CATALYTIC PERFORMANCE OF SiO_2-SUPPORTED $Fe(ClO_4)_3.6H_2O$ IN SYNTHESIS OF 2-SUBSTITUTED BENZIMIDAZOLES

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Benzimidazole derivatives have been synthesized using a catalytic amount of $Fe(ClO_4)_3/SiO_2$ at room temperature with excellent yields under solvent-free conditions. The solid phase conditions and use of a heterogeneous, and inexpensive catalyst are attractive features of this method.

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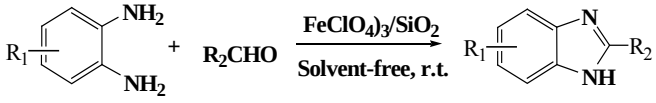
Introduction

Various pharmaceutical agents with a wide range of biological applications have benzimidazole derivatives.[1,2] Owing to their significant biological activity has prompted a very wide study for their synthesis. Benzimidazoles have been prepared by *o*-phenylenediamine (OPD) and carboxylic acids or their derivatives such as nitriles, chlorides, or orthoesters[3-6] under strong acidic conditions, and sometimes at high temperatures using polyphosphoric acid or by microwave irradiation and the oxidative cyclodehydration of OPD and aldehydes by using various reagents.[7-20] Although a variety of reagents/catalysts have been recently developed but unfortunately, many of these methods suffer from one or more limitations such as requiring harsh reaction conditions, low to moderate yields, long reaction times, tedious work-up procedures, and co-occurrence of several side products. The main disadvantage of most of these methods is that the catalysts are destroyed in the work-up procedure and cannot be recovered and reused. Therefore, there is still a demand for a simple, green and general procedure for the synthesis of tetrahydroquinolines under catalytic conditions. Additionally, $Fe(ClO_4)_3/SiO_2$ has been employed for various transformations in organic synthesis.[21] Ferric perchlorate adsorbed on silica gel has also been found to be effective for the rapid organic functional group transformations such as dimerization of alkynes, aromatic hydrocarbons, selective oxidation of thiols to disulfides, and transannular reaction in 1,5-cyclooctadienes on grinding using pestle and mortar in the solid state[22] and alumina-supported iron (III) perchlorate [$Fe(ClO_4)_3 \cdot Al_2O_3$] have been effectively used as a Lewis acid catalyst for Nazarov cyclization/Michael addition of pyrrole derivatives.[23]

We have also reported a variety of organic transformations.[24-26] In this communication, we wish to introduce a worth catalyst, $Fe(ClO_4)_3/SiO_2$, for the preparation of 2-substituted benzimidazoles in terms of operational simplicity, reusability and economic viability



Scheme 1. Synthesis of 2-substituted benzimidazoles

Experimental

General procedure for synthesis of bBenzimidazole derivatives

A mixture of o-phenyldiamine (1 mmol), benzaldehyde (1 mmol), and $Fe(ClO_4)_3/SiO_2$ (0.15 g) was stirred magnetically at room temperature, and the progress of the reaction was monitored by thin layer chromatography (TLC) till completing of the reaction. Then, the reaction mixture was diluted with ethyl acetate (20 ml), the catalyst was filtered off. The organic phase was dried with Na_2SO_4 and concentrated under reduced pressure. In all the cases, the product obtained after the usual workup gave satisfactory spectral data.

Recyclability of the catalyst

The reusability of the catalyst was also studied. At the end of the reaction, the catalyst was removed by filtration and washed with dichloromethane. The recycled catalyst could be subjected to a second or even another reaction. In the case of the model reaction, after four runs the catalytic activity of the catalyst was almost the same as those of the freshly used catalyst (Table 3).

Data

2-Phenyl-1H-benzimidazole (**1**): m.p. 290-293 ^{0}C (ref.[30] m.p. 290-292 ^{0}C). IR (KBr, cm^{-1}): 3435.55, 3059.40, 1602.27, 1493.62, 1276.30, 742.84. ^{1}H NMR ([D_6]DMSO,

400 MHz, δ ppm): 7.17-7.24 (m, 2H,Ar-H), 7.49-7.57 (m, 4H, Ar-H), 7.66 (d, 1H, Ar-H) 8.17 (d, 2H, Ar-H), 12.90. (s, 1H, N-H) .

