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Ultrasound promoted and SiO_2/CCl_3COOH mediated synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazole derivatives in aqueous media: An eco-friendly approach

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Abstract. Ultrasonic irradiation is an efficient and innocuous technique of reagent activation for synthesizing organic compounds. First one-pot synthesis of 2-aryl-1-arylmethyl-1H- benzimidazole derivatives from o- phenylenediamine and an aromatic aldehyde in the presence of silica gel supported trichloroacetic acid (SiTCA) was carried out with excellent yields at 50°C by sonication. This method provided several advantages such as green solvent, inexpensive catalyst, simple experimental methodology, shorter reaction time and higher yield.

Keywords. 2-Aryl-1-arylmethyl-1H-benzimidazoles; silica gel supported trichloroacetic acid (SiTCA); regioselective; one-pot synthesis; ultrasound irradiation.

1. Introduction

The preparation of small heterocyclic organic molecules by using ultrasound has received considerable attention in recent years. Use of ultrasound irradiation is known to accelerate a wide range of synthetically useful organic reactions.[1] The use of ultrasonic waves to promote chemical reactions is called sonochemistry which also shares approach with the green chemistry.[2] It reduces the amount of any hazardous substance and solvents, reduces energy consumption, and increases product selectivity.[1] Nowadays the heterocyclic organic molecules are important in several fields of science including organic, inorganic, bioorganic, agricultural, industrial, pharmaceutical, and medicinal chemistry, as well in material science.[3] The benzimidazole nucleus plays an important role in medicinal chemistry as it is present in pharmacophores showing biological activities against several viruses such as herpes (HSV-1), HIV, RNA, influenza and human cytomegalovirus (HCMV).[4] In addition, benzimidazole derivatives have been used as selective neuropeptide YY1 receptor antagonists,[5] 5-lipoxygenase inhibitors for use as novel antiallergic agents,[6] factor Xa (FXa) inhibitors,[7] poly (ADP-ribose) polymerase (PARP) inhibitors,[8] human cytomegalovirus (HCMV) inhibitors,[9] xanthine oxidase (XO) inhibitors[10] and treatment of ulcers as antihistaminics.[11]

This importance has led to the development of several methods for the synthesis of benzimidazoles during the last few years. Two protocols have been routinely followed. One is the coupling of ring substituted *o*-phenylenediamine derivatives with carboxylic acids or their derivatives that usually required harsh condensating conditions (170–180°C).[12] The other method involves condensation of *o*-phenylenediamine and aldehydes in the presence of acid catalysts under various reaction conditions followed by oxidative cyclo dehydrogenation.[13] The second approach became more popular because of the ease of accessibility of a variety of substituted aldehydes. The reported procedures for this protocol involved wide spectrum of reagents, including 1-Methyl-3-propylimidazolium tetrafluoroborate or [pmim]BF_4/1-Butyl imidazolium tetrafluoroborate or [Hbim]BF_4,[14a] 1-Methylimidazolium triflouroacetate or [Hmim]TFA/H_2O,[14b] $Bi(OTf)_3/H_2O$,[14c] L-proline/$CHCl_3$,[14d] Trimethylsilyl chloride or TMSCl/H_2O,[14e] (bromodimethyl) sulfonium bromide/MeCN,[14f] iodobenzene diacetate/1,4- dioxane,[14g] H_2O_2/HCl in MeCN,[14h]

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chlorotrimethylsilane/DMF[14i] and silica sulphuric acid/H_2O.[14j] Some other important reagents reported are I_2/KI/K_2CO_3/H_2O,[15a] air/dioxane,[15b] neat ytterbium triflate,[15c] *p*-TsOH/DMF,[15d] $Na_2S_2O_5$ in neat under microwave irradiation,[15e] [$(NH_4)H_2PW_{12}O_{14}$] in dichloroethane,[15f] H_2O_2/CAN,[15g] Graphite/$PhNMe_2$,[15h] ytterbium(III) perfluorooctanesulfonate,[15i] amberlite IR 120/EtOH-H_2O[15j] and Zn-proline/H_2O.[15k] Although these methods are quite satisfactory, many of them employed considerable amounts of hazardous organic solvents (for example, chloroform, dichloromethane, benzene, toluene, dimethyl formamide, etc.) either for carrying out the reactions or for extraction and purifications (column chromatography) or for both which are not environment friendly. Moreover, several reactions were also carried out at higher temperatures, using expensive reagents. However, one of the major limitations of these methodologies is poor selectivity in terms of N-1 substitution, which results in the formation of two compounds, i.e., the formation of 2-substituted benzimidazole along with 1, 2-disubstituted benzimidazole as a mixture. An attractive possible approach is based on ultrasound-promoted 1, 2-disubstituted benzimidazole heterocyclization reactions of suitably functionalized substrates, which could allow the regioselective synthesis of highly functional heterocycles using readily available starting materials under mild and selective conditions.

In recent years, heterogeneous catalysts are gaining more importance due to enviro-economic factors.[16] The catalyst is generally of low cost with easy handling. Use of these heterogeneous catalysts ensures less or no generation of an undesirable wastage as pollutant. Based on these advantages, the experiments were designed for synthesis of 1, 2-disubstituted benzimidazoles by condensation of *o*-phenylenediamine and aromatic aldehydes using heterogeneous catalyst with sonication (figure 1). To the best of our knowledge, there is no published report on the use of ultrasound mediated silica gel supported trichloroacetic acid (SiTCA) for synthesis of 1, 2-disubstituted benzimidazoles. The experimental procedure to use this catalyst was proved to be very simple which could also be easily removed by simple filtration.

