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Selectivity control during the solid supported protic acids catalysed synthesis of 1,2-disubstituted benzimidazoles and mechanistic insight to rationalize selectivity†

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Selectivity control during the formation of 1,2-disubstituted benzimidazoles has been achieved for the reaction of *o*-phenylenediamine with aldehydes in the presence of solid supported protic acids as catalysts and choosing an appropriate reaction medium. Perchloric acid adsorbed on silica-gel ($HClO_4$–SiO_2) was found to be the most effective catalyst system for the synthesis of 1,2-disubstituted benzimidazoles in EtOH at rt. Apart from the catalyst and solvent, the electronic and steric factors of the aldehyde and the electronic factor of the *o*-phenylenediamine are also significant contributory factors in dictating the selectivity. An understanding of the mechanistic course of the formation of the 1,2-disubstituted benzimidazoles has been outlined that would rationalise the origin of selectivity control under the set experimental parameters.

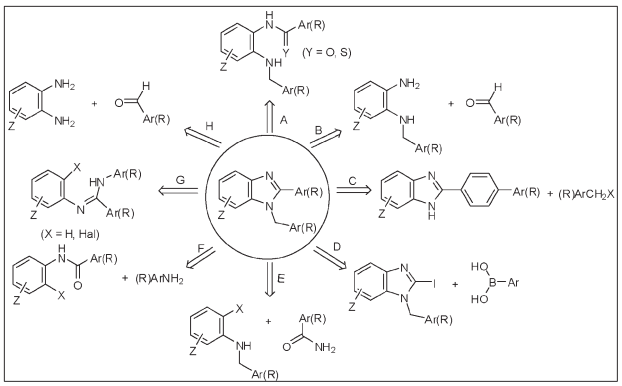
Introduction

In view of the role of the 1,2-disubstituted benzimidazole scaffold as a versatile pharmacophore for the generation of new chemical entities in diverse therapeutic areas,[1] the formation of these privileged class of compounds has generated interest to develop newer synthetic methods.

The various synthetic strategies (Scheme 1) adopted for the generation of this heterocyclic framework can be summarized by the following distinct routes: (i) cyclodehydration of *N*-alkyl-*N*-acyl-*o*-phenylenediamine (route A),[1h,1i] (ii) oxidative cyclocondensation of *N*-alkyl-*o*-phenylenediamine with aldehyde[1h,2] (route B), (iii) *N*-alkylation of 2-substituted benzimidazole[1b,d,g,k] (route C), (iv) Suzuki coupling of aryl boronic acids with 1-iodo-2-alkyl benzimidazoles[3] (route D), (v) copper-catalyzed amidation of *o*-halo *N*-alkylated anilines followed by cyclodehydration of the intermediately formed *N*-alkyl-*N*-acyl *o*-phenylenediamine[4] (route E), (vi) copper/palladium-catalyzed amination of *o*-halo *N*-acylated anilines followed by cyclodehydration of the intermediately formed *N*-alkyl-*N*-acyl *o*-phenylenediamine[5] (route F), (vii) palladium-catalysed intramolecular aryl-amination of (*o*-bromo/iodophenyl)amidines[6] or bis(trifluoroacetoxy)iodobenzene mediated intramolecular cyclisation of *N*-alkyl-*N*′-arylamidines[7] (route G). While the Buchwald and Suzuki chemistries (routes D–G) are used quite often by medicinal chemists, they require special efforts to prepare the desired starting materials.

Thus, a direct one-pot cyclocondensation of *o*-phenylenediamine with aldehydes (route H, Scheme 1) to prepare 1,2-disubstituted[8] benzimidazoles appears to be a straightforward approach and has received unabated attention from organic/medicinal chemists for the generation of new hits/leads for potential therapeutic applications that require a convenient, selective and high yielding synthetic method to meet the needs of the timely supply of designed molecules for biological evaluation.[9]

However, the synthetic design following route H poses a potential selectivity problem due to the possibility of competitive formation of the 1,2-disubstituted and the 2-substituted benzimidazoles, an issue that remains inadequately addressed so far. The present work aims to control the selectivity in the formation of 1,2-disubstituted benzimidazoles during the cyclocondensa-



Scheme 1 Synthetic strategies for the formation of 1,2-disubstituted benzimidazoles.

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tion of *o*-phenylenediamines with aldehydes and offer a mechanistic understanding that would rationalise the selectivity control.

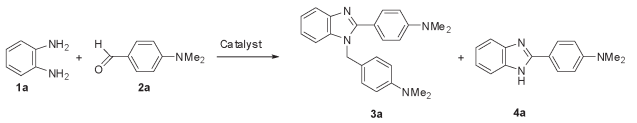
In view of the considerable awareness that has been generated for chemical processes on solid surfaces[10] and the implication of heterogeneous catalysts (solid acids) in devising greener synthetic processes/methods,[11] we describe herein a convenient and highly selective synthesis of 1,2-disubstituted benzimidazoles catalysed by solid acids such as $HClO_4$–SiO_2.[12]

Results and discussion

In a model study (Scheme 2), the cyclocondensation of *o*-phenylenediamine (**1a**) with two molar equivalents of 4-dimethylaminobenzaldehyde (**2a**) was performed separately in the presence of various catalyst systems. The use of $HClO_4$–SiO_2 (0.5 mol%) as the heterogeneous catalyst in EtOH at rt (25–30 °C) resulted in the formation of the desired 1,2-disubstituted benzimidazole 1-(4-*N*,*N*-dimethylaminophenylmethyl)-2-(4-*N*,*N*-dimethylphenyl)benzimidazole (**3a**) in 90% yield (Table 1).

