DOI: 10.1002/cjoc.201180461

A Green Route for the One-Pot Synthesis of 1,2-Disubstituted Benzimidazoles Using Iron(III) Phosphate under Solventless Conditions

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1,2-Disubstituted benzimidazoles are selectively synthesized in high yields under extremely mild conditions via the condensation of *o*-phenylenediamine derivatives with aldehyde derivatives using catalytic amount of iron(III) phosphate under solvent-free conditions. The use of readily available iron(III) phosphate as a reusable and recyclable catalyst makes this process quite simple, convenient, and environment-friendly.

Keywords 1,2-disubstituted benzimidazoles, iron(III) phosphate, solvent-free

Introduction

The most prominent benzimidazole compound in nature is *N*-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B_{12},[1] possessing selective neuropeptide YY1 receptor antagonists,[2] 5-lipoxygenase inhibitors,[3] 5-HT3 antagonists,[4] poly(ADP-ribose) polymerase (PARP) inhibitors[5] and factor Xa (Fxa) inhibitors.[6] In addition, they exhibit significant activity against several viruses, such as HIV, herpes (HSV-1), RNA influenza, and human cytomegalovirus (HCMV).[7] Benzimidazole derivatives have also found commercial applications in veterinarian medicine.[8] Medicinal chemists would certainly classify benzimidazoles as privileged substructures for drug design.[9] Consequently, a variety of methods have been developed for the preparation of substituted benzimidazoles.[10] Of these, one of the most traditional methods involves the condensation of an *o*-phenylenediamine with carboxylic acid or its derivatives.[11] Subsequently, several improved protocols have been developed for the synthesis of benzimidazoles via the condensation of *o*-phenylenediamines with aldehydes in the presence of acid catalysts under various reaction conditions.[12] However, many of these methods suffer from certain drawbacks, including longer reaction times, unsatisfactory yields, harsh reaction conditions, expensive agents, tedious work-up procedures, co-occurrence of several side reactions, and poor selectivity. Since benzimidazole derivatives are useful and important in the field of drugs and pharmaceuticals, the development of simple, convenient, high yielding and environmentally benign protocols is desirable. Therefore, the search continues for a better catalyst for the synthesis of benzimidazoles, in terms of operational simplicity, economic viability and selectivity.

On the other hand, iron(III) phosphate is a relatively cheap and safe catalyst that is prepared using $Fe_2(SO_4)_3$ and disodium phosphate[13] and purchased commercially. Iron(III) phosphate[14] is being petitioned for use as a pesticide (molluscicide) to prevent extensive damage to and/or destruction of vegetables, citrus and non-citrus fruit, berries, field crops, ornamentals, greenhouse and nursery plants, lawns, and gardens for seed production. It is not harmful to human health. Chemically, iron(III) phosphate is very stable and will not dissociate unless in the presence of concentrated acid, which is not present in natural surroundings, because of its low solubility in the aqueous agro ecosystem, there is little contamination beyond treated areas. Iron(III) phosphate has also been employed for the selective oxidation of CH_4 to CH_3OH[15] and benzene to phenol[16] and one-pot synthesis of dihydropyrimidinones and thiones[17] and synthesis of triarylated imidazoles[18] as a catalyst. Therefore, ongoing previously our works to introduce the green protocol for the synthesis of heterocyclic compounds using eco-friendly catalyst,[19] herein iron(III) phosphate is reported as a green, reusable, recyclable, environmentally safe, inexpensive and commercially available catalyst for the synthesis of 1,2-disubstituted benzimidazole derivatives under solventless conditions at room temperature (Scheme 1).