2. Experimental

2.1 *General*

All reagents were obtained from commercial sources and used without further purification. Infrared spectra were recorded on a Varian FT-IR spectrophotometer (model: Varian-640 IR, CA, USA) fitted with Attenuated Total Reflectance (ATR) accessories. ^1H and ^{13}C NMR spectra of $CDCl_3$ solutions were obtained with an Avance 500 (Model: Bruker, 11.4 Tesla, 500 MHz) spectrometer using tetramethylsilane (TMS) as the internal standard. Chemical shifts (δ) are expressed in ppm and coupling constants *J* are given in Hz. ESI-MS were obtained on a Varian 91 500-LC ion trap mass spectrometer. Sonication was performed in an ultrasonic processor, DAIGGER; model no. GE505 (with a frequency of 20 kHz, amplitude (72%) and a nominal power (500 W). Melting points determined on a digital Stuart SMP 10 melting point apparatus (ST15, OSA, UK) are uncorrected. The thin layer chromatography (TLC) was performed using the aluminum sheets coated with silica gel 60 (MERCK) containing fluorescent indicators, F254. The solvent for the development of the TLC plate was hexane: ethyl acetate (7:3).

2.2 *Preparation of silica supported trichloroacetic acid (SiTCA)*

In a 250 mL Pyrex conical flask 100 g silica (mesh size: 120–230) and 10 mL CCl_3COOH were added together. The reaction mixture was stirred and sonicated at 60°C for 30 min. Then it was dried under pressure and kept for further use. TEM image of SiTCA (figure 2) shows uniform particles of about 1 μm.

2.3 *General experimental procedure*

A suitable aromatic aldehyde (2.0 mmol) and *o*-phenylenediamine (1.0 mmol, 108.1 mg) was dissolved in 66% EtOH in H_2O (10 mL). To this solution 100 mg SiTCA (6.5 mole%) catalyst was added and the contents kept under sonication at 50°C until TLC indicated complete consumption of phenylenediamine

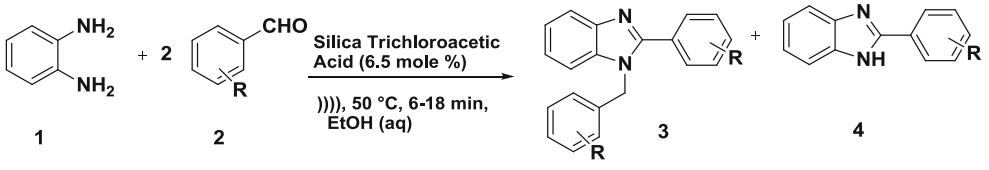


Figure 1. Scheme for synthesis of 1, 2-disubstituted benzimidazole derivatives.

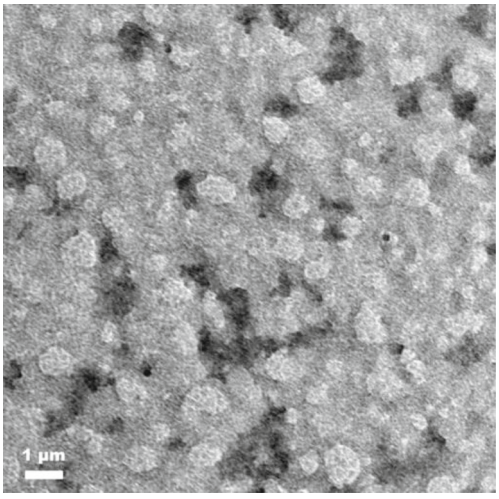


Figure 2. TEM images of SiTCA.

(6–18 min). Acoustic cavitation and mixing plays significant role in interaction of energy and matter. The termination of the reaction was monitored by TLC using hexane: ethyl acetate (7:3) as eluent. After completion of the reaction, the solution was filtered to remove the catalyst. The filtrate was concentrated under reduced pressure to furnish the crude product, which was recrystallized from methanol to afford the pure product. The catalyst could be reused thrice for fresh reactions to slight loss of activity (2–10%). It is hypothesized that, there is marginal loss of trichloroacetic acid atom during the reaction and recycling process. So it can be concluded that in SiTCA, CCl_3COOH moiety remains immobilized on silica gel support.The product's authenticity was established by ^{1}HNMR, ^{13}C NMR, FTIR-ATR, MS-ESI and their melting point compared with that of in literatures.

2.3a *1-(2-Chlorobenzyl)-2-(2-chlorophenyl)-1H-1, 3-benzimidazole (3a)*: Isolated yield = 92.3; Pale yellow crystal; M.p. 157–158°C; FT-IR-ATR (ν_{max}, cm $^{-1}$): 1615, 2845, 2980, 3036, 3067; ^{1}H NMR (500 MHz, $CDCl_3$):δ 5.38 (s, 2H, CH_2), 6.65 (d, J = 8.0 Hz, 1H), 7.16 (t, J = 7.5 Hz, 2H), 7.24 (d, J = 7.5 Hz, 1H), 7.29 (t, 2H), 7.37 (d, J = 8. 0 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.55 (t, J = 7.5 Hz, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$):δ 46.25, 112.4, 120.78, 123.44, 124.24, 128.5,128.59, 129.37, 130.54,130.58, 130.63, 130.85, 132.79, 133.02, 134.28, 136.07, 143.63, 151.93; MS (ESI, m/z): calcd for $C_{20}H_{14}N_2Cl_2$,(M^++1) 353.24, found: 353.2 (100%).

2.3b *1-(2-Hydroxybenzyl)-2-(2-hydroxyphenyl)-1H-1, 3-benzimidazole (3b)*: Isolated yield = 80.2; Brown crystal; M.p. 227–228°C; FT-IR-ATR (ν_{max}, cm $^{-1}$): 1465, 1558, 2935, 3039, 3260, 3355; ^{1}H NMR (500 MHz, $CDCl_3$):δ 5.63 (s, 2H, CH_2), 6.78–7.97 (m, 4H), 7.12–7.41 (m, 5H), 7.59 (d, J = 8.6 Hz, 2H), 7.81 (d, J = 8. 0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$):δ 43.25, 110.8, 115.0, 116.1, 116.4, 118.7, 118.9, 122.0, 122.6, 126.6, 128.3, 130.2, 131.3. 135.1, 141.8, 152.0, 154.4, 156.3; MS (ESI, m/z): calcd for $C_{20}H_{16}$ N_2O_2,(M^++1) 317.12, found: 317.2 (100%).

