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Facile Synthesis of 1,2-Disubstituted Benzimidazoles Using *p*-Toluenesulfonic Acid through Grinding Method

C. Kathing[a], N. G. Singh[a], J. World Star Rani[a], R. Nongrum[a], and R. Nongkhlaw[a,*]

[a] *Centre for Advanced Studies in Chemistry, North-Eastern Hill University, Shillong, Meghalaya, 793022 India*

**e-mail: rlnongkhlaw@nehu.ac.in*

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Abstract—An efficient synthetic method for the highly selective synthesis of pharmacologically active 1,2-disubstituted benzimidazole derivatives from *o*-phenylenediamine and various aromatic aldehydes catalyzed by *p*-toluenesulfonic acid through grinding under solvent-free condition is described. The reaction requires the catalyst only during the conversion of intermediate *N*,*N*′-dibenzylidene-*o*-phenylenediamine into the desired product. The products were obtained within a short time with good yields by using only a mortar and pestle, which makes the proposed method convenient and cost-effective.

Keywords: 1,2-disubstituted benzimidazole, *p*-toluenesulfonic acid, solvent-free reaction

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INTRODUCTION

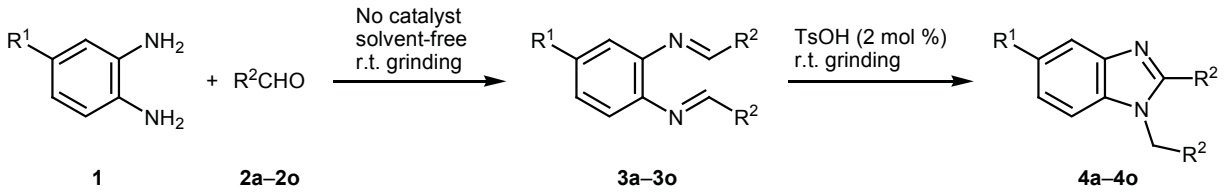
In the field of medicine, compounds containing a benzimidazole nucleus have been termed as "privileged structures" for drug design owing to their broad spectrum of biological activity [1]. Benzimidazole derivatives exhibit diverse pharmacological properties such as antihistamine [2, 3], antidiabetic [4], chemotherapeutic [5], antiparasitic [6, 7], antiproliferative [8], anti-HIV [9, 10], anticonvulsant [11], antineoplastic [12, 13], DNA binding agent [14], enzyme and receptor agonists or antagonists [15]. In addition, they have found applications in veterinary medicine as anthelmintic agents and have been used as organic ligands [16, 17], fluorescent whitening agents [18] and functional materials [19].

The synthesis of 1,2-disubstituted benzimidazole derivatives has been extensively studied, as evident from the growing number of publications. Despite the numerous records available it has been still explored rapidly due to its high profile of biological applications. General methods for the preparation of 2-substituted benzimidazole derivatives involve the condensation of *o*-phenylenediamines with carboxylic acids or their derivatives (nitriles, imidates, or ortho esters) in the presence of various acid catalysts [20–22]. The classical methods for the synthesis 1,2-disubstituted benzimidazole include *N*-alkylation of 2-substituted benzimidazole using a strong base [23, 24], reductive cyclization with *o*-nitroaniline and aldehydes [25, 26], cyclocondensation of *N*-substituted *o*-aminoanilides [27, 28], and condensation of *N*-substituted phenylenediamines with α-hydroxybenzylsulfonic acid sodium salt [29].