2-(2-Hydroxyphenyl)-1H-benzimidazole (**2**): m.p. 240-242 ^{0}C (ref[36] m.p. 242 ^{0}C IR (KBr, cm^{-1}): 3325.40, 3043.47, 1604.26, 1530.30, 1489.42, 1279.88, 1118.68, 753.12. ^{1}H NMR ([D6]$CDCl_3$, 300 MHZ, δ ppm): 5.79 (s, 1H), 6.94-7.06 (m, 2H), 7.13-7.25(m, 3H), 7.39-7.44(m, 2H),7.13-7.25 (m, 2H) 8.68(s, 1H), 12.26 (s, 1H).

2-(2-Chlorophenyl)-1H-benzimidazole (**3**): m.p. 232-235 ^{0}C (ref[30] m.p. 233-234 ^{0}C) IR (KBr, cm^{-1}): 3413.04, 1620, 1589, 1440.54, 1274.17, 1047.25, 743.29. ^{1}H NMR ([D_6]DMSO, 250 MHz, δ ppm): 7.20-7.24 (m, 2H), 7.48-7.51 (m, 2H), 7.54-7.68 (m, 3H), 7.89-7.93 (m, 1H), 12.74 (s, 1H).

2-(3-Methoxyphenyl)-1H-benzimidazole (**4**): m.p. 223-227 ^{0}C (ref[32] m.p. 205-206 ^{0}C) IR (KBr, cm^{-1}): 3430.28, 2930.75, 1602.95, 1456.20, 1264.06, 872.81, 788.93, 690.92, ^{1}H NMR ([D_6]DMSO, 250 MHz, δ ppm):

2-(2,4-Dichlorophenyl)-1H-benzimidazole (**5**): m.p. 220-223 ^{0}C (ref[37] m.p. 218-219 ^{0}C), IR (KBr, cm^{-1}): 3435.87, 3101.44, 1620.65, 1593.61, 1489.08, 1283.76, 783.54, 741.39. ^{1}H NMR ([D_6]DMSO, 300 MHz, δ ppm): 3.78 (s, 3H), 7.10 (d, J=8.8, 2H), 7.16 (q, J=3.01, 2H), 7.50 (m, 2H), 8.12(d, J=8.8, 2H), 12.76 (s, 1H).

2-(4-Methoxphenyl)-1H-benzimidazole (**6**): m.p. 224-225 ^{0}C (ref[31] m.p. 222-224 ^{0}C, IR (KBr, cm^{-1}): 3421.39, 3051.09, 2986.46, 1609.99, 1585.73, 1510.89, 1245.48, 1177.78, 744.06. ^{1}H NMR ([D_6]DMSO, 300 MHz, δ ppm): 3.78 (s, 3H), 7.10 (d, J=8.8, 2H), 7.16 (q, J=3.01, 2H), 7.50 (m, 2H), 8.12 (d, J=8.8, 2H), 12.76 (s, 1H).

2-(4-Bromophenyl)-1H-benzimidazole (**7**): m.p. 280-281 ^{0}C (ref[36] m.p. 283-284 ^{0}C, IR (KBr, cm^{-1}): 3435.87, 2928.57, 1593.98, 1446.34, 1399.20, 1270.26, 828.58. ^{1}H NMR ([D_6]$CDCl_3$, 300 MHz, δ ppm): 7.18-7.21 (m, 2H), 7.59 (m, 4H), 7.85-7.87 (d, 1H), 5.37 (s, 1H).

2-(4-Methylphenyl)-1H-benzimidazole (**8**): m.p. 269-273 ^{0}C (ref[30] m.p. 270-272 ^{0}C, IR (KBr, cm^{-1}): 3025.18, 2917.47, 1614.79,1515.56, 1481.56 , 1456.72, 821.30. ^{1}H NMR ([D_6]DMSO, 250 MHz, δ ppm): 2.35 (s, 3H), 7.15-7.2 (m, 2H), 7.33 (d, J=8.1, 2H), 7.46-7.56 (m, 2H), 8.07 (d, J=8.1, 2H), 12.84 (s, 1H).

2-(2-Pyridylphenyl)-1H-benzimidazole (**9**): m.p. 217-218 ^{0}C (ref[30] m.p. 218 ^{0}C, IR (KBr, cm^{-1}): 3435.97, 1603.21, 1591.82, 1441.75, 1279.38, 742.97. ^{1}H NMR ([D_6]DMSO, 250 MHz, δ ppm): 7.16-7.24 (m, 2H), 7.47-7.71 (m, 3H), 7.98 (dd, J_1 7.7, J_2=1.7, 1H) 8.3-8.34 (m, 1H) 8.71 (d, J=6.9, 1H), 13.01 (s, 1H).