2.3c *1-(4-Chlorobenzyl)-2-(4-chlorophenyl)-1H-1, 3-benzimidazole (3c)*: Isolated yield = 89.6; Light yellow crystal; M.p. 126–127°C; FT-IR-ATR (ν_{max}, cm $^{-1}$): 1620, 2858, 2974, 3045, 3087; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.40 (s, 1H), 7.19 (d, J = 7.1 Hz, 2H), 7.26 (d, J = 8.7 Hz, 1H), 7.27–7.35 (m, 4H), 7.42–7.47 (m, 2H), 7.58–7.59 (m, 2H), 7.86 (d, J = 7.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 47.7, 110.3, 120.1, 123.4, 127.2, 128.3, 129.1, 129.3, 130.4, 133.8, 134.6, 135.9, 136.3, 143.0, 152; MS (ESI, m/z): calcd for $C_{20}H_{14}N_2Cl_2$,(M^++1) 353.05, found: 353.2 (100%).

2.3d *1-(2-Methoxybenzyl)-2-(2-methoxyphenyl)-1H-1, 3-benzimidazole (3d)*: Yield = 93.2; Light yellow powder; M.p. 152–154°C; FT-IR-ATR (ν_{max}, cm $^{-1}$): 1617, 2859, 2932, 3051, 3078; ^{1}H NMR (500 MHz, $CDCl_3$):δ 3.58 (3H, s, CH_3), 3.77 (3H, s, CH_3), 5.23 (s, 2H, CH_2), 6.69 (m, 1H), 6.77 (t, J = 6.95 and 7.15 Hz, 2H, Ar-H), 6.83 (d, J = 8.2 Hz, 2H, Ar-H), 6.96 (d, J = 8.35, 1H), 7.03–7.09 (m, 2H), 7.15–7.3 (m, 2H, Ar-H), 7.43 (m, 2H, Ar-H), 7.53 (dd, J = 8.3 Hz, 1H, Ar-H), 7.82 (d, J = 8.0, 1H); ^{13}C NMR (125 MHz, $CDCl_3$):δ 43.3, 55.0, 55.1, 109.8, 110.6, 119.7, 120.3, 121.8,122.3, 124.4, 127.6, 128.3, 131.3, 132.2, 135.4, 143.2, 152.4, 156.3, 157.4; MS (ESI, m/z): calcd for $C_{22}H_{20}N_2O_2$,(M^++1) 345.4, found: 345.15 (100%).

2.3e *1-(4-Methylbenzyl)-2-(4-methylphenyl)-1H-1, 3-benzimidazole (3e)*: Yield = 90.6; Yellowish white crystal; M.p. 128–129°C; FT-IR-ATR (ν_{max}, cm $^{-1}$): 1249, 1411, 2862, 2919, 3027; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.28 (s, 3H), 2.40 (s, 3H), 5.40 (s, 2H), 6.98 (d, J = 7.95 Hz,1H), 7.12 (d, J = 7.85 Hz, 1H), 7.19–7.3 (m, 6H), 7.56 (d, J = 8.1 Hz, 2H), 7.78 (d, J = 8 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.27, 21.61, 48.41, 58.02, 110.72, 119.94, 122.80, 123.08, 126.10, 126.72, 129.21, 129.36, 129.65, 129.90, 136.24, 137.67, 140.30, 143.25, 154.57; MS (ESI, m/z): calcd for $C_{22}H_{20}N_2$,(M^++1) 313.1, found: 313.3 (100%).

2.3f *1-(4-Hydroxybenzyl)-2-(4-hydroxyphenyl)-1H-1, 3-benzimidazole (3f)*: Isolated yield = 86.1; Dark yellow powder; M.p. 208–209°C; FT-IR-ATR (ν_{max}, cm $^{-1}$): 1465, 2842, 2938, 3045; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.28 (s, 2H, CH_2), 6.88–6.91 (m, 3H), 7.03–7.1 (m, 3H), 7.19–7.27 (m, 4H), 7.78 (d, J = 8.0 Hz, 2H); MS (ESI, m/z): calcd for $C_{20}H_{16}N_2O_2$,(M^++1) 317.3, found: 317.2 (100%).

2.3g *1-(3-Nitrobenzyl)-2-(3-nitrophenyl)-1H-1,3-benzimidazole (3g)*: Isolated yield = 82.5; yellow crystal; M.p. 154–155°C; FT-IR-ATR (ν_{max}, cm $^{-1}$): 1348, 1532, 2842, 3178; ^{1}H NMR (500 MHz, $CDCl_3$):δ 5.40 (s, 2H, CH_2), 7.12–7.20 (m, 2H), 7.27 (d, 1H, J = 7.6 Hz), 7.29–7.34 (m, 2H), 7.64–7.70 (m, 2H), 7.81 (s, 1H), 7.80–7.82 (m, 2H), 8.22 (d, 2H, J = 8.22 Hz), 8.48 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 46.7, 111.1, 119.8, 121.3, 122.5, 122.8, 123.6, 123.7, 124.4, 130.7, 131.2, 132.7, 135.2, 136.0, 139.0, 142.4, 147.8, 150.9, 156.0; MS (ESI, m/z): calcd for $C_{20}H_{14}N_2O_4$,(M^++1) 375.1, found: 375.2 (100%).

2.3h *1-(3-Chlorobenzyl)-2-(2-chlorophenyl)-1H-1, 3-benzimidazole (3h)*: Isolated yield = 84.2; Pale yellow crystal; M.p. 166-167°C; FT-IR-ATR (ν_{max}, cm $^{-1}$): 1635, 2857, 2983, 3041, 3071; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.36 (s, 2H, CH_2), 6.93 (d, J = 7.2 Hz, 1H), 7.12 (s, 1H), 7.22–7.39 (m, 4H), 7.45–7.5 (m, 2H), 7.64 (m, 1H), 7.70 (m, 1H), 7.88 (d, J = 7.95 Hz, 1H), 7.98 (m, 1H); MS (ESI, m/z): calcd for $C_{20}H_{14}N_2Cl_2$,(M^++1) 353.24, found: 353.2 (100%).