The efficiency of $HClO_4$–SiO_2 was compared with the reported catalysts/processes. After the complete consumption of the starting materials, two new spots appeared in the TLC. The crude reaction mixtures were purified by column chromatography and the products eluted at different time intervals were identified as **3a** and 2-(4-*N*,*N*-dimethylaminophenyl)benzimidazole (**4a**) (Scheme 2 and Table 1). However, when $HClO_4$–SiO_2 was used as the catalyst, the crude product mixtures exhibited a single spot in the TLC and **3a** was obtained as the only product after purification either by crystallisation or column chromatography. The superiority of $HClO_4$–SiO_2 was clearly established both in terms of the product yields as well as the selectivity by comparing the results obtained for the reaction of **1a** with **2a** with those obtained using reported catalysts. While the use of $HClO_4$–SiO_2 afforded **3a** as the sole product in 90% yield, the reported catalysts were found to be less effective and lacked selectivity affording **3a** in 42–80% yields along with the formation of **4a** in 10–25% yields. The use of a catalyst was found to be essential as inferior yields and selectivity were observed on performing the reaction in the absence of any catalyst (entries 1 and 2, Table 1).

The reaction medium appears to have a significant influence in controlling the selective formation of the 1,2-disubstituted benzimidazole as evidenced by the results (product yield and selectivity) during the $HClO_4$–SiO_2 catalysed cyclocondensation of **1a** with **2a** performed in various protic polar, aprotic polar, halogenated, weakly polar (ethereal), and non-polar (hydrocarbon) solvents as well as under neat conditions.[13] The use of non polar, weakly polar, aprotic polar solvents and neat conditions decreased the selectivity and in each case **3a** was associated with the formation of **4a**. The best results were obtained in EtOH but the selectivity decreased when using other protic solvents such as MeOH, ^{i}PrOH, ^{t}BuOH, ethylene glycol and water. Inferior results were also obtained with PEG-200, DCE and PhMe.



Scheme 2 Selectivity of the formation of the 1,2-disubstituted benzimidazole **3a** and the 2-substituted benzimidazole **4a** during the reaction of **1a** with **2a** in the presence of various catalyst systems.

The efficiency of $HClO_4$–SiO_2, in comparison to that of other protic acids adsorbed on silica gel, is demonstrated by the results incorporated in Table 2. However, for this study for the reaction of **1a** we took 4-methylbenzaldeheyde (**2b**) instead of **2a** so as to avoid any influence of salt formation with the NMe_2 group of **2a** on the selectivity and product yield (Scheme 3).

The nature of the solid support was also found to be important in maintaining the selectivity as the use of neutral, basic or acidic alumina instead of silica-gel as the solid support decreased the selectivity inducing competitive formation of **4b** in 18–30% yields (entries 16–21, Table 2). Amongst the different varieties of silica gel used as the support, the 230–400 mesh size (henceforth in the text SiO_2 refers to the 230–400 mesh size silica gel only) proved to be the most effective support (entries 1–3, Table 2). As silica and montmorillonite clays themselves have the ability to catalyse various organic reactions[14] the catalytic efficiency of the solid support (various forms of silica gel) itself (without taking any protic acid) and other heterogeneous catalysts such as zeolites, clays, and amberlite (entries 16–27, Table 2) were tested and found to be inferior due to product yields and poor selectivity.

The efficiency of other inorganic and organic protic acids adsorbed on SiO_2 was compared with that of $HClO_4$–SiO_2 for the reaction of **1a** with 4-methylbenzaldeheyde (**2b**) (Scheme 3). Although good to excellent cyclocondensation took place with organic (entries 4–7, Table 2), other inorganic protic acids (entries 8–11, Table 2), and aq LiCl (in the presence/absence of any protic acid), the selectivity was inferior as the 2-substituted product **4b** was formed in 15–35% yields in addition to the 1,2-disubstituted product **3b** (15–72%). The best performance in terms of the amount of the catalyst, reaction time, product yield and **3b** : **4b** selectivity was exhibited by $HClO_4$–SiO_2.[13] The distinct advantage of using the supported protic acids instead of the protic acids as such was revealed during the reaction of **1a** with **2b** performed under the catalytic influence of the individual protic acids. In each case, the overall yield of the cyclocondensation products as well as the **3b** : **4b** selectivity was found to be inferior to the corresponding reactions performed using the protic acids supported on SiO_2.

The generality of the $HClO_4$–SiO_2 catalysed selective formation of 1,2-disubstituted benzimidazole is demonstrated through the reaction of **1a** with various aromatic, heteroaromatic, alicyclic and aliphatic aldehydes (Table 3). The desired 1,2-disubstituted benzimidazoles were obtained in 70–90% yields. However, the steric and electronic nature of the substrate (aldehyde) exhibited a significant influence on the outcome of the selectivity. Sterically hindered (entries 9 and 20, Table 3) and electron deficient (entry 10, Table 3) aldehydes afforded exclusively the 2-substituted benzimidazole. The catalysts were easily separated from the products by filtration. The isolated products were purified by crystallisation from aq EtOH or by passing through a column of silica-gel and eluting with 10% EtOAc in heptane, wherever required.

The recyclability of the catalyst was investigated during the reaction of **1a** with **2b**.[13] After the completion of the reaction, the

Table 1 The selectivity of the formation of **3a** and **4a** during the reaction of **1a** with **2a** (Scheme 2) in the presence of $HClO_4$–SiO_2 and various reported catalysts[a]

Entry	Catalyst (mol%)	Time (h)	Yield (%)[b,c] 3a	4a	Lit ref.
1	none[d]	1	trace	traces	this work[e]
2	none[f]	1	trace	traces	this work[g]
3	$HClO_4$–SiO_2 (0.5)	1	90	00	this work
4	montmorillonite K-10 (10)[h]	1	12	07	this work using the reported catalyst[8s]
5	montmorillonite K-10 (10)[h]	4	42	22	this work using reported catalyst[8s] for the time reported therein
6	montmorillonite K-10 (10)[h,i]	10 min	80	10	8*s*
7	H_2SO_4–SiO_2 (10)	1	37	15	this work using the reported catalyst[j 8b]
8	L-Proline (10)	1	15	traces	this work using the reported catalyst[k 8q]
9	L-Proline (10)[l]	1	12	traces	8*q*[m]
10	oxalic acid (10)	1	26	traces	this work using the reported catalyst[8d]
11	oxalic acid (10)	3	70	14	this work using reported catalyst[8d] for the time reported therein
12	$Fe(ClO_4)_3$ (10)	1	25	traces	this work using the reported catalyst[8e]
13	$Fe(ClO_4)_3$ (10)	3	72	10	this work using reported catalyst[8e] for the time reported therein
14	$Fe(ClO_4)_3$ (10)[n]	1	14	06	8*e*[o]
15	$Mg(HSO_4)_2$ (30)[p]	20 min	63	25	8*p*
16	$Mg(HSO_4)_2$ (30)[q]	1	25	08	8*p*[r]
17	$SiO_2/ZnCl_2$ (25)[n]	1	trace	traces	8*n*
18	amberlite-IR-20 (0.1 g)[s]	1	35	10	8*m*[t]
19	Me_3SiCl (50)[s]	1	16	traces	8*i*[u]
20	[Hmim][TFA] (10)[v]	1	15	traces	8*h*[w]