Results and discussion

Initially, in order to ascertain a suitable condition, we chose *o*-phenylenediamine (1 mmol) and benzaldehyde (2 mmol) to establish the conditions for the con-

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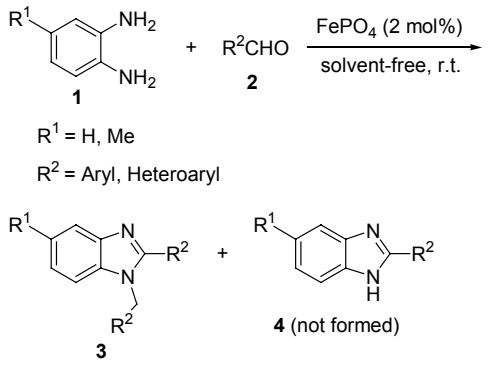
Received December 17, 2010; accepted September 29, 2011.

Scheme 1 Synthesis of 1,2-disubstituted benzimidazoles using $FePO_4$



densation reaction in the presence of 10 mol% of $FePO_4$ without solvent and at room temperature. The reaction mixture was stirred mechanically for appreciated time. It was found that when benzaldehyde (2 mmol) was stirred at room temperature in the presence of *o*-phenylenediamine (1 mmol), the mixture of 1,2-disubstituted and 2-substituted benzimidazole derivatives (70∶30, yield ratio) were obtained. To achieve 1,2-disubstituted benzimidazole as a target molecule, the reaction was tested by 3 mmol of benzaldehyde. In this case, 1,2-disubstituted benzimidazole derivative was afforded as the sole product respectively. For third time, the reaction was performed by 2.5 mmol of benzaldehyde. Interestingly, we obtained the same product as with 2.5 mmol of benzaldehyde (Table 1).

Table 1 Effect of varying amounts of benzaldehyde on the synthesis of 1-benzyl-2-phenyl benzimidazole

Enrty	Benzaldehyde/mmol	Time/min	Yield/% (**3**/**4**)	Conversion/%
1	2	20	70/30[a]	100
2	2.5 (10, 5, 2 mol% of $FePO_4$)	20	90/—[b]	100
3	3	20	90/—[b]	100

[a] The yield refer to GC analysis. [b] Isolated yield.

To obtain the optimized amount of the catalyst, we set up reaction using 5 and 2 mol% of $FePO_4$, 1 mmol of *o*-phenylendiamine, 2.5 mmol of benzaldehyde. In almost all the studied cases, the results were likely observed at 20 min (Table 2).

Eventually, we decided to go on the reactions using *o*-phenylenediamine derivatives (1 mmol), aldehyde derivatives (2.5 mmol) and 2 mol% of $FePO_4$ as a catalyst under solvent-free conditions and ambient temperature. In order to prove the generality of the optimized reaction, a variety of aromatic aldehyde derivatives and *o*-phenylenediamine derivatives were chosen. As shown in Table 3; aromatic aldehydes reacted without any significant difference in rate to give the corresponding 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles in good yields. The method has the ability to tolerate other functional groups such as methyl, methoxy, nitro, hydroxyl, *N*,*N*-dimethylamino and halo groups. Consequently several aromatic aldehydes with different substituents on the aromatic ring were subjected to the condensation reaction. In all cases the yields were very good and electron withdrawing groups were effective as well as electron-donating groups on reaction rates (Table 3). An aliphatic aldehyde such as hexanal was also subjected under similar reaction condition, but 2-pentyl benzimidazole was afforded.

Table 2 The condensation reaction of benzaldehyde (2.5 mmole) and *o*-phenylenediamine (1 mmol) using 2, 5, 10 mol% of $FePO_4$ as a catalyst at 20 min and ambient temperature

Entry	Aldehyde	Catalyst/mol%	Yield[a]/%
1	Benzaldehyde	10	90
2	—	5	90
3	—	2	90

[a] Isolated yield

Then we report $FePO_4$ as a green, reusable, inexpensive and environmentally benign catalyst for the synthesis of 1,2-disubstituted benzimidazoles. It is necessary to be mentioned that our group are researching on other application of $FePO_4$ in organic synthesis.