However, the most common method to access 1,2-disubstituted benzimidazoles is based on the direct coupling of *o*-phenylenediamines with aromatic aldehydes in the presence of acid catalysts [30–36]. The series of catalysts that have been used for the synthesis of 1,2-disubstituted benzimidazoles includes trimethylsilyl chloride [37], ceric ammonium nitrate [38], Dowex-50W [39], montmorillonite K-10 [40], SDS micelles [41], $SiO_2/ZnCl_2$ [42], nano-indium oxide [43], nano-ceria [44], iron(III) sulfate/silica [45], amberlite IR-120 [46, 47], silica sulfuric acid [48], glyoxalic acid [49], $In(OTf)_3$ [50], $Sm(OTf)_3$ [51], $HClO_4$-SiO_2 [52], CuI/L-proline [53], $AcOH/O_2$ [1], $SbCl_3/Al_2O_3$ [54], $FePO_4$ [55], oxalic acid [56], and $Cu(NO_3)_2 \cdot 3H_2O$ [57].

Despite the satisfactory results obtained with various catalysts, most of the described methods often led to a mixture of products because of competitive formation of 1,2- and 2-substituted benzimidazoles. In addition, the reactions were carried out in drastic conditions with the use of expensive reagents, they required a long time, and the starting materials were poorly available. Therefore, a direct synthetic method to furnish 1,2-disubstituted benzimidazoles with a greener protocol and

Scheme 1.



For R^1, R^2, see Table 1.

better selectivity remains the prime focus of researchers. The interesting and diverse biological properties of benzimidazoles offers great utility in clinical industries and prompted researchers to further develop efficient methods of synthesis. As per exhaustive literature survey, the production of benzimidazole compounds with the simple use of bare mortar and pestle has not been employed. In order to achieve the direct synthesis of 1,2-disubstituted benzimidazole derivatives, the reaction was carried out by grinding in the presence of *p*-toluenesulfonic acid (TsOH) under solvent-free conditions.

RESULTS AND DISCUSSION

With the aim to develop a facile and convenient protocol, our study focused on the synthesis of 1,2-disubstituted benzimidazoles **4** by grinding with a catalytic amount of TsOH (Scheme 1). The method is quite simple and convenient, and the desired products were obtained within a short time using only mortar and pestle.

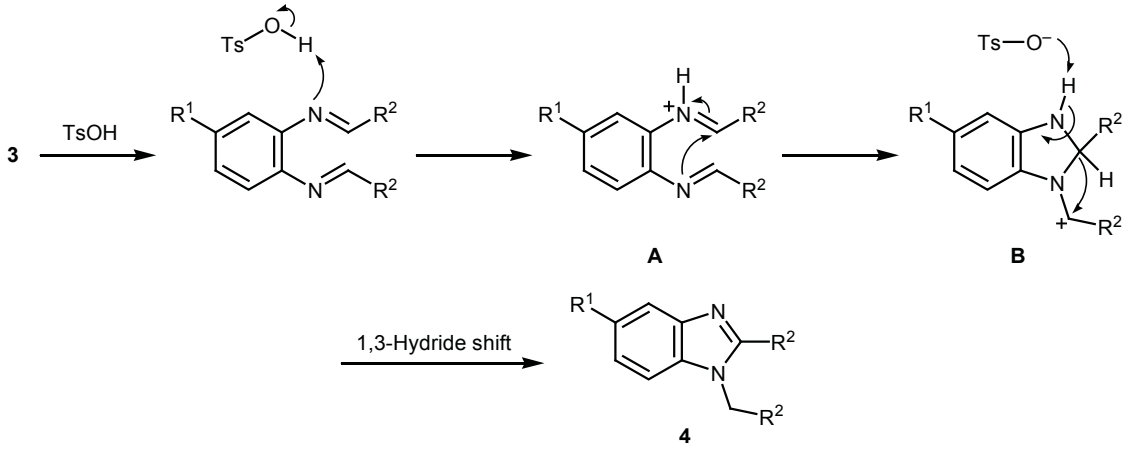
The reaction was initially performed by grinding the reactants, i.e., *o*-phenylenediamine **1** and aromatic aldehyde **2** at a molar ratio of 1:2 without catalyst and solvent. The reactants condensed rapidly to form a yellow solid intermediate, *N*,*N*′-dibenzylidene-*o*-phenylenediamine (**3**). However, no cyclization occurred on prolonged grinding. After addition of 2 mol % of TsOH, the reaction mixture immediately changed from yellow to brown, indicating the formation of 1,2-disubstituted benzimidazole **4**, which was monitored by TLC. Thus, a catalyst is required for ring closure to construct the 5-membered ring moiety of benzimidazole.