2.3i *1-(4-Fluorobenzyl)-2-(2-fluorophenyl)-1H-1, 3-benzimidazole (3i)*: Isolated yield = 90.0; Pale yellow powder; M.p. 98–99°C; FT-IR-ATR (ν_{max}, cm $^{-1}$): 1465, 2842, 2938, 3045; ^{1}H NMR (500 MHz, $CDCl_3$):δ 5.40 (s, 1H), 7.0–7.07 (m, 4H), 7.13–7.33 (m, 5H), 7.62–7.65 (m, 2H, ArH), 7.84 (d, J = 7.95.1H); MS (ESI, m/z): calcd for $C_{20}H_{14}N_2F_2$, (M^++1) 321.11, found: 321.2 (100%).

2.3j *1-Benzyl-2-phenyl-1H-1,3-benzimidazole (3j)*: Yield = 91.4; Light brown powder; M.p. 139–141°C; FT-IR-ATR (ν_{max}, cm $^{-1}$): 1358, 1457, 2949, 3035; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.45 (s, 2H, CH_2), 7.08–7.12 (m, 3H, Ar-H), 7.22–7.31 (m, 5H, Ar-H), 7.35–7.46 (m, 3H, Ar-H), 7.63 (dd, J = 8.0 and 2.0 Hz, 2H, Ar-H), 7.86 (d, J = 7.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$):δ 47.80, 110.32, 119.41, 122.23, 125.72, 127.31, 128.46, 128.78, 128.80, 129.42, 135.51, 135.84, 142.62, 149.82, 153.70; MS (ESI, m/z): calcd for $C_{20}H_{16}N_2$,(M^++1) 285.13, found: 285.3.

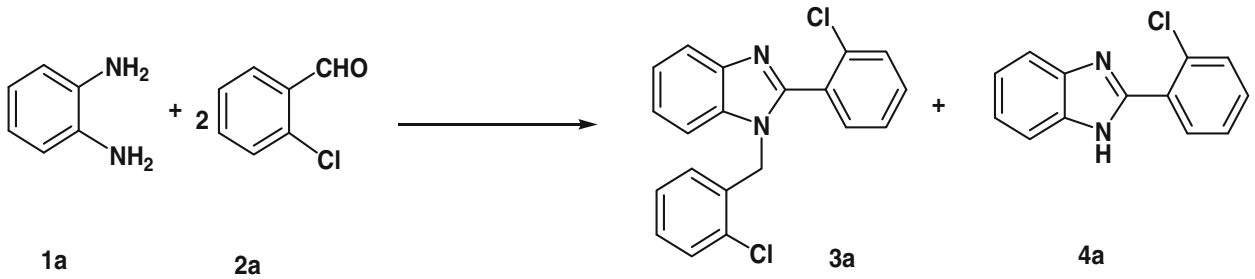
2.3k *1-((Pyridin-2-yl) methyl)-1H-1,3-benzimidazole (3k)*: Yield = 88.7; Light yellow powder; M.p. 129–130°C; FT-IR-ATR (ν_{max}, cm $^{-1}$):1356, 1446, 1675, 2991, 3055; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.29 (s, 2H, CH_2), 7.03–7.10 (m, 2H), 7.25–7.35 (m, 5H), 7.45–7.53 (m, 3H, Ar-H), 7.82–7.88 (m, 2H, Ar-H); MS (ESI, m/z): calcd for $C_{18}H_{14}N_4$,(M^++1) 287.12, found: 287.3 (100 %).

2.3l *1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-1H-1, 3-benzimidazole (3l)*: Isolated yield = 98%; Pale yellow crystal; M.p. = 126–127°C; FTIR-ATR (neat): 1619, 2856, 2965, 3026, 3077 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.78 (s, 3H,CH_3), 3.85 (s, 3H, CH_3), 5.38 (s, 2H, CH_2), 6.84 (d, J = 8.70 Hz, 2H), 6.96 (d, J = 8.85 Hz, 2H, Ar-H), 7.02 (d, J = 8.75 Hz, 2H, Ar-H), 7.21 (m, 2H), 7.27(m, 1H, Ar-H), 7.62 (d, J = 8.85 Hz, 2H, Ar-H), 7.83 (d, J = 8.0 Hz, 1H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 48.10, 55.52, 55.58, 110.61, 114.40, 114.64, 119.93, 122.68, 122.94, 127.43, 128.71, 130.92, 136.30, 143.38, 154.33, 159.33, 161.11; MS-ESI: *m/z* [M+H]$^+$calcd for $C_{22}H_{20}N_2O_2$: 345.41; found: 345.15.

3. Results and Discussion

In order to access the effect of ultrasound, the reaction of *o*-phenylenediamine **1a** with aromatic aldehyde **2a** in the presence of different catalysts (amberlite IR 120, SiTCA, $HClO_4$, TFA and $FeCl_3$) and organic solvents were carried out under sonication (table 1). The yield of product slightly increased with an increase in the quantity of catalyst and ratio of both expected products (table 1, **3a** and **4a**) based on the nature of the solvent. Interestingly, lowest yield was observed in the presence of acetone due to its volatilization and highest yield in the ethanol/water (2/1) mixture. The amount of **4a,** was formed in minor amount (12%, 15% and 25%) when the reaction was carried out in ethanol, methanol and water. The isolated yield of the desired product **3a** was less in all the solvents than in ethanol/water (2/1) mixture. So, ethanol/water mixture came out as the best choice of the solvents as the reaction medium. It can be explained that, when sound passes through a liquid, the formation, growth and implosive collapse of bubbles can occur. This process is called acoustic cavitation.[1] An acoustic wave is a pressure wave that has the ability

Table 1. Optimization of reaction conditions by using *o*-phenylenediamine and *o*-chlorobenzaldehyde at 50°C.



