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Highly selective synthesis of libraries of 1,2-disubstituted benzimidazoles using silica gel soaked with ferric sulfate

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ABSTRACT

An efficient and highly selective synthesis of functionalized 1,2-benzimidazoles has been developed under solvent-free conditions at ambient temperature using eco-friendly ferric sulfate soaked with silica [iron(III)sulfate–silica]. Recycling of the solid support up to six runs was investigated with appreciable yield and selectivity of the product.

Functionalized benzimidazoles represent an important class of N-containing heterocyclic compounds and have received considerable attention in recent times because of their vast applications as antiulcer, antihypertensive, antiviral, antifungal, anticancer, and antihistamine activities.[1] They are important intermediates in many organic reactions,[2] and also can act as ligands for complexation with transition metals, which are used for modeling biological systems.[3] Owing to broad range of biological and other technical interest of the benzimidazole family of compounds, several synthetic strategies have been developed for the preparation of functionalized benzimidazoles.

The most popular strategy utilizes either direct condensation–aromatization reaction of *o*-phenylenediamines (*o*-PDs) and aldehyde (Scheme 1) or reductive cyclization of *o*-nitroaniline with aldehydes,[4] for the synthesis of 2-substituted benzimidazole **4**,[5] and 1,2-disubstituted benzimidazole **3**.[6] Selective synthesis of 1,2-disubstituted benzimidazoles has been achieved by the direct condensation–aromatization reaction of *o*-PD and aldehyde using Zn-Proline,[6e] SDS micelle,[6g] TMSCl,[6h] Amberlite IR-120,[6i] glyoxalic acid,[6j] 1-(4-sulfonicacid)butyl-3-methylimidazolium hydrogen sulfate [$(CH_2)_4SO_3$–HMIM][HSO_4],[6k] nano indium oxide,[6l] in water and refluxing in glycerol at 90 °C.[6m] Alternative approaches include transition metal-catalyzed reactions such as Pd-catalyzed tandem carbonylation–cyclization reaction of *o*-PDs,[7a] Pd-catalyzed tandem dehydration-coupling reaction of *o*-bromoaniline,[7b] Rh-catalyzed hydroformylation reaction of *N*-alkenyl phenylenediamines etc.[7c] Solid-phase synthesis of benzimidazoles has also been developed.[8] Although, a large body of protocols has been developed for the synthesis of medicinally important benzimidazoles, primary precincts that require attention of synthetic chemists are: (i) strong acid-catalyzed conditions that limit functional group tolerance, (ii) transition metal-catalyzed methods pose a threat of contamination of toxic metals with the product, and (iii) while a vast methods are available for selective formation of 2-substituted benzimidazole **4**, synthetic methods for 1,2-disubstituted benzimidazole **3** often associate with co-occurrence of several side reactions and by-products. Therefore, the search remains to be continued for a better catalyst and greener protocol with greater selectivity in the synthesis of benzimidazoles.

Among some approaches involving solid-phase acid catalysts, Jacob et al. described silica-supported $ZnCl_2$ as catalyst for the selective preparation of 1,2-disubstituted benzimidazoles.[9] Although their method did work effectively in several cases, poor yields (35–40%) were reported in some examples. In contrast, iron is not only ubiquitous but also one of the most versatile transition metals,[10] and important redox center for life and natural transformation processes.[11] Although relatively underrepresented, the use of iron salts in the synthesis of benzimidazoles has been reported with limited success in terms of yield and selectivity.[12] Since there is no straightforward procedure involving iron-catalyzed benzimidazole formation, we explored direct condensation–aromatization reaction of *o*-PDs and aldehydes in the presence of silica-supported iron salts as a general procedure. Herein, we report an efficient, simple protocol for a highly selective synthesis of 1,2-disubstituted benzimidazole **3**, catalyzed by iron(III)sulfate