Table 1. Synthesis of 1,2-disubstituted benzimidazoles **4a**–**4o**

Comp. no.	R^1	R^2	Yield,[a] %	mp, °C	
				found	reported
4a	H	Ph	97	130–132	132 [40]
4b	H	4-$MeOC_6H_4$	94	130–131	131 [40]
4c	H	4-MeC_6H_4	95	127–128	128–129 [37]
4d	H	4-ClC_6H_4	93	136–138	137 [40]
4e	H	2-ClC_6H_4	92	154–156	154–156 [58]
4f	H	4-$O_2NC_6H_4$	94	200–201	192–194 [59]
4g	H	3-$O_2NC_6H_4$	93	119–120	120–121 [60]
4h	H	4-HOC_6H_4	91	206–208	208–209 [61]
4i	H	2-HOC_6H_4	90	192–194	200–204 [62]
4j	H	3-MeO-4-HOC_6H_3	92	168–170	184–186 [63]
4k	H	3,4-$(MeO)_2C_6H_3$	93	170–171	170–172 [38]
4l	H	Furan-2-yl	90	96–98	94–96 [63]
4m	H	(*E*)-PhCH=CH	88	88–90	[37, 64–67][b]
4n	4-Cl	Ph	85	138–140	172–174 [68]
4o	4-Cl	4-$MeOC_6H_4$	82	126–128	125 [69]

[a] Isolated yield.
[b] The nature of the compound does not match that reported in the literature, but its ^1H and ^{13}C NMR spectroscopic data are consistent with the reported data.

Scheme 2.



Various catalysts like benzyl(triethyl)ammonium chloride (BTEA), dodecylbenzenesulfonic acid (DBSA), $AlCl_3$, I_2, and $NaHSO_4$ were also investigated. Despite their effective catalytic action, the selectivity was poor, and a mixture of 2-mono- and 1,2-disubstituted products was formed. Thus, it was found that TsOH exhibited the best catalytic effect for the selective formation of 1,2-disubstituted benzimidazole **4** as compared to other catalysts. A TsOH amount of 2 mol % was sufficient to facilitate the conversion of intermediate **3** into the desired product; further increase of the catalyst amount up to 20 mol % did not enhance the yield.

Under the optimized conditions, a series of reactions were performed to furnish 1,2-disubstituted benzimidazoles **4a**–**4o** (Table 1). The effects of both electron-donating and electron-withdrawing substituents in aromatic aldehydes do not hamper the selective formation of compounds **4a**–**4o** as evident from the excellent yield of the products. The reaction also showed tolerance towards acid-sensitive aldehydes like furaldehyde (**3l**) and α,β-unsaturated aldehydes like cinnamaldehyde (**3m**), and the corresponding 1,2-disubstituted benzimidazole derivatives were formed in good yield.

A plausible mechanism for the formation of 1,2-disubstituted benzimidazoles **4** is shown in Scheme 2.

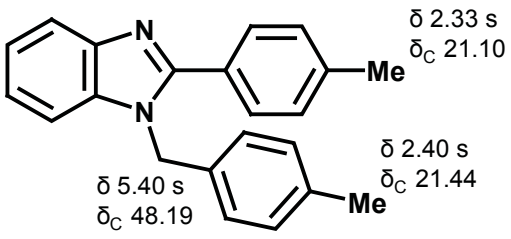


Fig. 1. Selected ^1H and ^{13}C NMR data of **4c**.