[a] **1a** (2.5 mmol) was treated with **2a** (5 mmol, 2 equiv.) in the presence of the catalyst (except for entries 1 and 2) in EtOH (5 mL) (except for entries 1, 5, 8, 11, 12, 13, 14, 15, 16 and 17.) at rt (~25–30 °C). [b] The isolated yield of **3a** and **4a** obtained after column chromatographic purification. [c] The products were characterised by NMR (^1H and ^{13}C) and MS (APCI). [d] The reaction was carried out at 130 °C (oil bath) under neat conditions in the absence of any catalyst. [e] The products **3a** and **4a** were obtained in 27 and 20% yield, respectively, on performing the reaction for 4 h. [f] The reaction was carried out at rt in EtOH in the absence of any catalyst. [g] The products **3a** and **4a** were obtained in 30 and 20% yield, respectively, on performing the reaction for 4 h. [h] A 10% w/w of the catalyst was used. [i] The reaction was carried out under microwave heating (600 W output) in a domestic microwave oven under neat conditions. [j] The products **3a** and **4a** were obtained in 65 and 25% yield, respectively, on performing the reaction for 1.5 h. [k] The products **3a** and **4a** were obtained in 75 and 15% yield, respectively, on performing the reaction for 7 h. [l] The reaction was carried out in $CHCl_3$ instead of EtOH. [m] The products **3a** and **4a** were obtained in 70 and 18% yield, respectively, on performing the reaction for 7.5 h following a reported[9q] procedure. [n] The reaction was carried out at rt under neat conditions. [o] The products **3a** and **4a** were obtained in 50 and 20% yield, respectively, on performing the reaction for 4 h at rt under neat conditions. [p] The reaction was carried out under neat conditions at 80 °C. [q] The reaction was carried out in water at 80 °C. [r] The products **3a** and **4a** were obtained in 65 and 20% yield, respectively, on performing the reaction for 3 h in water at 80 °C. [s] The reaction was carried out at rt. [t] The products **3a** and **4a** were obtained in 66 and 22% yield, respectively, on performing the reaction for 2 h at rt. [u] The products **3a** and **4a** were obtained in 73 and 10% yield, respectively, on performing the reaction for 5 h at rt. [v] The reaction was carried out in water at rt. [w] The products **3a** and **4a** were obtained in 72 and 16% yield, respectively, on performing the reaction in water at rt for 5 h.

catalysts were recovered by filtration and reused for a subsequent fresh batch of the reaction after reactivation. The catalytic activity was found to be retained up to a fifth run in carrying out the reactions in 50, 40, 30, 20, and 10 mmol scale with respect to **1a** affording 90, 90, 87, 85, and 85% yields with $HClO_4$–SiO_2. The feasibility for the large scale preparation of 1,2-disubstituted benzimidazole was demonstrated with 100 mmol scale reactions.

To rationalise the influence of the catalyst, solvent, and the steric and electronic nature of the substrate on the selectivity control, we set forth to understand the mechanistic course of the reaction. The cyclocondensation of *o*-phenylenediamines with aldehydes to form the 1,2-disubstituted benzimidazoles may proceed through two distinctly different pathways (Scheme 4): (i) a bis-imine-rearrangement route (path a)[8a,d,e,i,k,n,o,u] and (ii) a mono-imine-cyclocondensation-aminal/immonium-rearrangement route (path b).[8l,m,p] 'Path a', would involve the formation of the bis-imine **IIa** (this may arise in a stepwise fashion of mono-imine **Ia** formation followed by the formation of the bis-imine **IIa**), which may undergo rearrangement *via* intramolecular nucleophilic attack of the nitrogen electron lone pair of one of the imine groups to the C=N of the other imine group to from **IIIa** followed by a 1,3-hydride shift to generate the 1,2-disubstituted benzimidazole **3**. In the alternative route 'path b,' the reaction may proceed through the formation of the mono-imine **Ia**, followed by intramolecular nucleophilic attack of the adjacent amino group on the imine to form the benzimidazolidine **Ib**, which would react with another molecule of the aldehyde to form the aminal/immonium species **IIb**/**IIIb** that on 1,3-hydrogen shift would lead to **3**.

The involvement of the 1,3-hydrogen shift was corroborated by the formation of 2-phenyl-1-α-d_2-phenylmethyl-1*H*-benzimidazole **3c**–d[8i] during the reaction of deuterated benzaldehyde **2c**–*d* (2 molar equiv.) with **1a** (Scheme 5). However, the feasibility of the formation of **3** by 'path a' or 'path b' could not be distinguished.

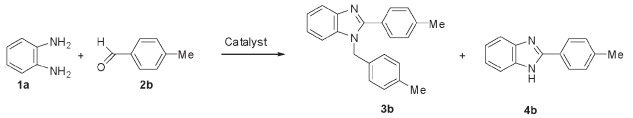
Thus, to demonstrate the mechanistic route for the progress of the formation of the 1,2-disubstituted benzimidazole, we planned to intercept the possible intermediates by various spectrometric studies. The formation of the 1,2-disubstituted benzimidazole *via* 'path b' seems unlikely as no ion peak corresponding to either of the aminal **IIb** or the immonium species **IIIb** (expected to be formed through the condensation of **Ib** with another molecule of the aldehyde) was detected (GCMS and LCMS) during the progress of the reaction of **1a** with **2b** (2 equiv.). The intermediate formation of **Ib** would further imply that the dehydrogenative conversion to

Table 2 Comparison of the efficiency of $HClO_4$–SiO_2 with that of other protic acids adsorbed on SiO_2 for the selectivity in the formation of **3b** and **4b** during the reaction of **1a** with **2b** (Scheme 3)[a]