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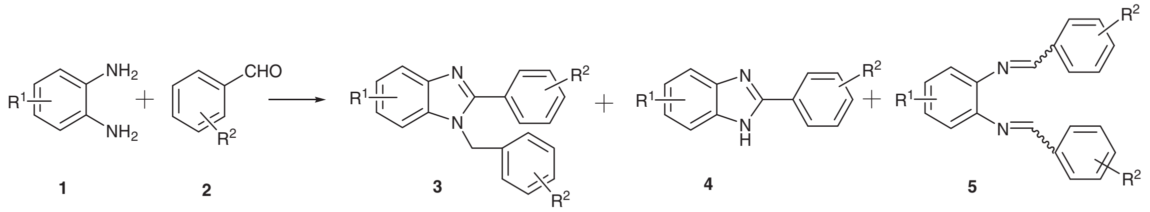


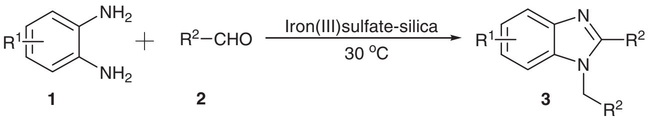
Scheme 1. Possible products for the direct condensation–aromatization reaction of *o*-PDs with aryl aldehydes.

Table 1
Reaction of *o*-PD and benzaldehyde using different catalyst systems

Entry	Catalyst system	*o*-PD/benzaldehyde	Time (h)	Temp. (°C)	% Yield[a]
1	1 mmol anhy. $FeCl_3$ in 1 g silica	1:2	2	30	**3a** (82); **4a** (9)
2	0.25 mmol anhy. $FeCl_3$ in 1 g silica	1:2	2	30	**3a** (75); **4a** (15)
3	1 mmol $Fe(NO_3)_3{\cdot}9H_2O$ in 1 g silica	1:2	2	30	**3a** (83); **4a** (8)
4	0.25 mmol $Fe(NO_3)_3{\cdot}9H_2O$ in 1 g silica	1:2	2	30	**3a** (78); **4a** (12)
5	1 mmol Fe_2O_3 in 1 g silica	1:2	8	30	**3a** (65); **4a** (22)
6	1 mmol $Fe_2(SO_4)_3{\cdot}xH_2O$ in 1 g silica	1:2	2	30	**3a** (89)
7	0.5 mmol $Fe_2(SO_4)_3{\cdot}xH_2O$ in 1 g silica	1:2	2	30	**3a** (89)
8	0.25 mmol $Fe_2(SO_4)_3{\cdot}xH_2O$ in 1 g silica	1:2	2	30	**3a** (89)
9	0.25 mmol $Fe_2(SO_4)_3{\cdot}xH_2O$ in 1 g silica	2:4	2	30	**3a** (78); **4a** (14)
10	0.5 mmol $Fe_2(SO_4)_3{\cdot}xH_2O$ in 1 g silica	2:4	2	30	**3a** (81); **4a** (12)
11	Silica 1 g	1:2	2	30	**3a** (32); **4a** (38); **5a** (25)
12	Silica 1 g	1:2	6	60	**3a** (30); **4a** (46); **5a** (15)

[a] Yields refer to pure product obtained by column chromatographic purification and characterized by ^1H and ^{13}C NMR spectral data.

Table 2
Reaction of different *o*-PDs with aldehydes



Entry	R^1	R^2	Time (h)	Temp. (°C)	Product	% Yield[a]
1	H	Ph	2	30	**3a**	89
2	H	4-$CH_3OC_6H_4$	2	30	**3b**	85
3	H	4-ClC_6H_4	1.5	30	**3c**	87
4	H	4-$NO_2C_6H_4$	8	30	**3d**	83
5	H	4-$Me_2NC_6H_4$	2	30	**3e**	86
6	H	4-Isopopyl C_6H_4	1.5	30	**3f**	84
7	H	3-$NO_2C_6H_4$	24	30	**3g**	84
8	H	3-OHC_6H_4	5	30	**3h**	86
9	H	3-$OPhC_6H_4$	3	30	**3i**	84
10	H	1-Naphthyl	6	30	**3j**	84
11	H	Furan-2-yl	4	30	**3k**	79
12	H	5-Bromo-thiophene-2-yl	6	30	**3l**	75
13	H	2-OHC_6H_4	15	90	**3m**	78
14	3-CH_3	5-Br-thiophene-2-yl	8	30	**3n**	77[b]
15	3-CH_3	2-ClC_6H_4	5	30	**3o**	75[b]
16[c]	3-COPh	Ph	14	30	**3p**	88
17	H	Cyclohexyl	4	30	**3q**	84
18	H	2-Methylpropyl	12	30	**3r**	78