Entry	Catalyst	Catalyst load (g)	Solvent (10 mL)	Ultrasound irradiation time (min)	Yield (3a)[a] (%)	Yield (4a)[a] (%)
1.	SiTCA	-	H_2O	18	72	28
2.	Amberlite IR 120	-	H_2O	25	56	44
3.	Amberlite IR 120	0.1	EtOH	12	84	16
4.	Amberlite IR 120	0.1	MeOH	12	83	17
5.	Amberlite IR 120	0.1	EtOH/H_2O(2/1)	12	89	11
6.	SiTCA	0.15	EtOH	12	90	10
7.	Amberlite IR 120	0.1	THF	12	70	30
8.	Amberlite IR 120	0.1	Acetone	12	22	78
9.	SiTCA	0.1	Toluene	17	58	42
10.	SiTCA	0.1	DCM	12	60	40
11.	SiTCA	0.1	MeOH	12	85	15
12.	SiTCA	0.1	EtOH	12	88	12
13.	SiTCA	0.1	H_2O	12	75	25
14.	SiTCA	0.1	EtOH/ H_2O (2/1)	09	96	04
15.	SiTCA	0.1	Acetone	12	18	82
16.	SiTCA	0.1	THF	12	77	23
17.	$HClO_4$	0.1[b]	H_2O	12	65	35
18.	$HClO_4$	0.1[b]	EtOH	12	75	25
19.	$HClO_4$	0.1[b]	EtOH/ H_2O (2/1)	12	78	22
20.	$HClO_4$	0.1[b]	Acetone	12	16	84
21.	Silica	0.1	EtOH/ H_2O (2/1)	12	40	60
22.	Silica	0.1	EtOH	12	38	62
23.	SiTCA	0.1	EtOH/ H_2O[c](2/1)	1 2	70	30
24.	Amberlite IR 120	0.1	EtOH/ H_2O[c](2/1)	12	64	36
25.	TFA	0.1[b]	EtOH/ H_2O (2/1)	12	66	34
26.	TFA	0.1[b]	-	12	50	50
27.	$FeCl_3$	0.1	EtOH/ H_2O	12	52	48
28.	TCA	0.1	EtOH/ H_2O (2/1)	12	72	28

[a]Isolated yield based on the aromatic aldehyde
[b]Quantity of catalyst in mL
[c]5 mL solvent

to break the intermolecular van der Waals forces maintaining the cohesion of the liquid. The cavitational collapse in a liquid produces intense local heating, high pressures, with very short lifetimes, i.e., an extraordinary heating and cooling rate ($>10^{10}$ K/s).[17] These transient, localized hotspots can cause the reaction to take place rapidly, and the hotspot has an equivalent temperature of roughly 5000°C, a pressure of about 2000 atmospheres.[17] Thus, catalyst (SiTCA) was more selective towards the formation of **3a**, 96% as compared to **4a,** 60% for 9 min as shown in entry 14, table 1. It could affect the reaction, but it gave a lower yield of the product with higher reaction time as compared to the sonochemical reaction. In the presence of a widely distributed roughness of the solid acid catalyst surface, sonication provides a unique interaction of energy and matter, and causes high energy chemical reactions to occur.

To study the effect of substituents on the reaction, the reaction was carried out with *o*-phenylenediamine and a wide range of structurally diverse aldehydes using SiTCA as a catalyst in the presence of ultrasonic irradiation under frequency of 20 kHz (72% amplitude) (table 2). All the reactions were carried out

Table 2. SiTCA catalyzed selective synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazole from *o*-phenylenediamine and various aldehydes at 50°C. The literature melting points is given in parentheses.