Entry	Catalyst (mol%)	Yield (%)[b,c] 3b	4b
1	$HClO_4$–SiO_2 [230–400] (0.5)	80	5
2	$HClO_4$–SiO_2 [100–200] (0.5)	55	09
3	$HClO_4$–SiO_2 [60–120] (0.5)	18	10
4	TfOH–SiO_2 (1)	61	12
5	TFA–SiO_2 (1)	48	13
6	*p*-TsOH–SiO_2 (1)	58	20
7	MSA–SiO_2 (1)	55	12
8	HBr–SiO_2 (1)	54	15
9	H_2SO_4–SiO_2 (10)	40	08
10	H_2SO_4–SiO_2 (10)[d]	42	10[e]
11	H_2SO_4–SiO_2 (10)[e]	38	08
12	—[f]	trace	trace
13	$HClO_4$–neutral Al_2O_3 (1)	45	12
14	$HClO_4$–basic Al_2O_3 (1)	48	15
15	$HClO_4$–acidic Al_2O_3 (1)	55	12
16	zeolite type Y (10)[g]	25	10
17	zeolite K L^{-1} (SAR 6.8)(10)[g]	21	10
18	zeolite ZSM 5 (SAR 6.8) (10)[g]	28	08
19	zeolite K L^{-1} (for synthesis) (10)[g]	21	08
20	zeolite Na/Fau(10)[g]	20	08
21	zeolite NH_4/Y(10)[g]	24	13
22	montmorillonite K-10 (10)[g]	15	09
23	montmorillonite KSF (10)[g]	12	08
24	SiO_2 [230–400] (10)[g]	trace	trace
25	SiO_2 [100–200] (10)[g]	trace	trace
26	SiO_2 [60–120] (10)[g]	trace	trace
27	amberlite (10)[g]	trace	trace

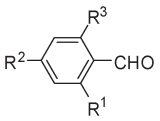
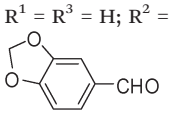
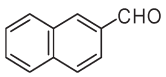
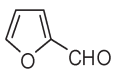
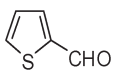
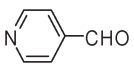
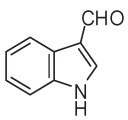
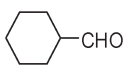
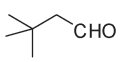
[a] **1a** (2.5 mmol) was treated with **2b** (5 mmol, 2 equiv.) in the presence of the catalyst in EtOH (5 mL except for entries 8–10) at rt (~25–30 °C) for 1.5 h unless specified. [b] The isolated yield of **3b** and **4b** after column chromatographic purification. [c] The products were characterised by NMR (^1H and ^{13}C) and MS (APCI). [d] The reaction was carried out in water. [e] The reaction was carried out in 1 M (5 mL) aq LiCl. [f] The reaction was carried out in 1 M (5 mL) aq LiCl in the absence of any added catalyst. [g] A 10% w/w of the catalyst was used.

the undesired product 2-substituted benzimidazole **4** would be accelerated under the presence of air/oxygen and on the other hand would be retarded under anaerobic conditions.[8l] The treatment of **1a** with **2b** (2 equiv.) under the catalytic influence of $HClO_4$–SiO_2 afforded **3b** in 78% yield using deoxygenated EtOH under nitrogen atmosphere compared to an 80% yield obtained in using EtOH in open air. Further, **3b** was formed in 80% yield during the $HClO_4$–SiO_2 catalysed reaction of **1a** with **2b** (2 equiv.) in EtOH while oxygen gas was bubbled into the reaction mixture. Thus, the presence or the absence of air/oxygen did not have any significant influence on the overall outcome of the reaction. These ruled out the involvement of **Ib**



Scheme 3 Selectivity of the formation of the 1,2-disubstituted benzimidazole **3b** and the 2-substituted benzimidazole **4b** during the reaction of **1a** with **2b** in the presence of various catalysts.

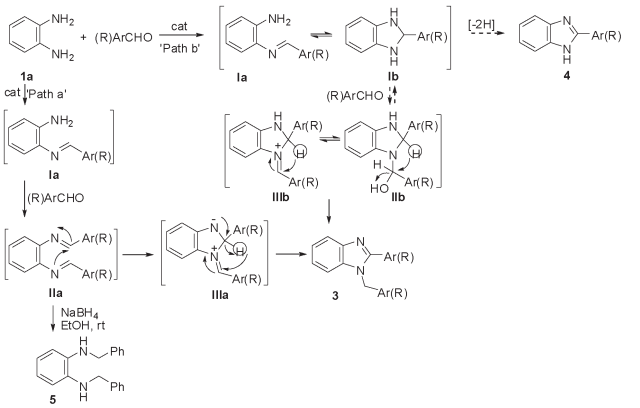
Table 3 1,2-Disubstituted benzimidazole formation by $HClO_4$–SiO_2 catalysed reaction of **1a** with various aldehydes[a]

Entry	Substrate	Time (h)	Yield (%)[b,c]
			
1	$R^1 = R^2 = R^3 = H$	2	80
2	$R^1 = R^3 = H$; $R^2 = Me$	1.5	80
3	$R^1 = R^3 = H$; $R^2 = OMe$	1	90
4	$R^1 = R^3 = H$; $R^2 = NMe_2$	1	90
5	$R^1 = R^3 = H$; $R^2 = Cl$	2	85
6	$R^1 = R^3 = H$; $R^2 = Br$	2	86
7	$R^1 = R^3 = H$; $R^2 = CF_3$	2	85
8	$R^1 = R^3 = H$; $R^2 = OCH_2Ph$	2	80
9	$R^1 = R^2 = R^3 = Me$	3	75[d]
10	$R^1 = R^3 = H$; $R^2 = NO_2$	2.5	86[d]
11		1	90
12		2	90
13		2	75
14		1	80
15		2	75
16		3	75
17		2	80
18		2	75
19		2	78
20		3	75[d]

[a] **1a** (2.5 mmol) was treated with the aldehyde (5 mmol, 2 equiv.) in EtOH (5 mL) separately in the presence of $HClO_4$–SiO_2 (0.5 mol%) at rt (~25–30 °C). [b] The isolated yield of the corresponding 1,2-disubstituted benzimidazole after column chromatographic purification. [c] The products were characterised by NMR (^1H and ^{13}C) and MS (APCI). [d] The corresponding 2-substituted benzimidazole was the sole product.