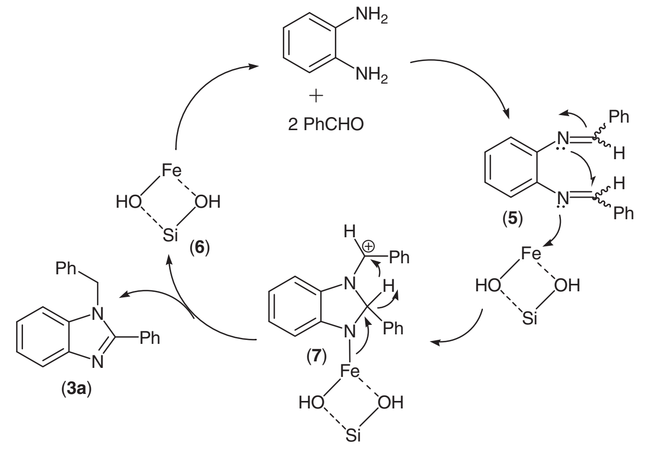
[a] Yields refer to pure product obtained by column chromatographic purification and characterized by ^1H and ^{13}C NMR spectral data.

[b] Mixture of regio-isomers, not separable by column chromatography, was obtained.

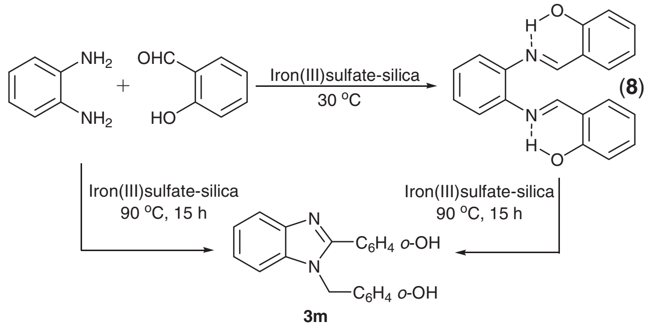
[c] M.P. and NMR spectral data were found to be identical with one of the isomers reported in the literature[6h] and its structure is 1-benzyl-2-phenyl-1*H*-benzo[*d*]imidazol-5-yl)(phenyl)methanone.

supported on silica at ambient temperature under solvent-free conditions.

Initially *o*-PD and benzaldehyde were chosen as the model substrates to optimize the catalyst and reaction conditions. The results are presented in Table 1. Use of SiO_2–$FeCl_3$ or SiO_2–$Fe(NO_3)_3$ showed some selectivity toward the formation of 1,2-disubstituted benzimidazole over 2-substituted benzimidazole (entries 1–4). Exploration with iron oxide (Fe_2O_3) also afforded a mixture of **3** and **4** in varying proportions (entry 5). In the search of more selectivity, we further investigated the reaction with silica-supported



Scheme 2. Plausible mechanism of the reaction furnishing 1,2-disubstituted benzimidazole.



Scheme 3. H-bonded Schiff base, undergoing cyclization and 1,3-H shift in presence of iron(III)sulfate–silica at 90 °C.