The reaction pathway is consistent with the earlier reported mechanism [30–36, 39, 42, 44] which is initiated by the formation of *N*,*N*′-dibenzylidene-*o*-phenylenediamine **3** via condensation of aldehyde **2** with diamine **1**. Protonation of **3** with *p*-toluenesulfonic acid, followed by cyclization, generated intermediate **B** which underwent aromatization via deprotonation and 1,3-hydride shift resulting in final product **4**.

All the compounds prepared were characterized and authenticated by melting point data, FT-IR, ^1H NMR, ^{13}C NMR, and mass spectrometry. In the ^1H NMR spectrum of **4c** (Fig. 1), the presence of a singlet at δ 5.40 ppm confirmed the formation of 1,2-disubstituted benzimidazole. The signal at δ_C 48.19 ppm in the ^{13}C NMR spectrum was assigned to the methylene carbon. Protons of two methyl groups in the aromatic rings resonated separately at δ 2.33 and 2.40 ppm.

The product structure was further confirmed by X-ray analysis of a single crystal of **4c** (Fig. 2), which was obtained by slow evaporation of its solution in ethanol.

In conclusion, a simple, efficient, and highly selective method has been developed for the synthesis of 1,2-disubstituted benzimidazoles by grinding at room temperature in the presence of *p*-toluenesulfonic acid. The method is quite economical compared to the other existing methods, as it required catalyst only for the conversion of intermediate into the desired product. The experimental simplicity (i.e., the use of a mortar and a pestle) makes the method convenient, environmentally friendly, and cost-effective. Furthermore, short reaction time, good yields, and the ease of isolation and purification of the product by simple recrystallization techniques are additional advantages of the proposed protocol.

EXPERIMENTAL

The melting points were determined in open capillary tubes with an Optics Technology melting point apparatus and are uncorrected. The infrared spectra were recorded in KBr on a Perkin Elmer Spectrum 400 FTIR instrument. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance II 400 and Bruker Avance III HD 300 spectrometers using $CDCl_3$ and DMSO-d_6 as solvents and tetramethylsilane as internal standard. The mass spectra were obtained on a Waters ZQ-4000/JMS-T100LC Accu TOF instrument. All reactions were monitored by TLC using precoated aluminum sheets (silica gel 60 F254, 0.2 mm thickness); visualization was done by treatment with iodine vapor or under a UVGL-15 lamp (λ 254 nm).

The X-ray diffraction data for compound **4c** were collected on an Agilent Xcalibur (Eos, Gemini) diffractometer equipped with a graphite monochromator (Mo K_α radiation, λ= 0.71073 Å) at 291.5(5) K. The structure was solved by the direct method and was refined by OLEX2. Figure 2 shows an ORTEP image of molecule **4c**. Crystal size 0.35×0.22×0.12 mm^3; $C_{22}H_{20}N_2$, M 312.42; triclinic crystal system, space group P-1; unit cell parameters: a = 9.6995(5), b = 10.4510(6), c = 17.8108(10) Å; α = 84.112(5), β = 81.452(4), γ = 75.822(4)°; V = 1726.92 Å^3; Z = 4; μ = 0.071 mm^{-1}; d_{calc} = 1.2015 g/cm^3. Index ranges $-12 \le h \le 12$, $-12 \le k \le 14$, $-23 \le l \le 23$; $5.94 \le \theta \le 57.5°$. Total of 13820 reflection intensities were measured, including 7799 independent reflections (R_{int} = 0.0326); goodness of fit (on F^2) S = 0.942. Final divergence factors: R_1 = 0.0609, wR_2 = 0.1470 [reflections with $I > 2\sigma(I)$]; R_1 = 0.1187, wR_2 = 0.1918 (all independent reflections); maximum/minimum residual electron density peaks 0.30/–0.33 $\bar{e}$/Å^3. The complete set of X-ray diffraction data for compound **4c** was deposited to the Cambridge Crystallographic Data Centre (CCDC entry no. 1 564 165).