('path b') during 1,2-disubstituted benzimidazole formation for which the reaction follows 'path a'.

To further demonstrate the progress of the reaction for 1,2-disubstituted benzimidazole formation *via* 'path a,' we tested the



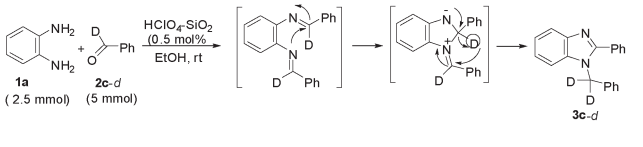
Scheme 4 Pathways of 1,2-disubstituted benzimidazole formation during the $HClO_4$–SiO_2 catalysed reaction of *o*-phenylenediamine with aldehyde.

feasibility of imine formation under the adopted experimental procedure. Treatment of aniline with benzaldehyde **2c** under the catalytic influence of $HClO_4$–SiO_2 under similar conditions formed the imine. Bis-imine formation also takes place when *m*-phenylenediamine is treated with two molar equivalents of **2c** in the presence of $HClO_4$–SiO_2 under similar conditions. These suggested that the reaction might proceed *via* 'path a' involving the formation of the bis-imine **IIa**. As a direct proof, the progress of the reaction of **1a** with **2c** (2 equiv.) was monitored by GCMS at 10, 20, 30, 40, and 50 min time intervals to 'fish out' any relevant intermediate. In each case, the ion peak at *m*/*z* 312 was detected. However, it remained unclear whether this could be due to the bis-imine **IIa** (Ar = Ph) or the corresponding 1,2-disubstituted benzimidazole (1-phenylmethyl-2-phenyl-1*H*-benzimidazole **3c**) as both are of the same molecular weight. Detailed MS^n studies also proved to be inconsequential with respect to the identity/authenticity of the species of *m*/*z* 312 as **IIa** (Ar = Ph) or **3c**. However, when an aliquot of sample withdrawn from the reaction mixture of **1a** with **2c** (2 equiv.) was subjected to LCMS studies during a 5–60 min reaction period, the ion peak corresponding to the mono-imine of **1a** and **2c** could be detected. The height/area of this ion peak was found to decrease with time with a concomitant appearance of the peak at *m*/*z* 312 corresponding to the bis-imine with increasing intensity.

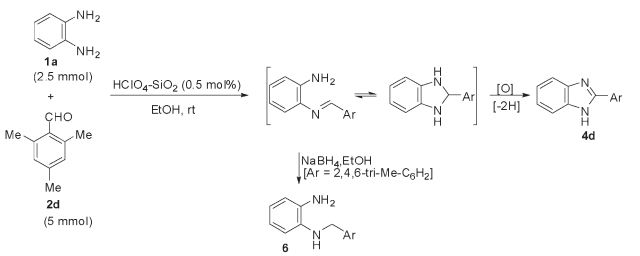
Finally, the formation of 1,2-disubstituted benzimidazole *via* 'path a' was validated by the isolation and characterisation (NMR) of N^1,N^2-dibenzylbenzene-1,2-diamine (**5**) formed by the *in situ* reduction ($NaBH_4$) of the intermediately formed bis-imine (Scheme 4) during the course of the reaction between **1a** and **2c** providing for the first time crucial evidence that the reaction proceeds *via* path a.

Therefore, the selectivity of the 1,2-disubstituted and 2-substituted benzimidazole formation lies in the feasibility of the formation of the bis-imine under the prescribed set of experimental condition(s). A stronger catalyst (supported protic acid) and polar reaction medium should assist in bis-imine formation. Hence, EtOH (protic polar) is the most effective reaction medium for the 1,2-disubstituted benzimidazole formation. The intermediacy of the bis-imine **IIa** is the crucial and determining factor for 1,2-disubstituted benzimidazole formation and hence directing/controlling the 1,2-disubstituted *vs.* 2-substituted benzimidazole selectivity is demonstrated by the observation that the reaction of **1a** with two molar equivalents of 2,4,6-trimethylbenzaldehyde **2d** forms only the 2-(2,4,6-trimethyl)phenyl-1*H*-benzimidazole **4d** in EtOH in the presence of $HClO_4$–SiO_2 (entry 9, Table 3). Due to the steric crowding surrounding the aldehyde group in **2d**, the bis-imine is not feasible and the 2-substituted benzimidazole **4d** is formed exclusively. To demonstrate that the reaction of **1a** with **2d** only forms the mono-imine (which on intramolecular nucleophilic attack by the adjacent amino group results in the formation of **4d** *via* the corresponding imidazoline), the reaction mixture was subjected to treatment with $NaBH_4$ (Scheme 6). The formation of 2-*N*-(2,4,6-trimethyl)aminomethylaniline **6** justified that the lack of formation of the expected 1,2-disubstituted benzimidazole from the reaction of **1a** with **2d** is due to the feasibility of only mono-imine formation. The implication of the steric factor in suppressing the bis-imine formation (and hence directing the selectivity towards the formation of 2-substituted benzimidazole) can also be realized with a sterically hindered aliphatic aldehyde. Thus, the reaction of **1a** with pivalaldehyde (2 equiv.) under the catalytic influence of $HClO_4$–SiO_2 in EtOH forms exclusively the 2-substituted benzimidazole (entry 20, Table 3), as the steric effect of the ^{t}Bu group in pivalaldehyde does not permit the bis-imine formation with **1a**.

The selective formation of the 2-substituted benzimidazole from an electron deficient aldehyde such as 4-nitrobenzaldehyde **2e** (entry 10, Table 3), under conditions conducive to form 1,2-disubstituted benzimidazole, could be due to the fact that because of the highly electrophilic character of the aldehyde carbonyl, rapid formation of the mono-imine takes place and before the second amino group of **1a** is involved in imine formation with another molecule of **2e** it undergoes an intramolecular nucleophilic attack on the C=N of the mono-imine (due its high electrophilic character



Scheme 5 Evidence for the 1,3-hydrogen shift during the formation of 2-phenyl-1-α-d_2-methylphenyl-1*H*-benzimidazole by the $HClO_4$–SiO_2-catalysed reaction of *o*-phenylenediamine with deuterated benzaldehyde.

