Research Article

Ultrasound promoted synthesis of 1, 2-disubstituted benzimidazoles using aqueous hydrotropic solution

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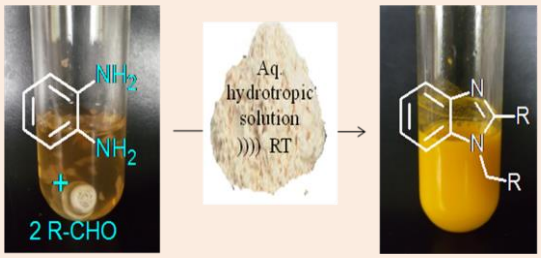
Abstract

The present work deals with the green efforts for C-N bond fabrication of *N*-arylmethyl-2-substituted benzimidazole by using efficient combination of ultrasound (US) and aqueous hydrotropic solution (50% NaPTS) at ambient temperature. The method offers outstanding compensations such as gentle reaction conditions, simple procedure, and use of water as green solvent, catalyst-free conditions with good yields of products in short time. Ultrasound irradiation is well suited for aqueous hydrotropic solution and effectively decreases the reaction time and increases the final yield of products.



Keywords: 1,2-disubstituted benzimidazole, hydrotrope, ultrasound, green chemistry, Ultrasound irradiation

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Introduction

As benzimidazole nucleus offers a new meadow for drug designing, it stays in minds of organic chemists from last decades. 1,2-disubstituted benzimidazoles have broad range of biological activities such as antiulcer [1], anticancer [2] antiviral [3] antifungal [4], antiallergic [5], antibacterial [6,7], antidiabetic [8], anti-AIDS [9]. Many of their derivatives acts as factor Xa inhibitor [10], poly (ADP-ribose) polymerase inhibitors [11], Burkitt's lymphoma promotion inhibitors [12] and as human cytomegalovirus inhibitors [13]. Moreover, many of 1,2-disubstituted benzimidazoles show ferroelectric [14] as well as photoluminescent properties [15]. In spite of their proven importance in biomedical research there are limited synthetic tactics adopted for the synthesis of 1,2-disubstituted benzimidazoles due to steric hindrance. The most common strategy employed for the synthesis of 1,2-disubstituted benzimidazoles include condensation of *o*-phenylenediamine with aldehydes. Various catalysts such as L-Proline [16], $SiO_2/ZnCl_2$ [17], silica sulfuric acid [18], sodium dodecylsulfate (SDS) [19], $Bi(OTf)_3$ [20], thiamine hydrochloride [21], and TMSCl [22] have been employed for this transformation. However, many of the reported protocols suffer from serious drawbacks such as long reaction time, low yield of products, tedious workup procedures and use of expensive catalysts, environmentally unsafe organic solvents.

With the introduction of newer methodologies in the synthetic arena, to venture out in the hunt of applicability to organic reactions is ever increasing. One such lane, which requires persistent research, is green chemistry [23]. In order to conserve the biodiversity on the Earth, scientists around the world are adopting techniques which are eco-friendly and non detrimental to mankind. The intriguing line of development in this regard is use of water as a reaction medium, which minimizes impact of hazardous solvents on the environment. Despite of many advantages, there is a major problem of scarce solubility of organic compounds in water. To alleviate this drawback, several strategies such as particle size reduction, complexation, sonication, use of co-solvents, surfactants, supercritical fluids

have been employed. The "hydrotropes" which were introduced by Carl Neuberg about a century ago, serves as promising aspect of solubility enhancement [24]. But the magical days for this "young" branch came from last two decades. The term hydrotrope refers to a different class of water soluble surface active compounds. Hydrotropic solutions can also be used to extract hydrophobic drugs without the need of organic solvents [25]. Their hydrophile-lipophile balance being on the higher side, water solubility of hydrotrope is significantly more than that of traditional surfactants. In addition, the problem of formation of emulsion during extraction of product is also reduced. Most hydrotropic solutions precipitate the solute on dilution with water which permits the ready recovery of the hydrotropic solvent for re-use. On this background, Mckee in 1946 reported the use of hydrotrope in industries [26]. Besides being cheap, non-toxic, and eco-friendly aqueous hydrotropic solutions possess the other physico-chemical characteristics required for green reaction media. In spite of their interesting properties, the systematic exploration of aqueous hydrotropic solutions as solvent in organic synthesis has not yet been extensively pursued.