General procedure for the preparation of 1,2-disubstituted benzimidazoles 4a–4o. A mixture of 108 mg (1 mmol) of *o*-phenylenediamine and aromatic aldehyde (2 mmol) was ground with a pestle in a mortar for 5–10 min. A catalytic amount of *p*-toluenesulfonic acid (3.8 mg, 2 mol %) was then added, and the mixture was ground until the reaction was complete (TLC). The mixture was extracted with methylene chloride (3×10 mL), and the combined extracts were washed with water [(2–3)×15 mL], dried over anhydrous Na_2SO_4, and evaporated under reduced pressure on a rotary evaporator. The solid residue was almost pure product **4**; it was further purified by recrystallization from hot ethanol.

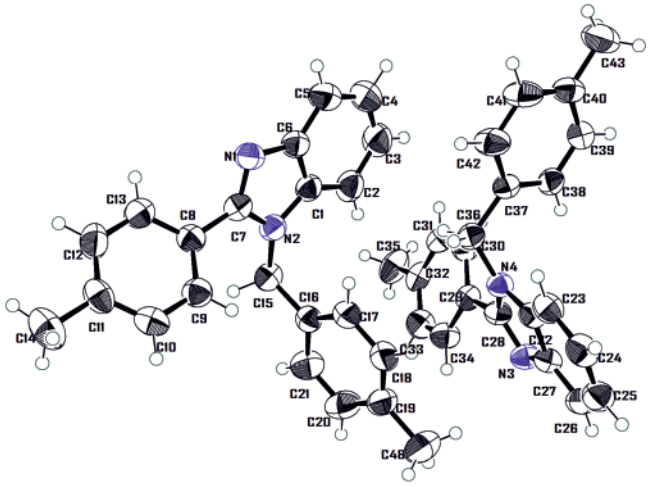


Fig. 2. ORTEP image of **4c** (CCDC entry no. 1564165).

Spectral data for some selected compounds are given below.

1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-1*H*-benzimidazole (4b) [40]**.** Light brown solid. IR spectrum, ν, cm^{-1}: 1611 (C=N), 2961 (C–H_{aliph}), 3055 (C–H_{arom}). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 3.78 s (3H, OCH_3), 3.85 s (3H, OCH_3), 5.38 s (2H, CH_2), 6.82–7.82 m (12H, H_{arom}). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ_C, ppm: 48.09, 55.49, 55.57, 110.61, 114.40, 114.64, 119.92, 122.71, 122.93, 127.42, 128.70, 130.92, 136.30, 143.37, 154.31, 159.34, 161.12. Mass spectrum: m/z 345 $[M + H]^+$.

1-(4-Methylbenzyl)-2-(4-methylphenyl)-1*H*-benzimidazole (4c) [58]**.** Colorless solid. IR spectrum, ν, cm^{-1}: 1612 (C=N), 2918 (C–H_{aliph}), 3024 (C–H_{arom}). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 2.33 s (3H, CH_3), 2.40 s (3H, CH_3), 5.40 s (2H, CH_2), 6.98–7.86 m (12H, H_{arom}). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ_C, ppm: 21.10, 21.40, 48.19, 110.52, 119.79, 122.57, 125.88, 127.10, 129.16, 129.45, 129.98, 133.42, 136.07, 137.44, 140.06, 143.07, 154.31. Mass spectrum: m/z 313 $[M + H]^+$.

1-(4-Chlorobenzyl)-2-(4-chlorophenyl)-1*H*-benzimidazole (4d) [40]**.** Off-white solid. IR spectrum, ν, cm^{-1}: 1620 (C=N), 2920 (C–H_{aliph}), 3040 (C–H_{arom}). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 5.40 s (2H, CH_2), 7.19–7.34 m (4H, H_{arom}), 7.44 d (2H, H_{arom}, J = 8.8 Hz,), 7.59 d (2H, H_{arom}, J = 8.4 Hz,), 7.87 d (2H, H_{arom}, J = 8.0 Hz). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ_C, ppm: 47.97, 110.49, 120.37, 123.24,

123.66, 127.43, 128.53, 129.34, 129.57, 130.62, 134.03, 136.10, 136.53, 143.26, 153.06. Mass spectrum: *m*/*z* 353 $[M + H]^+$.