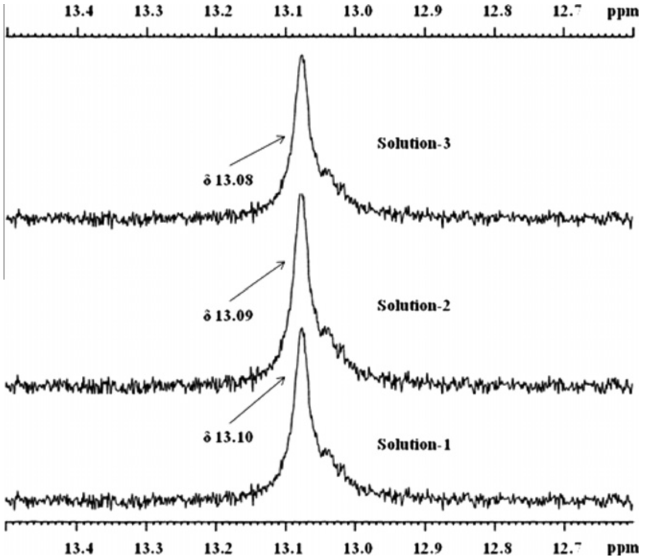


Fig. 1. The δ position (ppm) of the OH of **8** at different concentrations: Solution 1 (100 mg), Solution 2 (50 mg), Solution 3 (20 mg), dissolved in 1.5 mL $CDCl_3$.

Table 3
Recycling of iron(III)sulfate–silica in catalyzing the reaction of *o*-PD and benzaldehyde

Entry	No. of cycle	% Yield[a]
1	0	89
2	1	86
3	2	88
4	3	89
5	4	86
6	5	88

[a] Yields refer to the pure product obtained by column chromatographic purification.

ferric sulfate. Indeed, we were able to find that 1 mmol of ferric sulfate adsorbed onto 1 g of silica can afford highly selective formation of the 1,2-disubstituted benzimidazole **3** in excellent yield (entry 6). Lowering of the catalyst loading per gram of the solid support up to 0.25 mmol of ferric sulfate also showed complete selectivity toward the formation of 1,2-disubstituted benzimidazole (entries 7, 8).[13] Further lowering of the quantity of ferric sulfate per gram of silica gel with reference to reactant ratios resulted in the loss of selectivity (entries 9, 10).

In order to check the role of silica, which is often used as dehydrating agent, similar reactions were carried out only on silica surface, which led to a mixture of **3**, **4**, and **5** in varying proportions (entries 12, 13). Thus we have the optimized reaction conditions as follows: 0.25 mmol of the iron(III)sulfate·xH_2O adsorbed onto silica gel (1 g) for the reaction of 1:2 mmol of *o*-PD and benzaldehyde, having stirred in neat at ambient temperature under open atmosphere.[14]

Following identification of the optimal conditions, the scope and limitations of the reaction were examined by subjecting different 1,2-diamines and aldehydes. The results are shown in Table 2. Aryl aldehydes bearing different functional groups as well as heteroaryl aldehydes reacted smoothly with *o*-PD leading to the formation of corresponding 1,2-disubstituted benzimidazoles highly selectively and in good to excellent yields (Table 2, entries 1–12). No electronic or steric impact was found to be prominent in the selective formation of **3a–l**. However, In the case of *o*-salicylaldehyde, the reaction occurred at higher temperature (90 °C) (entry 13). The *o*-PDs possessing different substituents also afforded similar reactions resulting in the formation of corresponding benzimidazoles (**3n–p**) selectively in good yields (entries 14–16). Further extension of the protocol to aliphatic aldehydes also afforded selective formation of the corresponding 1,2-disubstituted benzimidazoles (**3q**, **3r**) at ambient temperature (entries 17, 18).