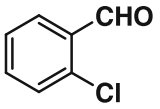
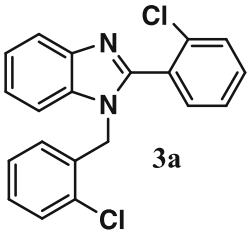
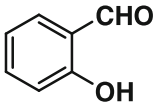
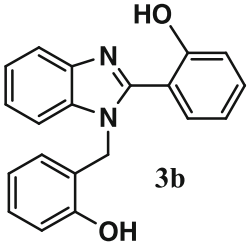
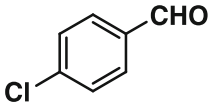
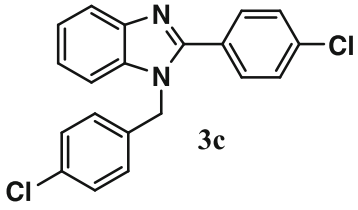
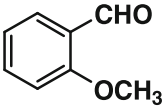
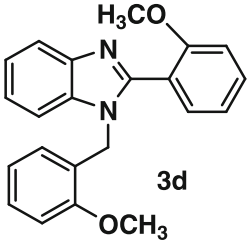
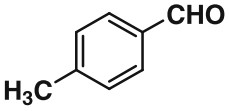
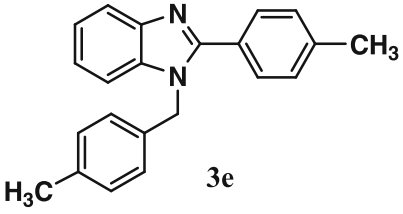
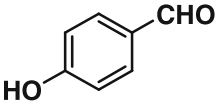
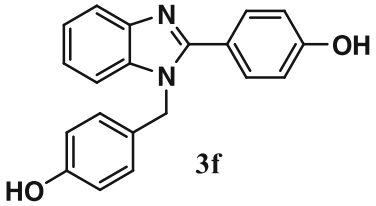
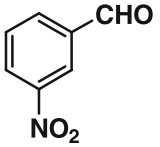
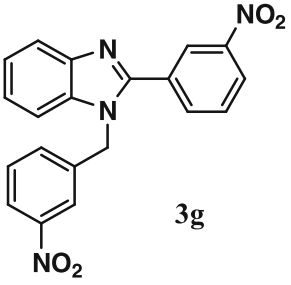
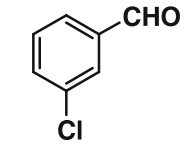
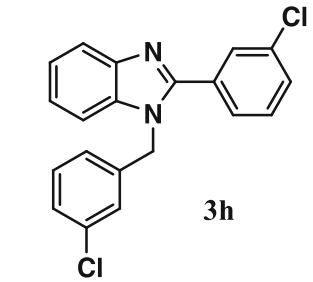
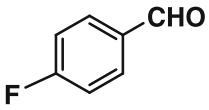
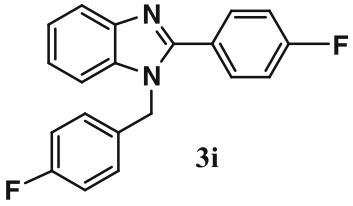
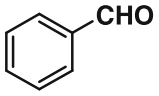
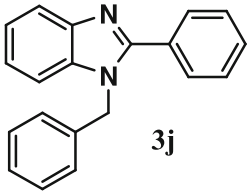
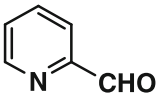
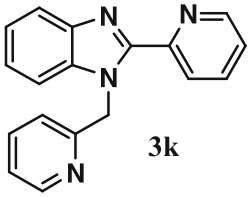
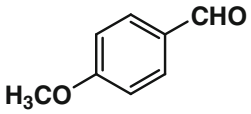
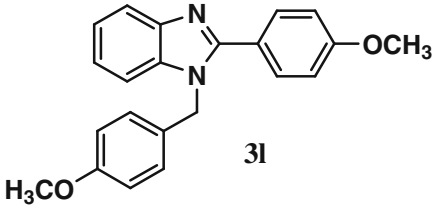
Entry	Aldehyde (**2**)	Product (**3**)	Ultrasonic irradiation time (min)	Yield (%)[a]	M.p.°C (Obs.)
1		 **3a**	09	96	157-158
2		 **3b**	12	88	227-228
3		 **3c**	12	91	126-127
4		 **3d**	12	95	153-154
5		 **3e**	06	93	128-129
6		 **3f**	09	89	208-209
7		 **3g**	17	84	154-155

Table 2. (continued)

Entry	Aldehyde (**2**)	Product (**3**)	Ultrasonic irradiation time (min)	Yield (%)[a]	M.p.°C (Obs.)
8		 **3h**	12	87	166-167
9		 **3i**	09	92	98-99
10		 **3j**	12	93	139-141
11		 **3k**	12	89	129-130
12		 **3l**	08	98	126-127

[a]Isolated yield based on the aromatic aldehyde

at 50°C and drastic reduction in time was observed in contrast to the reported methods, due to the synergestic effect of sonication under the temperature of 50°C. These results are consistence with the literature, because as the ultrasonic frequency is increased, the production of cavitation in liquids decreases.[18] Reactions with *o*-phenylenediamine, SiTCA and formaldehyde failed to give the expected 1, 2-disubstituted benzimidazole. It was observed that SiTCA could catalyze the reaction efficiently than amberlite IR 120 and $HClO_4$ in presence of ultrasonic waves. To rationalize the result, it was speculated that the SiTCA powder was more selective due to the catalytic activities of trichloroacetic acid on the rough surface of silica powder, which provided greater surface area with proper chemical polarization towards the substrates to accomplish facile bimolecular condensation. Herein, we wish to report the ultrasonically catalyzed two components N-alkylation-cyclization of aldehyde and *o*-phenylenediamine (figure 1).

o-Chlorobenzaldehyde and *o*-phenylenediamine was used as standard substrates to search for a suitable solvent in favour of the SiTCA, amberlite IR 120, $HClO_4$, TFA and $FeCl_3$catalyzed 1, 2 disubstituted benzimidazole synthesis. Among the solvent tested, $EtOH/H_2O$ (2/1, v/v) was best reaction medium for this ultrasound mediated one-pot synthesis. At the completion of the reaction, the use of $EtOH/H_2O$ influenced the reaction

of aldehyde and *o*-phenylenediamine with better yield. Slight lower yields were obtained while using methanol and ethanol as solvent (table 1, entries **11**, **12**). Toluene, dichloromethane, water and tetrahydrofuran afford the product in only low or moderate yields (table 1, entries **9, 10**, **13**, **16**). Undesired product was detected by NMR when the reaction was carried out in acetone (table 1, entry **8, 15**). It was also observed that yield of product in a 0.1 M solution was more than 0.2 M (table 1, entries **14**, **23**) because at lower concentration, two molecules of benzaldehyde approaches to *o*-phenylenediamine more efficiently than higher concentrations. The chemical effects of ultrasounds have been attributed to the implosive collapse of the cavitation bubbles and associated shock waves.[1] The bubbles are generated at localized sites in the liquid mixture that contain small amounts of dissolved gases. When these bubbles burst, it results in high temperature and high pressure which facilitate the intermolecular reaction. When one of the phases is a solid, the ultrasonic irradiation has several additional enhancement effects, and this is especially useful when the solid acts as a catalyst.[19] No significant difference was observed while slightly increasing the catalyst loading in solvent (table 1, entry **6**). When silica and trichloroacetic acid were used separately, no good results were found (table 1, entries **21, 28**). It was surprising that the reaction proceeded to give 1, 2-disubstituted benzimidazole as a single product, when we employed 1:1 or 1:2 or 1:3 mol *o*-phenylenediamine and benzaldehyde for reaction. The optimized reaction condition under sonication includes 1.0 equiv mol of *o*-phenylenediamine, 2.0 equiv. mol of aromatic aldehyde and 0.1 g of SiTCA (6.5 mole %) in 10 mL EtOH/ H_2O (2/1) solvents at 50°C. It is found that ultrasonic mediated reaction is more selective.[20]

