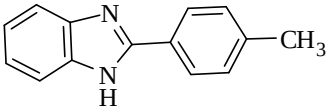
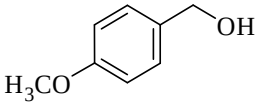
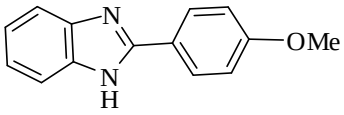
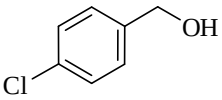
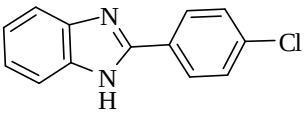
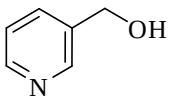
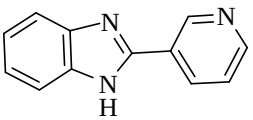
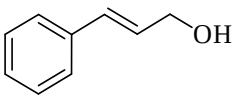
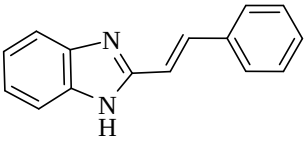
Entry	Solvent	Yield (%)
1	C_2H_5OH	70
2	CH_3CN	74
3	CH_2Cl_2	23
4	$CHCl_3$	40

[a] Reaction conditions: benzyl alcohol (1 mmol), OPD (1 mmol), $MgBr_2$ (0.2 mmol), UHP (8 mmol), SiO_2-OPO_3H_2 (0.1 g), CH_3CN (5 ml), 1 h at reflux conditions.

cheap and similarly active catalytic system including MnO_2 and silica phosphoric acid as a bifunctional catalyst for the synthesis of benzimidazoles. The use of manganese dioxide in the presence of HCl for the one-pot preparation 2-substituted benzimidazoles from alcohols has been previously reported [36]. This methodology is ideal for preparing 1-alkylated-2-substituted benzimidazoles from activated alcohols but not for the direct preparation of the corresponding parent 1H-benzimidazoles.

We performed a set of preliminary experiments on benzyl alcohol and 1,2-phenylendiamine in the presence of MnO_2/SiO_2-OPO_3H_2 as catalyst. We were surprised and pleased to see that a significant amount of the desired 2-phenylbenzimidazole was produced under these conditions while MnO_2/HCl is ideal for preparing 1-alkylated-2-substituted benzimidazoles. Then, we examined the temperature, MnO_2/SiO_2-OPO_3H_2 ratio, and the effect of different solvent to establish the conditions for the condensation reaction. It was found that when 1,2-phenylenediamine (1 mmol) and benzyl alcohol (1 mmol) was stirred at reflux in the presence of MnO_2/SiO_2-OPO_3H_2 (6 mmol/0.1g) in acetonitrile, the reaction proceeded slowly to afford 2-phenyl-1H-benzoimidazole in 70% yield. With the initial success of this reaction, we set out to determine the scope and variability of the procedure. The condensation of various

Table 3. Synthesis of benzimidazole derivatives from aromatic alcohols and 1,2-phenylenediamine[a].

Entry	Alcohol	Product	Yield[b] (%)		Ref.
			UHP	MnO_2	
1			74	70	[15]
2			50	40	[15]
3			43	55	[16]
4			67	60	[15]
5			60	67	[15]
6			78	63	[15]
7			66	60	[16]
8			53	65	[15]
9			30	30	[32]

[a]Reactions were performed at reflux by using 1 mmol of alcohol, 1 mmol diamine, UHP/SiO_2-OPO_3H_2 (8 mmol/0.1g) and $MgBr_2$ (0.2 mmol) for 1 h or MnO_2/ SiO_2-OPO_3H_2 (6 mmol/0.1 g) for 2 h in 5 mL of acetonitrile.
[b]Isolated yields.

of various benzyl alcohols with 1,2-phenylenediamine have been examined (Scheme 1). The results are summarized in Table 3. The key advantage of these approaches is that from a common benzylic alcohols scaffold, by simply using common reagents and a common operation, 2-substituted benzimidazoles can be easily accessed. The proposed

mechanism for synthesis of 2-substituted benzimidazoles may be visualized to occur via reactions as depicted in Scheme 2. UHP or MnO_2 oxidized alcohol to aldehyde, silica phosphoric acid activated the aldehydic carbonyl oxygen to form the benzylidene-1,2-phenylenediamine and ring closure leading to a five membered ring. Finally, oxidation followed to produce 2-substituted benzimidazoles.

4. Conclusion

In summary, we have described a simple and efficient, one-pot procedure for the generation of 2-substituted benzimidazoles directly from easily available benzyl alcohols, using inexpensive catalysts. The present protocol has several advantages: short reaction times, easy preparation of the catalysts, operational and experimental simplicity.

Acknowledgements

Financial support from the Research Council of Shahrekord University is gratefully acknowledged.