Although the exact mechanism is not clear, the Lewis acid-mediated mechanism is expected to play (Scheme 2). Adsorption of iron(III)sulfate on the surface of silica is believed to make bond with the silanol groups in a manner analogous to the formation of OH-bridges in the polynuclear iron(III)hydroxyl complexes **6**.[15] Silica being a water adsorbent could facilitate formation of the bis-Schiff base **5**, which has been reported and indeed was isolated when the reaction was stopped after 20 min. The Schiff base **5** may undergo cyclization followed by 1,3-hydride shift,[6e,6h] (**7**), induced by electrophilic catalyst, as shown in Scheme 2, resulting in the formation of the 1,2-disubstituted benzimidazole **3**. The 1,3-hydride shift was tested previously by incorporating deuterium.[6g] An indirect evidence in favor of 1,3-hydride shift may be proposed, as we observed that the corresponding Schiff base **5**, isolated from *o*-PD and salicylaldehyde (**8**), showed reluctance to undergo cyclization at room temperature. This is possibly because of intramolecular H-bonding with *o*-OH group,[16] making nitrogen less nucleophilic, and thus required higher temperature (90 °C) for the cyclization (Scheme 3). The existence of intramolecular hydrogen bonding in the Schiff base (**8**) was also checked by ^1H NMR studies at varying concentrations of the Schiff base in $CDCl_3$. The spectra (Fig. 1) show that the hydroxyl proton appears at δ 13.09 ± 0.01 ppm for compound **8** (solution 1: 100 mg in 1.5 mL $CDCl_3$), (solution 2: 50 mg in 1.5 mL $CDCl_3$), and (solution 3: 20 mg in 1.5 mL $CDCl_3$).

Finally, the advantage of using the silica-supported ferric sulfate in this reaction was examined by its recovery and reuse after the first run. Accordingly, after the reaction of *o*-PD and benzaldehyde, the solid mixture was washed repeatedly with ethyl acetate and filtered off. The solid was then washed with acetone followed by drying in a hot air oven at 150 °C for 24 h and then dried under vacuum. The next batch of reaction was performed with the recovered silica-supported ferric sulfate and found to be equally active in catalyzing the process. Table 3 showed the results of six consecutive recycle runs.

In conclusion, we have developed an efficient and highly selective procedure for the synthesis of 1,2-disubstituted benzimidazoles via one-step condensation–aromatization reaction of *o*-PDs with electronically divergent aldehydes under mild conditions promoted over the surface of iron(III)sulfate–silica. The new method requires only inexpensive eco-friendly reagents and the catalytic system is recyclable. Further applications of iron(III)sulfate−silica are currently underway in this laboratory.

Acknowledgments

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13. *Preparation of ferric sulfate adsorbed on silica:* To a hot solution of iron(III) sulfate·xH_2O (1 g, 2.5 mmol; $x = 0$) in water (20 mL) at 70 °C, silica gel (10 g, particle size: -325 mesh, source. SRL, India) was added. This mixture was stirred at 70 °C for 2 h. The solvent was evaporated under vacuo and the solid mass was kept in a hot air oven at 150 °C for 24 h. This pale yellow solid mass was further dried under vacuum (0.5 torr) for 2 h and the resulting free-flowing iron(III)sulfate supported silica gel was used for the reaction and can be kept under nitrogen for several weeks.
14. *Representative procedure for the synthesis of 1,2-disubstituted benzimidazole:* To a mixture of *o*-phenylenediamine (1 mmol) and iron(III)sulfate–silica (1 g) was added benzaldehyde (2 mmol) and the resulting reaction mixture was intimately mixed in a mortar pestle. Then the mixture was magnetically stirred at 30 °C for 2 h under open atmosphere. After the completion of the reaction (checked by tlc), the solid reaction mixture was washed repeatedly with ethyl acetate (10×3 mL) and the washings were combined and evaporated under vacuum. The crude solid product, although pure enough on tlc, was then passed through a short column of silica gel to afford pure product **3a** (mp 134–136 °C, lit.[17] mp 134 °C). It was characterized by spectral data (IR and ^{1}H and ^{13}C NMR). Characterization of other compounds was made by spectral data and compared to those reported. Compound **3a**: IR (KBr) ν_{max} cm^{-1}: 3031, 2935, 1449, 1391, 1365, 1326, 1277, 1249, 1160. ^{1}H NMR (DMSO-d_6, 300 MHz) δ/ppm 7.75–7.23 (m, 3 H), 7.53–7.45 (m, 4 H), 7.29–7.21 (m, 5 H), 7.00 (d, 2 H, $J = 7.5$ Hz), 5.58 (s, 2 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ/ppm 153.2, 142.6, 136.8, 135.8, 130.1, 129.7, 128.9, 128.7, 127.4, 125.9, 122.6, 122.1, 119.2, 111, 47.4.
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