Application of ultrasound in organic transformation serves as an excellent alternative of energy source and has proved to be an important tool in enhancing reaction rates and improving yields [27]. Water acts as the best solvent in sonochemistry as its cavitation energy has maximal effect at room temperature. Driving force for the reaction is result of acoustic cavitations produced in ultrasound, that is, the formation, growth, and implosive collapse of bubbles produced in aqueous solution. The impulsive collapse of the bubbles creates a hot spot by adiabatic compression within the gas phase of the collapsing bubble. This collapsing of bubbles can persuade a shock wave in the solution and drive rapid impact of the liquid to the surface of the particles. As a result, ultrasound energy can trigger reactant molecules which are capable of penetrating the atmosphere of the bubble [28]. Thus, compared with conventional methods it enhances the rate of reactions and product yields in short time.
In order to expand the application of ultrasound with hydrotropic solution, herein we report an efficient and eco-friendly method for the synthesis of 1,2-disubstituted benzimidazoles from aldehyde and *o*-phenylenediamine in aqueous hydrotropic solution using sonication.

Experimental

Materials and Reagents

All the chemicals were obtained from Sigma Aldrich/Spectrochem and were used without further purification. The hydrotropes were prepared following the literature procedure [29]. Melting points were determined with DBK melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) spectrometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as an internal standard. Infrared spectra were recorded on Perkin–Elmer FTIR spectrometer. The samples were examined as KBr discs. GC-MS were recorded on Shimadzu QP2010. Sonication was performed in SPECTRALAB-UCB-30 ultrasonic bath with a frequency of 40 kHz and a nominal power of 100 W. The temperature of the ultrasonic bath was maintained at 25–30^{o}C.

The proposed reaction was carried out as follows: A mixture of aldehyde (2 mmol), *o*-phenylenediamine (1 mmol) in 5 mL of 50% aq. hydrotropic solution (NaPTS) was stirred to get clear solution. The reaction mixture was irradiated under ultrasonic waves at ambient temperature. The progress of reaction was monitored by TLC (petroleum ether/ethyl acetate, 7:3, v/v). After completion of reaction, the crude product obtained by addition of cold water was filtered, washed with water and further recrystallised from ethanol to afford pure 1,2-disubstituted benzimidazoles.

1-benzyl-2-phenyl-1*H*-benzimidazole (Table 2, Entry 3a)
White solid, mp- 132^{o}C. IR (KBr, cm^{-1}): 3035 (C–H stretching of aromatic ring), 2929 (C–H stretching of aliphatic), 1602 (C=N stretching of imidazole ring), 1584, 1557, 1538 (C=C stretching of aromatic ring), 1392 (C–N stretching of imidazole ring); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 5.45 (2H, S, CH_2), 7.05-7.69 (14H, m, Ar-H); ^{13}C-NMR (75 MHz, $CDCl_3$, δ ppm): 48.2, 110.3,118.8, 121.9, 124.7, 128.1, 128.8,128.9, 129.7, 134.8, 136.4, 143.1, 155.4; MS(m/z): 284(M+).

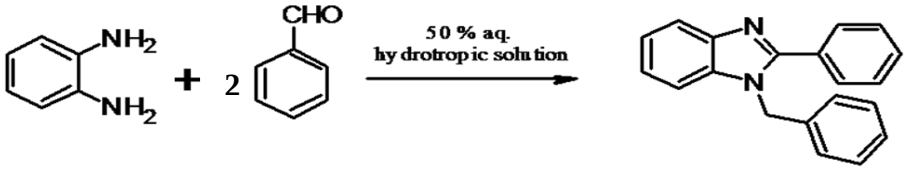
1-(4-Nitrobenzyl)-2-(4-nitrophenyl)-1*H*-benzimidazole (Table 2, Entry 3e)
Green solid, mp- 193°C. IR (KBr, cm^{-1}): 3092 (C–H stretching of aromatic ring), 2984 (C–H stretching of aliphatic), 1602 (C=N stretching of imidazole ring), 1533, 1529, 1488 (C=C stretching of aromatic ring), 1524, 1348 (NO_2 stretching), 1354 (C–N stretching of imidazole ring); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 5.60 (2H, S, CH_2), 7.22-8.33 (12H, m, Ar-H); ^{13}C-NMR (75 MHz, $CDCl_3$, δ ppm): 48.0, 110.2, 120.8, 123.8, 124.2, 124.5, 124.6, 126.7, 130.0, 135.7, 135.9, 142.8, 143.2, 148.7, 151.3; MS (m/z): 374 (M+)

1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-1*H*-benzimidazole (Table 2, Entry 3h)
White solid, mp- 130°C. IR (KBr, cm^{-1}): 3026 (C–H stretching of aromatic ring), 2943 (C–H stretching of aliphatic), 1591 (C=N stretching of imidazole ring), 1538, 1528, 1481 (C=C stretching of aromatic ring), 1388 (C–N stretching of imidazole ring), 1226 (C–O stretching of methoxy group); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 3.81 (3H, S, OCH_3), 5.43 (2H, S, CH_2), 6.87-7.94 (12H, m, Ar-H); ^{13}C-NMR (75 MHz, $CDCl_3$, δ ppm): 48.1, 55.3, 55.4, 110.6, 114.4, 114.5, 119.1, 123.4, 127.2, 127.8, 130.9, 159.3, 161.4; MS (m/z): 344 (M+).