To explore the scope of ultrasound in the synthesis of 1, 2-disubstituted benzimidazoles, various aldehydes were used as a substrates under the optimized reaction conditions and the results are summarized

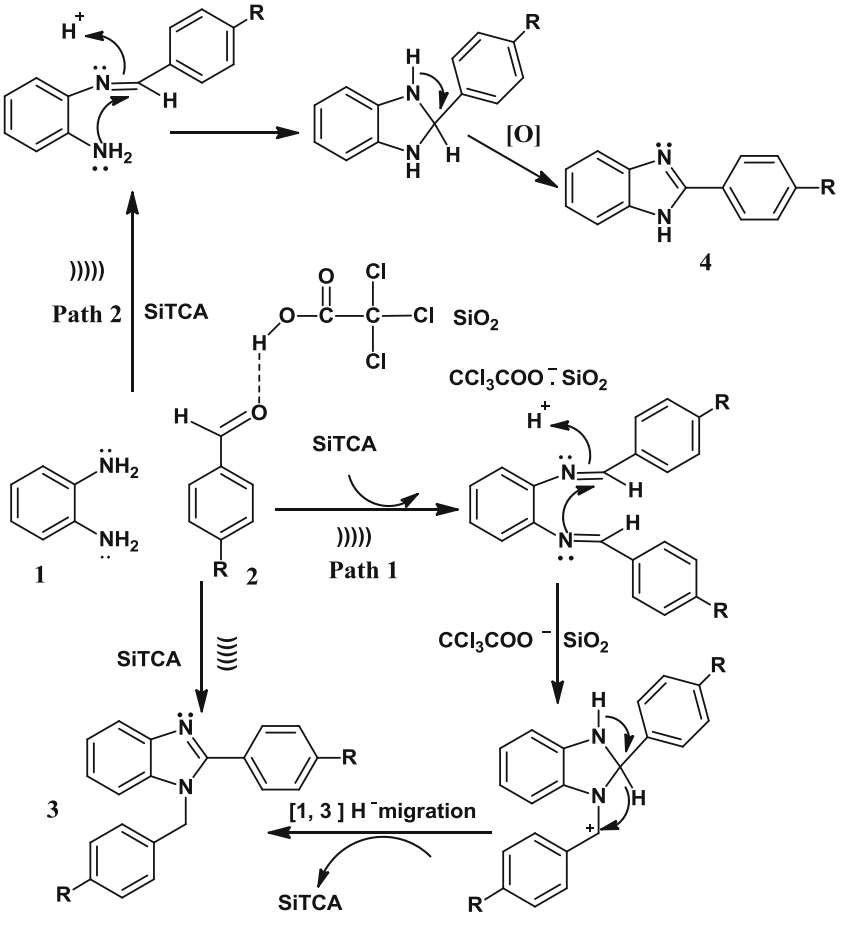


Figure 3. The proposed mechanism for SiTCA catalyzed 1, 2- disubstituted and monosubstituted benzimidazole synthesis.

in table 2. All the known products were characterized by comparing their physical and spectral (^{1}H NMR, ^{13}C NMR, ESI-MS and IR) data with those of the authentic samples reported in the literature.[14,15] As mentioned method, the undesired mono substituted benzimidazoles products were found to be 2–15% respectively.

In general, aromatic aldehydes underwent the addition reaction smoothly to provide the desired product in good (table 2, entry **7**) to excellent yield (table 2, entries **4**, **12**). However, SiTCA catalyzed N-alkylation cyclization reaction was found to be strongly influenced by the nature of aldehyde. As shown in table 2, *o*, *p*- chlorobenzaldehydes in entry **1** and **3** are more efficient than *m*-chlorobenzaldehyde in entry **8**. Salicylaldehyde gave lower yields under the standard condition than *p*-hydroxy benzaldehyde (table 2, entries **2**, **6**) due to the existence of intramolecular hydrogen bond, which prevents cyclization. In a similar fashion, heteroaromatic aldehyde also reacted well with *o*-phenylenediamine to furnish the corresponding product in good yields (table 2, entry **11**). The present protocol is equally effective for aromatic aldehydes bearing either electron donating (such as alkyl, or alkoxyl group) or electron withdrawing substituent (such as halide, nitro) under the same reaction conditions. The proposed mechanism for SiTCA catalyzed synthesis of 1, 2- disubstituted benzimidazoles may follow the sequence of reactions mentioned in figure 3. In path 1, when 1 and 2 reacted in the presence of SiTCA, the bis-imine product was obtained. The aldehyde 2 was partially converted to 3 with SiTCA within a limited period of time without any formation of 4 (monosubstituted benzimidazole). When the reaction was sonicated in the presence of SiTCA, 2 was completely consumed and 3 (1, 2-disubstituted benzimidazoles) was formed exclusively. Whereas in path 2, SiTCA is less selective for the formation of 3 (monosubstituted benzimidazole), the reaction remained incomplete and the product 3 was obtained with lower yield.

4. Conclusion

We report the development of an ultrasonic assisted speedy, clean and regioselective organic transformation protocol. The one-pot synthesis of 1, 2-disubstituted benzimidazole derivatives using SiTCA and sonication in aqueous media are environmentally benign, selective and easy to manipulate. It allowed us to synthesize structurally diverse 2-aryl-1-arylmethyl-1*H*-benzimidazole derivatives with good to excellent yield. In addition, the SiTCA as a heterogeneous catalyst could be reused thrice for fresh reactions to slight loss of activity.

Supplementary Information

The electronic supplementary information can be seen in www.ias.ac.in/chemsci.