The plausible mechanism for the synthesis of 1,2-disubstituted benzimidazoles may probably be imagined to occur via reactions as revealed in Scheme 2. $FePO_4$ activated the aldehydic carbonyl oxygen to form the dibenzylidene-*o*-phenylene diamine and ring closure leading to a five membered ring. Finally, 1,3-hydride-transfer followed to produce 1,2-disubstituted benzimidazoles.[20] Recently Jacob and *et al*.[27] proved when the reaction in the presence of deuterated solvents such as D_2O and CH_3OD was performed; any amount deuterated benzimidazole was detected. The mechanism can be enhanced that the reaction probably occurs according to Scheme 2.

Experimental

Mps were measured by using the capillary tube

Scheme 2 The suggested mechanism for preparation of 1,2-disubstituted benzimidazole derivatives

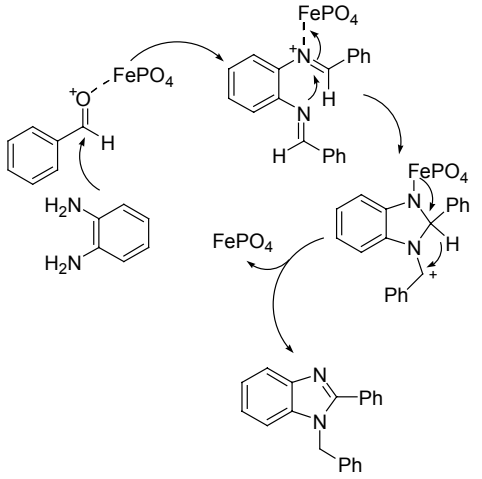
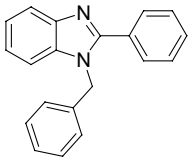
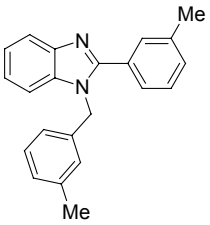
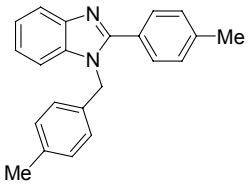
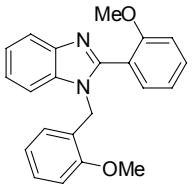
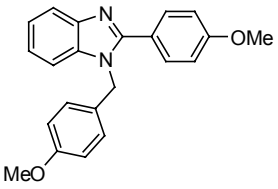
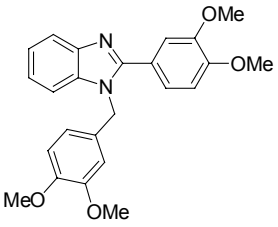
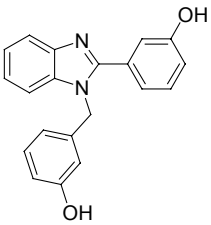
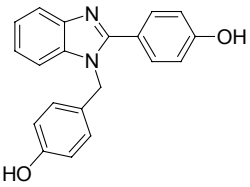
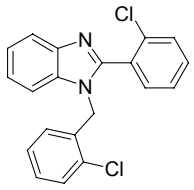
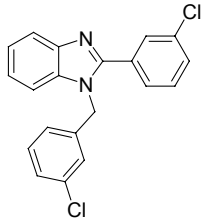
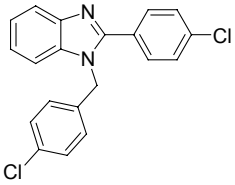
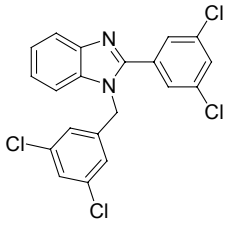
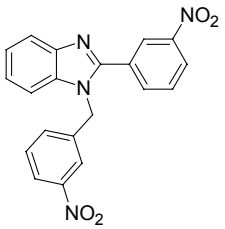
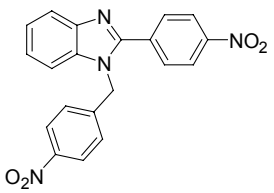
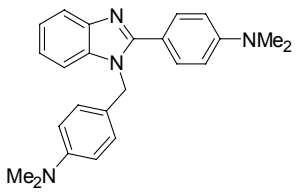