Results and Discussion

To find out the suitable conditions for the reaction, a series of experiments were performed with benzaldehyde (2 mmol) and *o*-phenylenediamine (1 mmol) as model substrates.

At the inception study, we tried to optimize the reaction conditions by determining the efficiency of several hydrotropes chosen as the medium for comparison. In each case, the reactants were stirred at room temperature in 50 % aqueous hydrotropic solution (5 mL). Among the several hydrotropes such as sodium cumene sulphonate (NaCuS), sodium *p*-xylene sulphonate (NaXS), sodium salicylate (NaSaI) and sodium *p*-toluene sulphonate (NaPTS), the formation of desired 1-benzyl-2-phenyl-1*H*-benzimidazole (**3a**) was more facile and proceeded to give good yield using sodium *p*-toluene sulphonate (NaPTS) (**Table 1**). The higher activity of NaPTS was rationalized on the basis of an overall planar structure of hydrophobic and hydrophilic regions giving rise to self associated configuration, offering a good micro-environment of lower polarity and stabilizes the reactants through a cooperative mechanism. The reaction performed at room temperature need more time for completion. Therefore, to minimize reaction time ultrasound has been used as an alternative energy source.



1 2a 3a

Table : Screening of hydrotropes and effect of ultrasound irradiation[a]

Entry	Name of hydrotrope	With Ultrasound[b]		Silent[c]	
		Time (min)	Yield (%)[d]	Time (min)	Yield (%)[d]
1	Sodium xylene sulphonate	20	62	120	59
2	Sodium cumene sulphonate	20	57	120	55
3	Sodium *p*-toluene sulphonate	20	91	120	72
4	Sodium salicylate	20	45	120	38

[a] Conditions: *o*-phenylenediamine (1 mmol), benzaldehyde (2 mmol), 50% aq. hydrotropic solution (5 mL).
[b] Reactions were performed using ultrasound irradiations.
[c] Reactions were performed at room temperature without use of ultrasound irradiations.
[d] Isolated yields.

The model reaction was carried out under ultrasonic irradiation. In all cases, the experimental results show that the yields of the products enhanced dramatically with significant reduction in reaction time (**Table 1**). The plausible reason for the rate enhancement observed under sonication can be accounted on the basis of acoustic cavitation process. Aqueous hydrotropic solutions provide an interesting approach to control the chemical contents of bubble due to a combination of the low vapour pressure and increased viscosity of the aqueous hydrotropic solutions relative to pure water. Chemical control of the vapour content of the collapsing bubble allows for a stronger collapse that leads to greater compressional heating of reactants as the ultrasonic intensity in aqueous solutions is higher because of the low sound absorption coefficient results in enhancement of the reaction rate.

As excellent results were obtained with NaPTS under ultrasonication, we employed this particular hydrotrope for subsequent studies. We have also studied the effect of concentration of aq. NaPTS. The efficiency of model reaction varied significantly with respect to concentration of hydrotrope and was maximum when 50% of aq. NaPTS was used as a reaction medium (**Figure 1**).

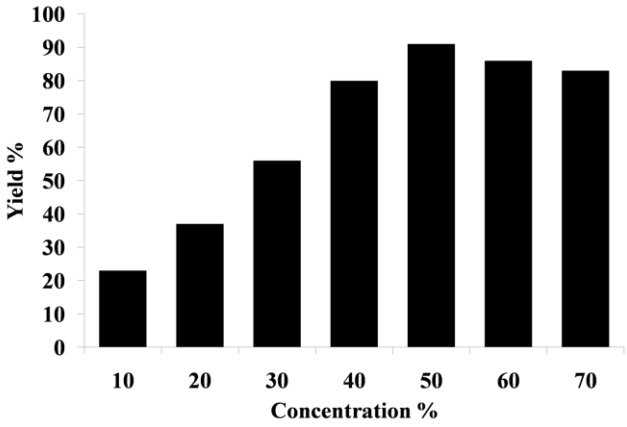
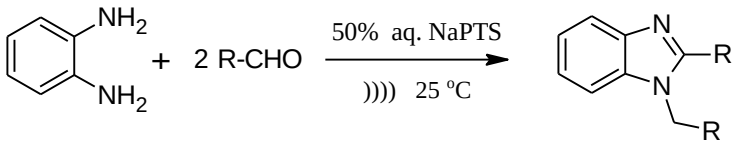


Figure 1 Effect of NaPTS concentration on the yield of 1,2-disubstituted benzimidazole.