2-(2-Furylphenyl)1-H-benzimidazole (**10**): m.p. 287-288 ^{0}C (ref[36] m.p. 288 ^{0}C, IR (KBr, cm^{-1}): 3435.92, 3120.87, 2923.7, 1614.58 , 1508.93, 1456.81, 1100.17, 1013.07, 745.66, 593.50. ^{1}H NMR ([D_6]DMSO, 250 MHz, δ ppm): 6.69 (dd, J_1=3.4, J_2=1.7, 1H), 7.16-7.20 (m, 4H), 7.53 (d, J=3.1, 1H), 7.56 (d, J= 3.1, 1H), 7.89 (s, 1H).

5-Nitro-2-phenyl-1H-benzimidazole (**11**): m.p. 206-209 ^{0}C (ref[34] m.p. 207-208 ^{0}C, IR (KBr, cm^{-1}): 3377.57,1625.56, 1519.21, 1335.77, 694.57, 735.32. ^{1}H NMR ([D_6]DMSO, 300 MHz, δ ppm): 7.57 (m, 2H), 7.59 (m, 1H), 7.74 (d, 1H), 8.09-8.12 (m, 1H), 8.18-8.2 (m, 2H), 8.45 (s, 1H), 13.60 (s, 1H).

5-Methyl-2-phenyl-1H-benzimidazole (**12**): m.p. 240-242 ^{0}C (ref[9] m.p. 242-243 ^{0}C, IR (KBr, cm^{-1}): 3412.81, 1603.91, 1453.77, 1101.52, 806.88, 698.23. ^{1}H NMR ([D_6]DMSO, 400 MHzZ, δ ppm): 2.41 (s, 3H), 6.97-7.03 (m, 1H), 7.38 (d, 2H), 7.43-7.46 (m, 2H), 7.49-7.53 (m, 2H), 8.12 (d, 1H) 12.69 (s, 1H).

2-(2,4-Dichlorophenyl)-5-methylbenzimidazole (**13**): m.p. 103-106 ^{0}C (ref[38] m.p. 104-106 ^{0}C, IR (KBr, cm^{-1}): 3444.39, 3053.83, 2912.08, 1604.95, 1594.99, 1558.56, 1234.60, 754.51, 702.52. ^{1}H NMR ([D_6]DMSO, 400 MHz, δ ppm): 2.42 (s, 3H), 7.05 (d, 1H), 7.40 ((s, 1H) 7.50 (d, 1H), 7.59-7.62 (m, 1H), 7.79 (d, 1H), 12.63 (s, 1H).

6-Methyl-2-(4-methylphenyl)-1H-benzimidazole (**14**): m.p. 100-104 ^{0}C (ref[39] m.p. 101-102 ^{0}C, IR (KBr, cm^{-1}): 3421.53, 2919.35, 1615.03, 1448.01, 804.87, 827.88. ^{1}H NMR ([D_6]$CDCl_3$, 250MHZ, δppm): 2.21 (s, 3H), 2.34 (s, 3H), 6.99-7.08 (m,3H), 7.48 (s, 1H), 7.54 (d, J=1.8, 1H), 8.15 (d, J=8.1, 2H), 12.65 (s, 1H).

Results and discussion

To establish the optimum condition for this reaction, various ratios of anhydrous $Fe(ClO_4)_3/SiO_2$ were examined using *o*-phenylenediamine and benzaldehyde under solvent-free at room temperature in 5.0 minutes as a model reaction (Table 1). We observed that very little of the desired products were obtained in the absence of $Fe(ClO_4)_3/SiO_2$. The best yields were obtained with 0.15 gr (2.0 mol% of the catalyst loading) of $Fe(ClO_4)_3/SiO_2$. Thus the catalyst is efficient component for the synthesis of 2-substituted benzimidazoles.

Table 1. Optimization of the catalyst amount

Entry	Catalyst, g	Yield, %
1	Free	5
2	0.05	10
3	0.1	60
4	0.15	92

To evaluate the scope and limitations of this work, we focused our attempts on the synthesis of the benzimidazoles using differently substituted *o*-phenylendiamine and aldehydes. A wide variety of compounds were applied under optimal reaction conditions to prepare benzimidazoles. The results are summarized in Table 2. A variety of aldehydes aromatic compounds possessing both electron-donating and electron-withdrawing groups were employed for benzimidazole formation, and in all cases, the yields were excellent (Table 2).

Table 2 Synthesis of benzimidazoles by $Fe(ClO_4)_3/SiO_2$ at room temperature.