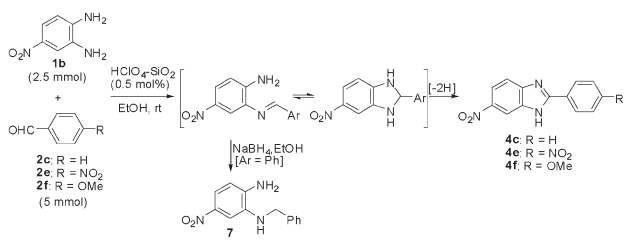


Scheme 6 Formation of 2-substituted benzimidazole during the $HClO_4$–SiO_2 catalysed reaction of **1a** with **2d**.

owing to the 4-nitro group) leading to the formation of the intermediate imidazoline and subsequent dehydrogenation to the 2-substituted benzimidazole as the final/end product.

To assess the influence of the electronic effect of the *o*-phenylenediamine component on the selectivity of formation of the 1,2-disubstituted and 2-substituted benzimidazoles, 4-nitro-*o*-phenylenediamine **1b** was treated separately with 2 equiv. each of benzaldehyde **2c**, 4-nitrobenzaldehyde **2e**, and 4-methoxybenzaldehyde **2f** (Scheme 7) under conditions that would favour the formation of 1,2-disubstituted benzimidazole. However, in each case the corresponding 2-substituted benzimidazoles were obtained as the only product.

The origin of the selective formation of the 2-substituted benzimidazoles from the reactions of **1b** could be due to its ability to form the mono-imine only as the electronic withdrawing effect of the nitro group makes the *para* amino group less nucleophilic. To prove that the reaction of **1b** with an aldehyde can only form the mono-imine, the reaction mixture of **1b** and **2c** was treated with $NaBH_4$ to trap any intermediately formed imine by converting it to the corresponding reduced product which was found to be 4-nitro-2-methylphenylaminoaniline **7**. The formation of the mono-*N*-benzylated product of **1b** confirmed that only the mono-imine is formed although 2 molar equiv. of the aldehyde was used. That the 2-amino group (*meta* to the nitro group) in **1b** undergoes imine formation was confirmed by comparison of the ^{1}H NMR (the benzylic protons being the probe nuclei) of the reductive alkylation product from the reaction of **1b** and **2c** with that of the *N*-benzylated 4- and 3-nitro anilines (prepared by reductive amination of 4- and 3-nitro anilines with benzaldehyde). The benzylic protons in *N*-benzyl-4-nitroaniline and *N*-benzyl-3-nitroaniline appear at δ 4.43 and 4.39, respectively. The benzyl protons of the reductive alkylation product obtained from the reaction of **1b** with **2c** appeared at δ 4.38 suggesting it to be **7** (Scheme 7). However, we realised that the tiny chemical shift difference between *N*-benzyl 4-nitro aniline and *N*-benzyl 3-nitro aniline cannot differentiate the regioisomers unambiguously. A recent literature report[15] on the reductive amination of **1b** and **2c** came to our notice which, although, claimed the formation of **7**, the ambiguity remains with respect to the identity of the product either as **7** or as **7a**. In order to resolve this issue, we carried out various NMR experiments such as DEPT 135 and 2D (HSQC and NOESY) of **7** and confirmed its structure as 4-nitro-2-methylphenylaminoaniline (supporting information†).



Scheme 7 $HClO_4$–SiO_2-catalysed reaction of 4-nitro-*o*-phenylenediamine with **2c**, **2e**, and **2f**.

Conclusions

This study provides an account on the issue of competitive formation of the 1,2-disubstituted and 2-substituted benzimidazoles during direct cyclocondensation of *o*-phenylenediamine aldehyde. The scope and limitation of various protic acids on a solid support as well as the reaction medium have been studied to derive that the best operative reaction conditions are the treatment of the *o*-phenylenediamine with two molar equiv. of an aldehyde in EtOH at rt in the presence of catalytic quantities of $HClO_4$–SiO_2 (0.5 mol%) to form exclusively/selectively the 1,2-disubstituted benzimidazoles. Other solid supports such as alumina (acidic/basic/neutral) gave inferior results both in terms of product yield and selectivity. The catalyst system $HClO_4$–SiO_2 is distinctly superior to the reported catalysts/procedures that are associated with the competitive formation of the 2-substituted benzimidazoles. A mechanistic outline has been derived for the $HClO_4$–SiO_2 catalysed formation of the 1,2-disubstituted benzimidazoles, which follows bis-imine formation, rearrangement, and a 1,3-hydride shift pathway. The origin/rationale of selectivity resides on furthering or suppressing the bis-imine formation using a judicial choice of the supported protic acid catalyst as well as an appropriate reaction medium. The steric and electronic factors of the aldehyde and the electronic factor of the *o*-phenylenediamine component also exhibit significant influence on the selectivity. Sterically hindered and electron deficient aldehydes and electron deficient *o*-phenylenediamine afforded the 2-substituted benzimidazoles under conditions that are conducive for 1,2-disubstituted benzimidazole formation.

Preparation of perchloric acid adsorbed on silica-gel ($HClO_4$–SiO_2)

The $HClO_4$–SiO_2 was prepared following the procedure first reported by its inventors.[12] To a suspension of silica gel (23.75 g, 230–400 mesh) in Et_2O (50 mL), was added $HClO_4$ (1.25 g, 12.5 mmol, 1.78 mL of a 70% aq solution of $HClO_4$) and the mixture was stirred magnetically for 30 min at rt. The Et_2O was removed under reduced pressure (rotary evaporator) and the residue heated at 100 °C for 72 h under vacuum (10 mm Hg) to afford $HClO_4$–SiO_2 (0.5 mmol g^{-1}) as a free flowing powder.