In order to check the generality of this methodology, a series of 1,2-Disubstituted benzimidazoles were prepared by reaction of *o*-phenylenediamine with various aryl aldehydes. The results are summarized in **Table 2**. We were gratified to find that with both electron-poor and electron-rich benzaldehydes, the corresponding products were obtained in excellent yields. The reaction of the sterically hindered *o*-hydroxybenzaldehyde (**2b**) even gave higher yields highlightening the general applicability of the protocol.



1 **2a-2l** **3a-3l**

Table 2 Synthesis of 1,2-disubstituted benzimidazoles using 50 % aq. NaPTS solution[a]

Entry	R	Product	Without Ultrasound[b]		With Ultrasound[c]		Mp ^{o}C [Lit.][Ref]
			Time (min)	Yield[d] (%)	Time (min)	Yield[d] (%)	
	2	**3**					
a	Ph	**3a**	120	72	20	91	132 [132][18]
b	2-OH	**3b**	105	30	68	86	163 [165-166][30]
c	4-Cl	**3c**	90	71	25	88	136 [134][18]
d	4- $N(CH_3)_2$	**3d**	90	65	30	84	250 [253][18]
e	4- NO_2	**3e**	80	75	20	92	213 [213-214][30]
f	3- NO_2	**3f**	90	71	20	89	121 [120][31]
g	4- OH	**3g**	100	69	35	83	225 [226][18]
h	4- OCH_3	**3h**	130	65	35	84	126 [127][18]
i	4- CH_3	**3i**	150	67	40	85	126 [126-128][18]
j	2- furyl	**3j**	60	81	15	93	94 [96][18]
k	4- CN	**3k**	50	77	15	92	112 [113-115][32]
l	2- pyridyl	**3l**	85	70	30	87	125 [126][18]

[a] Conditions: *o*-phenylenediamine (1 mmol), aldehyde (2 mmol), 50% NaPTS solution (5 mL).
[b] Reactions were performed at room temperature without use of ultrasound irradiations.
[c] Reactions were performed using ultrasound irradiations.
[d] Isolated Yield.

In addition, heteroaromatic aldehydes such as furfuraldehyde (**2j**) and pyridine-2-aldehyde (**2l**) reacted efficiently affording the desired product in good yields. The striking feature of all the reactions was the isolation of products. During the course of the reaction the product precipitates out and isolated simply by filtration. The identity of all the compounds was ascertained on the basis of IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy data. The physical and spectroscopic data are in consistent with the proposed structures and are in harmony with the literature values [17-21].

In order to show the virtues of our method, we have compared the reported catalytic systems for the synthesis of **3a**. From **Table 3**, it is observed that our methodology is more efficient than the reported ones.

Compared with traditional solvents, easy recycling is an interesting property of aqueous hydrotropic solutions. To investigate the possibility of hydrotrope recycling, the model reaction was carried out over five times using the recovered hydrotropic solution. We were delighted to find that the hydrotropic solution could be reused without any decibel drop in the yield of the products.

Table 3 A comparison of efficiency of various catalytic systems in the reaction of *o*-phenylenediamine and benzaldehyde

Entry	Condition	Time (h)	Yield[a] (%)	Ref.
1	L-Proline in Chloroform	5	95	16
2	$SiO_2/ZnCl_2$ (25%)	20 min	72	17
3	Silica Sulfuric Acid in Ethanol	1.5	75	18
4	SDS in Water, 25 ^oC	22 min	97	19
5	Thiamine Hydrochloride in DMF	1.5	91	21
6	TMSCl in Water	5	87	22
7	50% NaPTS,))) 25 ^oC	20 min	91	This work

[a]Isolated yields

Conclusions

In summary, we have developed an efficient and green method for C-N bond fabrication of 1,2-disubstituted benzimidazoles in aqueous hydrotropic solution using ultrasound irradiation at room temperature. Shorter reaction time, high yields and clean reactions make this protocol a smart alternative to the existing methods. In addition, this method serves as green tool from environment point of view which is a basic need of many pharmaceutical industries now a day.

Acknowledgments

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