1-(3-Nitrobenzyl)-2-(3-nitrophenyl)-1*H*-benzimidazole (4g) [61]**.** Off-white solid. IR spectrum (KBr), ν, cm^{-1}: 1613 (C=N), 2927 ($C–H_{aliph}$), 3075 ($C–H_{arom}$). ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 5.52 s (2H, CH_2), 7.21–8.29 m (12H, H_{arom}). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ_C, ppm: 47.84, 110.27, 120.70, 121.14, 123.36, 123.69, 123.92, 124.39, 124.80, 130.26, 130.58, 131.42, 131.79, 134.95, 135.85, 137.92, 143.02, 148.33, 148.77, 151.17. Mass spectrum: *m*/*z* 375 $[M + H]^+$.

4-[1-(4-Hydroxybenzyl)-1*H*-benzimidazol-2-yl]-phenol (4h) [62]**.** Light yellow solid. IR spectrum (KBr), ν, cm^{-1}: 1611 (C=N), 2926 ($C–H_{aliph}$), 3025 ($C–H_{arom}$), 3305 (O–H). ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 5.37 s (2H, CH_2), 6.73–7.74 m (12H, H_{arom}), 9.13 s (1H, OH), 9.60 s (1H, OH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ_C, ppm: 52.43, 115.86, 120.66, 123.89, 125.70, 127.01, 127.24, 131.91, 132.39, 140.87, 147.78, 158.92, 161.88, 164.09. Mass spectrum: *m*/*z* 317 $[M + H]^+$.

1-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)-1*H*-benzimidazole (4k) [38]**.** Light brown solid. IR spectrum, ν, cm^{-1}: 1611 (C=N), 2936 ($C–H_{aliph}$), 3064 ($C–H_{arom}$). ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 2.93 s (6H, OCH_3), 3.00 s (6H, OCH_3), 5.37 s (2H, CH_2), 6.67–7.82 m (10H, H_{arom}). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ_C, ppm: 40.21, 40.55, 48.04, 110.41, 111.80, 112.47, 112.79, 117.29, 119.21, 122.17, 124.29, 126.92, 130.30, 136.35, 143.23, 149.95, 151.19, 155.02. Mass spectrum: *m*/*z* 405 $[M + H]^+$.

2-[(*E*)-2-Phenylethenyl]-1-[(*E*)-3-phenylprop-2-en-1-yl]-1*H*-benzimidazole (4m) [37, 64–67]**.** Brown solid. IR spectrum, ν, cm^{-1}: 1634 (C=N), 2925 ($C–H_{aliph}$), 3053 ($C–H_{arom}$). ^1H NMR spectrum (400 MHz, $CDCl_3$), δ_C, ppm: 5.06 d (2H, CH_2, J = 4.4 Hz), 6.35 t.d (1H, CH=CH, J = 16.0, 4.4 Hz), 6.43 d (1H, CH=CH, J = 16.0 Hz), 7.11 d (1H, CH=CH, J = 15.6 Hz), 7.23–7.60 m (10H, H_{arom}), 7.59 d (2H, H_{arom}, J = 7.2 Hz,), 7.81 d (2H, H_{arom}, J = 7.6 Hz), 8.00 d (1H, CH=CH, J = 16.0 Hz). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ_C, ppm: 45.23, 109.56, 112.99, 119.45, 122.79, 122.83, 123.27, 126.52, 127.32, 128.17, 128.65, 128.86, 129.13, 132.40, 135.39, 135.69, 135.96, 137.60, 143.22, 150.90; Mass spectrum: *m*/*z* 337 $[M + H]^+$.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIALS

Supplementary materials are available for this article at https://doi.org/10.1134/S1070428020090201 and are accessible for authorized users.

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