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References

1. (a) Suslick K S 1990 *Science* **247** 1439; (b) Mason T J 1997 *Chem. Soc. Rev.* **26** 443 (c) Cravotto G and Cintas P 2006 *Chem. Soc. Rev.* **35** 180; (d) Suslick K S and Price G J 1999 *Annu Rev Mater Sci.* **29** 295
2. Fillion H and Luche J L 1998 In *Synthetic Organic Sonochemistry*, Luche JL (Eds.) (NY: Plenum)
3. Eicher T and Hauptmann S 2003 *The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications* (2nd ed.) (Weinheim: Wiley-VCH)
4. (a) Preston P N 2000 In *Chemistry of Heterocyclic Compounds*, Weissberger A and Taylor E C (Eds.) (John Wiley and Sons) **40**; (b) Chi Y C and Sun C M 2000 *Synlett* 591; (c) Huang W and Scarborough R M 1999 *Tetrahedron Lett.* **40** 2665; (d) Dudd L M, Venardou E, Garcia-Verdugo E, Licence P, Blake A J, Wilson C and Poliakoff M 2003 *Green Chem.* **5** 187
5. Zarrinmayeh H, Nunes A M, Ornstein P L, Zimmerman D A, Gackenheimer S L, Bruns R F, Hipskind PA, Britton T C, Cantrell B E and Gehlert D R J 1998 *Med. Chem.* **41** 2709
6. Nakano H, Inoue N, Kawasaki, Miyataka H, Matsumoto H, Taguchi T, Inagaki N, Nagai H and Satoh T 2000 *Bioorg. Med. Chem.* **8** 373
7. Zhao Z S, Arnaiz D O, Griedel B, Sakata S, Dallas J L, Whitlow M, Trinh L, Post J, Liang A, Morrissey M M and Shaw K J 2000 *Bioorg. Med. Chem. Lett.* **10** 963
8. White A W, Almassy R, Calvert A H, Curtin N J, Griffin R J, Hostomsky Z, Maegley K, Newell D R, Srinivasan S and Golding B T 2000 *J. Med. Chem.* **43** 44084
9. Zhu Z, Lippa B, Drach J C and Townsend L B 2000 *J. Med. Chem.* **43** 2430
10. Nile S H, Kumar B and Park S W 2013 *Chem. Biol. Drug Des.* **82** 290
11. Spasov A A, Yozhitsa I N, Bugaeva L I and Anisimova V A 1999 *Pharm. Chem. J.* **33** 232
12. (a) Wang Y, Sarris K, Sauer D R and Djuric S W 2006 *Tetrahedron Lett.* **47** 4823; (b) Lin S Y, Isome Y, Stewart E, Liu J F,Yohannes D and Yu L 2006 *Tetrahedron Lett.* **47** 2883; (c) Nadaf R N, Siddiqui S A, Daniel T,

Lahoti R J and Srinivasan K V 2004 *J. Mol. Catal. A: Chem.* **214** 155

13. Kim B H, Han R, Kim J S, Jun Y M, Baik W and Lee B M 2004 *Heterocycles* **63** 41
14. (a) Saha D, Saha A and Ranu B C 2009 *Green Chem.* **11** 733; (b) Dabiri M, Salehi P, Baghbanzadeh M and Nikcheh M S 2008 *Synth. Commun.* **38** 4272; (c) Yadav J S, Reddy B V S, Premalatha K and Shankar K S 2008 *Can. J. Chem.* **86** 124; (d) Varala R, Nasreen A, Enugala R and Adapa S R 2007 *Tetrahedron Lett.* **48** 69; (e) Wan J P, Gan S F, Wu J M and Pan Y 2009 *Green Chem.* **11** 633; (f) Das B, Holla H and Srinivas Y *Tetrahedron Lett.* **48** 61; (g) Du L H and Wang Y G 2007 *Synthesis* 675; (h) Bahrami K, Khodaei M M and Karianinia I 2007 *Synthesis* 547; (i) Ryabukhin S V, Plaskon A S, Volochnyuk D M and Tolmachev A A 2006 *Synthesis* 3715; (j) Salehi P, Dabiri M, Zolfigol M A, Otokeshb S and Baghbanzadehb M 2006 *Tetrahedron Lett.* **47** 2557
15. (a) Gogoi P and Konwar D 2006 *Tetrahedron Lett.* **47** 79; (b) Lin S and Yang L 2005 *Tetrahedron Lett.* **46** 4315; (c) Curini M, Epifano F, Montanari F, Rosati O and Taccone S 2004 *Synlett* 1832; (d) Xiangming H, Huiqiang M and Yulu W 2007 *ARKIVOC* 150; (e) Vazquez G N, Diaz H M, Soto S E, Piedra M T, Rivera I L, Tlahuext H, Muniz O M and Gomez H T 2007 *Synth. Commun.* **37** 2815; (f) Giri B Y, Devi B L A P, Gangadhar K N, Lakshmi K V, Prasad R B N, Lingaiah N and Prasad P S S 2007 *Synth. Commun.* **37** 2331; (g) Bahrami K, Khodaei M M and Naali F J 2008 *Org. Chem.* **73**, 6835; (h) Sharghi H, Asemali O and Tabaei S M H 2008 *J. Het.Chem.* **45** 1293; (i) Shen M G and Cai C J 2007 *Fluorine Chem.* **128** 232; (j) Sharma S D and Konwar D 2009 *Synth. Commun.* **39** 980; (k) Varala R, Enugala E, Kotra V and Adapa S R 2007 *Chem. Pharm. Bull.* **55** 1254
16. (a) Mizuno N and Misono M 1998 *Chem. Rev.* **98** 199; (b) Thomas J M and Raja R 2006 *Topics in catalysis* **40** 3
17. Suslick K S, Choe S B, Cichowlas A A and Grinstaff M W 1991 *Nature* **353** 414
18. Li J, Zhang X and Lin Z 2007 *Beilstein J. Org. Chem.* **3** 13
19. Suslick KS 1998 *Kirk-Othmer Encyclopedia of Chemical Technology*, (4th Ed.) (New York: J Wiley & Sons) **26** p517
20. Bonrath W 2005 *Ultrasonics Sonochemistry* **12** 103