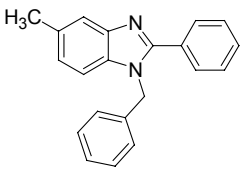
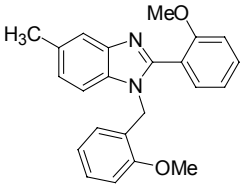
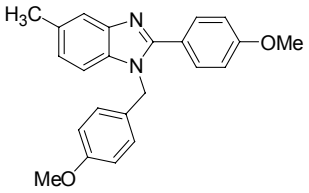
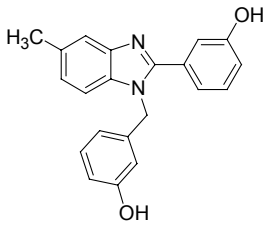
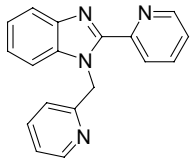
Table 3 Synthesis of 1,2-disubstituted benzimidazole derivatives using *o*-phenylenediamine derivatives and aldehyde derivatives in the presence of iron(III) phosphate as catalyst

Entry	R^1	Aldehyde	Product	Time/min	Yield[a]/%	Ref.
1	H	C_6H_5CHO		20	90	12a
2	H	3-MeC_6H_4CHO		23	80	25
3	H	4-MeC_6H_4CHO		25	85	12a
4	H	2-$MeOC_6H_4CHO$		32	88	21
5	H	4-$MeOC_6H_4CHO$		30	94	21
6	H	3,4-$(MeO)_2C_6H_3CHO$		45	80	22
7	H	3-HOC_6H_4CHO		55	85	22
8	H	4-HOC_6H_4CHO		50	89	22

Continued

Entry	R^1	Aldehyde	Product	Time/min	Yield[a]/%	Ref.
9	H	2-ClC_6H_4CHO		20	87	12a
10	H	3-ClC_6H_4CHO		30	85	25
11	H	4-ClC_6H_4CHO		20	90	12a
12	H	3,5-$(Cl)_2C_6H_3CHO$		40	92	NEW
13	H	3-$NO_2C_6H_4CHO$		20	94	23
14	H	4-$NO_2C_6H_4CHO$		10	96	21
15	H	4-$(Me)_2NC_6H_4CHO$		40	92	12a

Continued

Entry	R^1	Aldehyde	Product	Time/min	Yield[a]/%	Ref.
16	CH_3	C_6H_5CHO		15	80	24
17	CH_3	2-$MeOC_6H_4CHO$		28	80	NEW
18	CH_3	4-$MeOC_6H_4CHO$		25	85	26
19	CH_3	3-HOC_6H_4CHO		45	82	NEW
20	H	2-Pyridinecarbaldehyde		45	85	24

[a] Isolated yield.

method with an electro thermal 9200 apparatus. IR spectra were recorded on Perkin Elmer FT-IR spectrometer scanned between 4000—400 cm^{-1}. ^1H NMR and ^{13}C NMR spectra were obtained on Bruker DRX-400 MHZ NMR instrument in $CDCl_3$ and DMSO. Chemical shifts (δ) are reported relative to tetramethylsilane (δ 0.0) as internal standard. Elemental analyses were performed by Elemental analyzer Vario EL. Analytical TLC of all reactions was performed on Merck precoated plates (silica gel 60F-254 on aluminium). All starting materials were purchased from Merck Company.