Typical experimental procedure for the synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles using $HClO_4$–SiO_2 (Entry 4, Table 3)

The mixture of *o*-phenylenediamine **1a** (0.27 g, 2.5 mmol, 1 equiv.), 4-dimethylaminobenzaldehyde **2a** (0.74 g, 5 mmol, 2 equiv.), and $HClO_4$–SiO_2 (25 mg, 0.012 mmol, 0.5 mol%) in EtOH (10 mL) was stirred magnetically at rt (~25–30 °C). After completion of the reaction (TLC, 3 : 1 *n*-hexane–EtOAc), the mixture was filtered, washed with EtOH (2 × 5 mL), and the combined filtrates were concentrated under rotary vacuum evaporation. The crude product was purified by crystallisation from aq EtOH or passed through a column of silica gel and eluted with 10% EtOAc in hexane to afford 1-(4-dimethylaminophenylmethyl)-2-(4-dimethylaminophenyl)-1*H*-benzimidazole **3a** (0.83 g, 90%) as a white solid; mp = 255–256 °C; IR (KBr) ν_{max} = 3038, 1610, 1562, 1482, 1251, 1168 cm^{-1}; ^{1}H NMR (300 MHz, 25 °C, $CDCl_3$): δ = 7.80 (d, J = 7.8 Hz, 2 H; Ar–H), 7.63 (d, J = 8.7 Hz, 2 H; Ar–H), 7.19 (t, J = 8.5 Hz, 3 H; Ar–H), 7.01 (d, J = 8.5 Hz, 2 H;

Ar–H), 6.66–6.78 (m, 4 H; Ar–H), 5.37 (s, 2 H; CH_2), 3.00 (s, 3 H; CH_3), 2.92 (s, 3 H; CH_3); MS (APCI) *m/z*: 371 $(M+H)^+$.[8c]

Typical experimental procedures for mechanistic insights

Monitoring the progress of the reaction of 1a with two molar equivalents of 2b performed in EtOH at rt in the presence of $HClO_4$–SiO_2 by GCMS. The mixture of **1a** (0.27 g, 2.5 mmol), **2b** (0.6 g, 5 mmol, 2 equiv.), and $HClO_4$–SiO_2 (25 mg, 0.012 mmol, 0.5 mol%) in EtOH (5 mL) was stirred magnetically at 25–30 °C. Aliquot (0.5 mL) portions of the reaction mixture were taken out after 10, 20, 30, 40, 50 and 60 min and on each occasion was diluted with EtOH (1 mL). The resultant solution (1 μL) was subjected to GCMS to identify the ion peaks of any of the intermediates depicted in Scheme 4. In each case the ion peak at *m/z* 312 corresponding to the bis-imine (or the resultant 1,2-disubstituted benzimidazole **3b**) was detected.

Monitoring the progress of the reaction of 1a with two molar equivalents of 2b performed in EtOH at rt in the presence of $HClO_4$–SiO_2 by APCI mass spectroscopy. The mixture of *o*-phenylenediamine **1a** (0.27 g, 2.5 mmol), 4-methylbenzaldehyde **2b** (0.6 g, 5 mmol, 2 equiv.), and $HClO_4$–SiO_2 (25 mg, 0.012 mmol, 0.5 mol%) in EtOH (5 mL) was stirred magnetically at 25–30 °C. Aliquot (20 μL) portions of the reaction mixture were taken out after 10, 20, 30, 40, 50 and 60 min and on each occasion was diluted with EtOH (1 mL). From the resultant solution an aliquot amount (10 μL) was subjected to +ve APCI-MS to identify the ion peaks of any of the intermediates depicted in Scheme 4. In the case of samples of the 10 and 20 min periods the ion peaks corresponding to the mono-imine along with the ion peak at *m/z* 312 were observed. The remaining samples showed only the presence of the ion peak at *m/z* 312.

Formation of N^1,N^2-dibenzylbenzene-1,2-diamine 4 during the *in situ* reduction (with $NaBH_4$) of the presumably formed bis-imine during the synthesis of the 1,2-disubstituted benzimidazole from 1a with 2c. The mixture of *o*-phenylenediamine **1a** (0.27 g, 2.5 mmol), benzaldehyde **2c** (0.6 g, 2.5 mmol, 1 equiv.), and $HClO_4$–SiO_2 (25 mg, 0.012 mmol, 0.5 mol%) in EtOH (5 mL) was stirred magnetically at 25–30 °C. After 30 min, $NaBH_4$ (7.5 mmol, 3 equiv.) was added and the resultant mixture was stirred for further 30 min. The mixture was dissolved in EtOAc (5 mL), adsorbed on silica gel (1 g, 230–400 mesh) and concentrated under rotary vacuum evaporation. The resultant solid mass was charged on to flash chromatography column and eluted with hexane–EtOAc (85 : 15) to afford N^1, N^2-dibenzylbenzene-1,2-diamine **5** (86 mg, 12%). Low melting solid; IR (KBr) ν_{max} = 3435, 2972, 1612, 1451, 1325, 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ: 7.39–7.36 (m, 4H), 7.34–7.29 (m, 4H), 7.27–7.24 (m, 2H), 6.80–6.77 (m, 2H), 6.73–6.70 (m, 2H), 4.31 (s, 4H), 3.64 (brs, 2H); MS (EI) *m/z*: 289.4 $(M+H)^+$.

Formation of 2-phenyl-1-α-D_2-phenylmethyl-1*H*-benzimidazole during the reaction of 1a and 2c-D_1 in the presence of $HClO_4$–SiO_2. The mixture of **1a** (0.1 g, 1 mmol, 1 equiv.), **2c**–d_1 (0.21 g, 2 mmol, 2 equiv.), and $HClO_4$–SiO_2 (10 mg, 0.005 mmol, 0.5 mol%) in EtOH (5 mL) was stirred magnetically at rt (~25–30 °C). After completion of the reaction (TLC, 3 : 1 *n*-heptane–EtOAc), the mixture was filtered, washed with EtOH (2 × 5 mL), and the combined filtrates were concentrated under rotary vacuum evaporation. The crude product was purified by passing through a column of silica gel and eluting with 10% EtOAc in heptane to afford 2-phenyl-1-α-d_2-phenylmethyl-1*H*-benzimidazole **3c**–*d* (0.20 g, 72%) as a white solid; ^1H NMR (400 MHz, 25 °C, $CDCl_3$): δ = 7.87 (d, *J* = 2 Hz, 1 H; Ar–H), 7.70–7.68 (m, 2 H; Ar–H), 7.48–7.42 (m, 3 H; Ar–H), 7.36–7.29 (m, 4 H; Ar–H), 7.24–7.20 (m, 2 H; Ar–H), 7.12–7.10 (m, 2 H; Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.1, 143.2, 136.2, 136.0, 130.0, 129.9, 129.2, 129.0, 128.7, 127.8, 126.0, 123.0, 122.6, 120.0, 110.5; MS (APCI) *m/z*: 287.4 $(M+H)^+$.[8i]