References

[1] K.F. Ansari, C. Lal, Eur. J. Med. Chem. 44 (2009) 2294-2299.
[2] H. Goker, S. Ozden, S. Yildiz, D.W. Boykin, Eur. J. Med. Chem. 40 (2005) 1062-1069.
[3] S.M. Sondhi, N. Singh, A. Kumar, O. Lozach, L. Meijer, Bioorg. Med. Chem. 14 (2006) 3758-3765.
[4] M. Mor, F. Bordi, C. Silva, S. Rivara, V. Zuliani, F. Vacondio, M. Rivara, E. Barocelli, S. Bertoni, V. Ballabeni, F. Magnanini, M. Impicciatore, P.V. Plazzi, Bioorg. Med. Chem. 12 (2004) 663-674.
[5] M. Rivara, V. Zuliani, G. Cocconcelli, G. Morini, M. Comini, S. Rivara, M. Mor, F. Bordi, E. Barocelli, V. Ballabeni, S. Bertoni, P.V. Plazzi, Bioorg. Med. Chem. 14 (2006) 1413-1424.
[6] S. Demirayak, U. Abu Mohsen, A.C. Karaburun, Eur. J. Med. Chem. 37 (2002) 255-260.
[7] T. Yamori, A. Matsunaga, S. Sato, K. Yamazaki, A. Komi, K. Ishizu, I. Mita, H. Edatsugi, Y. Matsuba, K. Takezawa, O. Nakanishi, H. Kohno, Y. Nakajima, H. Komatsu, T. Andoh, T. Tsuruo, Cancer Res. 59 (1999) 4042-4049.
[8] W. Nawrocka, B. Sztuba, M.W. Kowalska, H. Liszkiewicz, J. Wietrzyk, A. Nasulewicz, M. Pelczynska, A. Opolski, Farmaco (Lausanne) 59 (2004) 83-91.
[9] D. Agic, M. Hranjec, N. Jajcanin, K. Starcevic, G. Karminski-Zamola, M. Abramic, Bioorg. Chem. 35 (2007) 153-169.
[10] M.A. Ismail, R. Brun, T. Wenzler, F.A. Tanious, W.D. Wilson, Boykin, D.W. Bioorg. Med. Chem. 12 (2004) 5405-2413.
[11] K. Starcevic, M. Krajl, K. Ester, I. Sabol, M. Grce, K. Pavelic, G. Karminski- Zamola, Bioorg. Med. Chem. 15 (2007) 4419-4426.
[12] Y.C. Chi, C.M. Sun, Synlett (2000) 591-594.
[13] W. Huang, R.M. Scarborough, Tetrahedron Lett. 40 (1999) 2665-2668.
[14] L.M. Dudd, E. Venardou, E. Garcia-Verdugo, P. Licence, A.J. Blake, C. Wilson, M. Poliakoff, Green Chem. 5 (2003) 187-192.
[15] A.B. Allouma, K. Bougrin, M. Soufiaoui, Tetrahedron Lett. 44 (2003) 5935-5937.
[16] A.R. Momeni, S. Bagheri, Iranian J. Catal. 2 (2012) 31-35.
[17] B. Das, H. Holla, Y. Srinivas, Tetrahedron Lett. 48 (2007) 61-64.
[18] P. Ghosh, A. Mandal, Catal. Commun. 12 (2011) 744–747.
[19] H. Xiangming, M. Huiqiang, W. Yulu, ARKIVOC 2007 (xiii) 150-154.
[20] P. Salehi, M. Dabiri, M.A. Zolfigol, S. Otokesh, M. Baghbanzadeh, Tetrahedron Lett. 4 (2006) 2557-2560.
[21] Z.H. Zhang, L. Yin, Y.M. Wang, Catal. Commun. 8 (2007) 1126–1131.
[22] K. Niknam, A. Fatehi-Raviz, J. Iran. Chem. Soc. 4 (2007) 438-443.
[23] C. Mukhopadhyay, P.K. Tapaswi, Tetrahedron Lett. 49 (2008) 6237-6240.
[24] T. Kondo, S. Yang, K.T. Huh, M. Kobayashi, S. Kotachi, Y. Watanabe, Chem. Lett. (1991) 1275-1278.
[25] V.R. Ruiz, A. Corma, M.J. Sabater, Tetrahedron Lett. 66 (2010) 730-735.
[26] K.D. Parghi, R.V. Jayaram, Catal. Commun. 11 (2010) 1205-1210.
[27] A.R. Momeni, M. Sadeghi, Appl. Catal. A 357 (2009) 100-105.
[28] A.R. Massah, M. Dabagh, M. Afshar, A.R. Momeni, H. Aliyan, H.J. Naghash, Turk. J. Chem. 31 (2007) 611-616.
[29] H. Aliyan, R. Fazaeli, H.J. Naghash, A.R. Massah, A.R. Momeni, Z. Iravani, Heteroatom Chem. 20 (2009) 325-331.
[30] Y.Wang, K.Sarris, D.R. Sauer, S.W. Djuric, Tetrahedron Lett. 473 (2006) 4823-4826.
[31] R.P. Karuvalam, M. Siji, N. Divia, K.R. Haridas J. Korean Chem. Soc. 54 (2010) 589-593.
[32] R.R. Nagawade, D.B. Shinde, Chin. Chem. Lett. 17 (2006) 453-456.
[33] M.A. Zolfigol, F. Shirini, K. Zamani, E. Ghofrani, S. Ebrahimi, Phosphorus Sulfur 179 (2004) 2177-2188.
[34] A.J. Fatiadi, Synthesis (1976) 65-104.
[35] H.J. Park, J.C. Lee, Synlett (2009) 79-80.
[36] C. Wilfred, R.J.K. Taylor, Synlett (2004) 1628-1630.