General procedure for the synthesis of 1,2-disubstituted benzimidazole derivatives

In a beaker, aldehyde (2.5 mmol), and *o*-phenylenediamine (1 mmol) were mixed mechanically for 1 min without solvent and at room temperature. To this mixture then $FePO_4$ (2 mol%) was added and the reaction mixture was stirred for the indicated time (Table 3). After completion of the reaction [monitored by TLC; eluent, V(*n*-hexane) : V(ethylacetate) = 3 : 1], ethyl acetate (20 ml) was added and the catalyst filtered off. The crude product was afforded after evaporation of solvent under reduced pressure. Next the residue was directly recrystallized from ethanol.

Recycling and reusing of $FePO_4$

After completion of the reaction, $FePO_4$ was filtrated, washed by CH_2Cl_2, dried at 50 ℃ for 1 h and reused for four runs. As it has been shown in Table 4, the reactions were carried out without observation of appreciable loss in catalyst activity.

New compounds data

1-(3,5-Dichlorobenzyl)-2-(3,5-dichlorophenyl)-1*H*-1,3-benzimidazole (Entry 12) Pale yellow solid; m.p. 155—157 ℃; ^1H NMR ($CDCl_3$, 400 MHz) δ: 5.30 (s, 2H), 7.26—7.50 (m, 8H), 7.86—8.19 (m, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 153.5, 138.9, 136.2, 130.4, 125.5, 115.3, 48.0; GC/mass *m*/*z*: (422, M^+). Anal. calcd for $C_{20}H_{12}Cl_4N_2$: C 56.90, H 2.871, Cl 33.59, N

Table 4 Recycling and reusing of the catalyst

Entry	Runs	Aldehyde	Time/min	Yield[a]/%
1	Fresh	4-Chlorobenzaldehyde	20	90
2	First	—	20	90
3	Second	—	20	87
4	Third	—	20	87
5	Fourth	—	20	85

[a] Isolated yield.

6.44; C 56.65, H 2.67, Cl 33.45, N 6.44.

1-(2-Methoxybenzyl)-2-(2-methoxyphenyl)-5-methyl-1*H*-1,3-benzimidazole (Entry 17) Solid light brown, m.p. 185—187 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.49 (s, 3H, CH_3), 3.60 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 5.22 (s, 2H, CH_2), 6.69—7.75 (m, 11H, ArH); ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 160.0, 157.7, 153.3, 138.8, 132.7, 131.3, 125.8, 123.0, 114.2, 55.9, 49.0, 24.3; GC/mass *m*/*z*: (358, M^+). Anal. calcd for $C_{23}H_{22}N_2O_2$: C 77.07, H 6.19, N 7.82; found C 76.87, H 6.11, N 7.63.

1-(3-Hydroxybenzyl)-2-(3-hydroxyphenyl)-5-methyl-1*H*-1,3-benzimidazole (Entry 19) Solid brown; m.p. 215—219 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.39 (s, 3H, CH_3), 5.43 (s, 2H, CH_2), 6.64—7.53 (m, 11H, ArH), 9.3 (s, 1H), 9.65 (s, 1H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ: 158.4, 153.3, 137.7, 134.3, 130.1, 123.0, 115.3, 112.9, 49.3, 27.3. GC/mass *m*/*z*: (330, M^+). Anal. calcd for $C_{21}H_{18}N_2O_2$: C 76.34, H 5.49, N 8.48; found C 76.25, H 5.31, N 8.39.

Conclusions

In summary, the present work has reported a general, efficient, convenient, catalytic and improved methodology for the selective synthesis of 1,2-disubstituted benzimidazole derivatives by the condensation of *o*-phenylenediamines and aldehydes using $FePO_4$ catalyst. This general, simple, fast and clean protocol removed the organic solvent and energy demands, as well as the reaction time could be reduced from hours to a few minutes under solvent free conditions at room temperature.

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(E1012174 Cheng, F.; Fan, Y.)