Formation of 2-(2,4,6-trimethyl)phenyl-1*H*-benzimidazole during the reaction of *o*-phenylenediamine and 2,4,6-trimethylbenzaldehyde in the presence of $HClO_4$–SiO_2. The mixture of *o*-phenylenediamine **1a** (0.27 g, 2.5 mmol, 1 equiv.), 2, 4, 6-trimethylbenzaldehyde (0.74 g, 5 mmol, 2 equiv.), and $HClO_4$–SiO_2 (25 mg, 0.012 mmol, 0.5 mol%) in EtOH (10 mL) was stirred magnetically at rt (~25–30 °C). After completion of the reaction, the mixture was filtered, washed with EtOH (2 × 5 mL), and the combined filtrates were concentrated under rotary vacuum evaporation. The crude product was purified by flash chromatography to afford 2-(2,4,6-trimethyl)-phenyl 1*H*-benzimidazole **4d** (0.44 g, 72%) as a white solid; mp = 282–284 °C; IR (KBr) ν_{max} = 1264, 1479, 1617, 1653, 3260 cm^{-1}; ^1H NMR (400 MHz, 25 °C, DMSO): 7.64 (d, *J* = 6.4 Hz, 1H; Ar–H), 7.47 (d, *J* = 7.64 Hz, 1H; Ar–H), 7.19 (s, 2H; Ar–H), 6.98 (s, 2H; Ar–H), 2.29 (s, 3H; CH_3), 2.04 (s, 6H; CH_3); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): 151.7, 143.8, 138.9, 134.9, 129.2, 128.4, 122.5, 121.6, 119.1, 111.6, 21.2, 20.1; MS (APCI) *m/z*: 237 $(M+H)^+$; Anal. Calcd. For $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85% Found: C, 81.35; H, 6.81; N, 11.86%.

Formation of N^1-benzyl-5-nitrobenzene-1,2-diamine 7 during the *in situ* reduction (with $NaBH_4$) of the presumably formed mono-imine during the reaction between from 1b and 2d. The mixture of 4-nitro *o*-phenylenediamine **1b** (0.39 g, 2.5 mmol), benzaldehyde **2c** (0.5 g, 5 mmol, 2 equiv.), and $HClO_4$–SiO_2 (25 mg, 0.012 mmol, 0.5 mol%) in EtOH (10 mL) was stirred magnetically at 25–30 °C. After 1 h, $NaBH_4$ (2 equiv.) was added and the resultant mixture was stirred for a further 2 h. The mixture was filtered to remove the catalyst, the filtrate was concentrated under rotary vacuum evaporation and the isolated crude product was purified by flash chromatography (15% EtOAc in hexane as eluent) to afford N^1-benzyl-5-nitrobenzene-1,2-diamine **7**; ^1H NMR (400 MHz, 25 °C, $CDCl_3$): δ = 7.41 (dd, *J* = 8.7 Hz & *J* = 2.5 Hz, 1 H; Ar–H), 7.33–7.40 (m, 4H; Ar–H), 7.25 (t, *J* = 7.0 Hz, 1 H; Ar–H), 6.58 (d, *J* = 2.4 Hz, 1 H; Ar–H), 6.58 (d, *J* = 8.7 Hz, 1 H; Ar–H), 6.28 (d, *J* = 6.3 Hz, 1 H; NH), 5.72 (t, *J* = 5.5 Hz, 1 H; NH), 4.38 (t, *J* = 5.1 Hz, 2 H; $PhCH_2$); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): 14.3, 139.6, 137.5, 135.4, 128.9, 127.7, 127.4, 116.3, 111.5, 104.6, 47.2; MS (APCI) *m/z*: 244.2 $(M+H)^+$.[15]

Representative procedure for the reductive amination (synthesis of *N*-benzyl-4-nitroaniline):[16a]. To a stirred solution of 4-nitrobenzaldehyde (0.138 g, 1 mmol) and aniline (0.093 g, 1 mmol, 1 equiv.) in 1,2-dichloroethane (5 mL) was added the sodium triacetoxyborohydride (0.32 g, 1.5 mmol, 1.5 equiv.) under neutral conditions (pH 7). The mixture was stirred at rt under a N_2 atmosphere for 24 h. After completion of reaction, the reaction mixture was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the crude product was purified by silica gel column chromatography with *n*-hexane–EtOAc as the eluent to afford the desired product (0.19 g, 85%); ^1H NMR (400 MHz, 25 °C, $CDCl_3$): 8.05–8.09 (m, 2 H; Ar–H), 7.29–7.39 (m, 5 H; Ar–H), 6.55–6.58 (m, 2 H; Ar–H), 4.09 (bd, s, 1 H, NH), 4.42 (d, *J* = 5.6 Hz, 2 H; CH_2); MS (APCI) *m/z*: 229.3 (MH^+).[16b] The synthesis of *N*-benzyl-3-nitroaniline was carried out

following a similar procedure (0.18 g, 81%): ^{1}H NMR (400 MHz, $CDCl_3$): 7.53 (d, J = 8.0 Hz, 1 H; Ar–H), 7.43 (s, 1 H; Ar–H), 7.24–7.37 (m, 6 H; Ar–H), 6.87 (d, J = 8.0 Hz, 1 H; Ar–H), 4.39 (bs, 3 H; NH); MS (APCI) m/z: 229.3 $(M+H)^+$.[16c]

Note added after first publication

This article replaces the version published on 6th November 2012, which contained errors in the title.

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