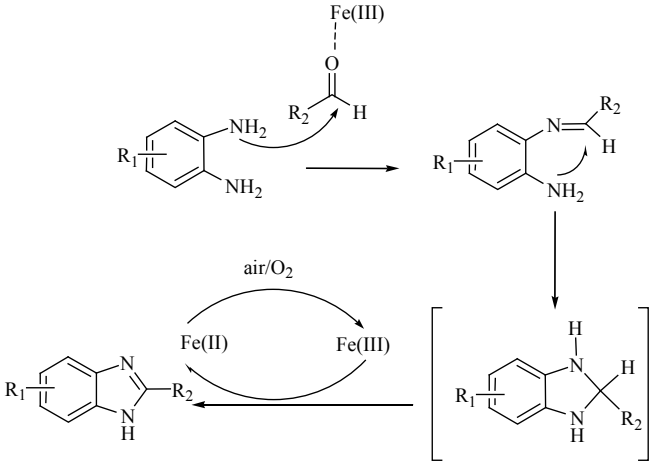
Entry	R_1	R_2	Time, min	Yield, %	M.p(°C)	
					Found	Reported
1	H	C_6H_5-	10	92	290-293	290-292[30]
2	H	2-HOC_6H_4-	40	85	240-242	242[36]
3	H	2-ClC_6H_4-	40	90	232-235	233–234[30]
4	H	3-$MeOC_6H_4$-	25	91	223-227	205-206[32]
5	H	2,4-$Cl_2C_6H_3$-	20	90	220-223	218-219[37]
6	H	4-$MeOC_6H_4$-	45	87	224-225	222-224[31]
7	H	4-BrC_6H_4-	30	92	280-281	283-284[36]
8	H	4-MeC_6H_4-	60	95	269-273	270-272[30]
9	H	2-pyrydil	180	85	217-218	218[36]
10	H	2-Furyl	120	85	287-288	288[36]
11	4-Nitro	C_6H_5-	30	40	206-209	207-208[34]
12	4-Me	C_6H_5-	15	87	240-242	242-24[39]
13	4-Me	2,4-$Cl_2C_6H_3$-	20	95	103-106	104-106[38]
14	4-Me	4Me	45	93	100-104	101-102[39]

Table 3. Synthesis of 2-phenyl-1*H*-benzimidazole was catalyzed using anhydrous $Fe(ClO_4)_3/SiO_2$ (0.15 g)/air in the presence of benzaldehyde and o-phenylene diamine.

Entry	Catalyst	Conditions	Time, min	Yield, %	Ref.
1	$Fe(NO_3)_3.9H_2O$ (10 mol%)/ H_2O_2(0.4 ml)	Solvent-free/50°C	2.0	98	27
2	$FeBr_3$ (5.0 mol %)	DMF/60 °C	25	88	28
3	$Fe(NO_3)_3.9H_2O$(10 mol%)	DMF/60 °C	25	85	28
4[a]	$FeCl_3$ /PANI	EtOH/r.t.	30	90	29
5[b]	T(*o*-Cl)PPFe^{III}Cl (5.0 mol%)	EtOH/r.t.	30	97	30
6[b]	T(*o*-Cl)PPFe^{III}–SiO_2 (5.0 mol%)	EtOH/r.t.	90	95	30
7	$Fe(ClO_4)_3/SiO_2$(2.0 mol %)	Solvent free/r.t	10	92	This work

a) $FeCl_3$ /PANI = $FeCl_3$-doped polyaniline; b) T(*o*-Cl)PPFe^{III}Cl= *meso*-tetrakis(*o*-chlorophenyl)porphyrin–Fe^{III}Cl

To show the merits of this catalytic method in comparison with those of reported protocols, we compiled the results of the formation of 2-phenyl-1*H*- benzimidazoles in the presence of a variety of catalysts, especially iron (III) salts and complexes. From the results given in Table 3, the advantages of our method are evident, regarding the catalyst amounts which are very important in chemical industry especially when it is combined with easy separation.



Scheme 2. Mechanism of the 2-susbtituted benzimidazoles formation

The proposed mechanism for Fe(III)-catayzed synthesis of 2-substituted benzimidazoles may be visualized to occur via a sequence of reactions as depicted in Scheme 2.

Table 3 Reusablity of the catalyst was survived for the model reaction(entry 1, Table 2).

Entry	Runs	Yield, %
1	First	92
2	2th	90
3	3th	90
4	4th	85

Conclusion

In conclusion, $Fe(ClO_4)_3/SiO_2$ has been employed as a novel and efficient catalyst for the synthesis of benzimidazoles in good yields from *o*-phenylenediamine and a wide variety of aldehydes. All the reactions were carried out at room temperature, while using $Fe(ClO_4)_3/SiO_2$. The reaction conditions were very mild, and the isolation of products was very easy and the catalyst was reusable.

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