Communication

Tetrabutylammonium Fluoride (TBAF) Catalysed Synthesis of 2-Arylbenzimidazole in Water under Ultrasound Irradiation

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One-pot multistep reactions involving a new environmentally friendly catalytic procedure have been developed for the synthesis of benzimidazole. The reaction of the substituted aldehyde with *o*-phenylenediamine in water under ultrasonic irradiation at ambient temperature for appropriate time using 5 mol% of TBAF furnish the desired product in good to excellent yield. The process is green, mild, inexpensive, excellent chemo selectivity, and excellent yields are the main advantages of this procedure.

Keywords: Tetrabutylammonium fluoride (TBAF); Water; 2-Benzimidazole; Ultrasonication; Green synthesis.

INTRODUCTION

Benzimidazole compounds have a wide range of biological activities, ranging from widely used human and veterinary anthelmintic[1-2] to anticancer properties.[3] The spectrum of the pharmacological activity of benzimidazole has been reviewed by several authors.[4-7] Along with this, benzimidazole derivatives with different pharmacological properties such as, anti ulcer,[8-10] cardiotonic,[11] antihypertensive[12] etc., have already been reported. The literature precedence reveals that the substitution at 1, 2 and 5, positions of the benzimidazole moiety is crucial in point of view the medicinal chemistry to exhibit wide range of pharmacological activities.

There are two general methods for the synthesis of 2-substituted benzimidazole. One is coupling of *o*-phenylenediamines and carboxylic acids[13] or their derivatives (nitriles, imidates, or orthoesters),[14] which often requires strong acidic conditions, and sometimes combines with very high temperature or the use of microwave irradiation.[15] The other way involves a two-step procedure that is oxidative cyclodehydrogenation of aniline schiff's bases, which are often generated in situ from the condensation of *o*-phenylenediamines and aldehydes. Various oxidative reagents such as nitrobenzene,[16] 1,4-benzoquinone,[17] DDQ,[18] tetracyano ethylene,[19] benzofuroxan,[20] MnO_2,[21] $Pb(OAc)_4$[22] oxone,[23] $NaHSO_3$,[24] and $Na_2S_2O_5$,[25] DMP,[26] and NH_4VO_3[27] have been employed.

However, it is noticed that all these methods are not straightforward and involve various disadvantages such as low yields, prolonged reaction times, and expensive catalyst. In view of the conservation of the environment combining with economic aspects, literature demands the application of metal ion free, environmentally safe, and convenient reagents in the multicomponent reactions.

Ultrasound accelerated chemical reactions are well known and proceed *via* the formation and adiabatic collapse of transient cavitations bubbles. Ultrasound irradiation has been demonstrated as an alternative energy source for organic reactions ordinarily accomplished by heating. Many homogeneous and heterogeneous reactions can be conducted smoothly by sonication to provide improved yields and increased selectivities therefore ultrasound irradiation has been established as an important technique in organic synthesis.

RESULTS AND DISCUSSION

We herein, report an eco-friendly, facile and efficient methodology for the synthesis of 2-benzimidazole by using the Tetrabutylammonium fluoride (TBAF).[28] It is well known that TBAF is a cheap and non-toxic reagent. Quaternary ammonium fluoride salts are gaining increasing importance in chemistry a**s** organic-soluble sources of fluoride ion. Of these, tetra-n-butylammonium fluoride (**TBAF**) has found widespread use as a reagent to promote various

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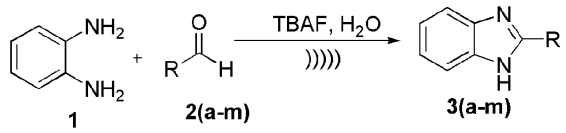
silylation/desilylation reactions, often under aprotic or anhydrous conditions.[28] It is therefore of almost important to evolve simple and its derivatives that cover the concept of "Green Chemistry". The uses of environmentally benign solvents like water represent green solvent being economically and eco-friendly fro synthetic transformations. However, low solubility of reactant, incompatibility of certain intermediate or competition between the desired reaction and hydrolysis restrict the use of H_2O as a common solvent, although many reactions have been studied in H_2O using different catalyst.

Our research group devoted particular attention to the development of environmentally friendly and efficient protocols by using water as the reaction medium or by working under solventless conditions.[29] Here, we wish to report the use of a catalytic Tetrabutylammonium fluoride (TBAF) is an efficient catalyst synthesis of various benzimidazole derivatives from 1,2-phenylendiamines and variety of aromatic aldehydes in water under ultrasonic irradiation This methodology gives the milder condition for synthesis of 2-substituted benzimidazole (Scheme I).

Scheme I



We also performed a set of preliminary experiments on benzaldehyde and 1,2-phenylendiamine in the presence of different amounts TBAF and different solvent under ultrasonic irradiation. Firstly, in search of an efficient reaction condition, the reaction of benzaldehyde (10 mol **1a** and *o*-phenylenediamine (10 mol) **2** in presence of TBAF at ultrasonic irradiation at ambient temperature the influence of has been considered as model reaction at ambient temperature.

We have optimized catalyst concentration on model reaction the best result was obtained on the 5mol% of the TBAF in water at ultrasonic irradiations at ambient temperature.

The lower amount of the catalyst effect on the yields of product longer time span for the reaction and on further increasing the amount of catalyst, the yield of the corresponding product decreased, ascribable to increased acidity. Even absence of the catalyst, reaction did not precede the after extensive reaction time. The results are summarized in the Table 1.

Table 1. Screening of catalyst concentration on model reaction[a]

Entry	Catalyst (mol %)	Time (min)	Yield[b] (%)
1	0	30	No reaction
2	1	30	23
3	2	30	32
4	3	30	56
5	4	30	76
6	5	30	93
7	6	30	93

[a] Reaction of benzaldehyde with *o*-phenylene diamine in presence of TBAF (5 mol%) under ultrasonic waves for 30 minute. [b] Isolated yield.

We kept catalyst concentration constant and used different solvents like dichloromethane, acetonitrile, methanol, ethanol-water and water under ultrasonic irradiations. Firstly, we have tried this reaction under solvent free condition, but the result of the reaction was reaction goes sluggish and a yield of the product was very low. In protic solvent the reaction go smoothly as comparatively aprotic solvent because the when the reaction carried out in the aprotic solvent such as acetonitrile, DCM it takes longer reaction time and the yields are comparatively low. Due to we have concluded that the reaction go smoothly at protic solvent such as methanol, ethanol, ethanol-water. After screening different solvents, it was found that the best solvent in terms of fast conversion, non-toxic and quantified yield is water. The obtained results summarized in (Table 2, entries 1–8).

We have studied the different reaction conditions on model reaction. The result revealed that, when the reaction was carried at room temperature and reflux condition it gave lower yield of product even after prolonged reaction time. But at the same time the reaction was carried out under ultrasonication we have got the excellent yields of product in short span.

It was found that the ultrasonic irradiation was very simple and convenient for the synthesis of 2-substituted benzimidazole using ultrasonic cleaner with a frequency of 40 KHZ and a nominal power 100W. In experiment the ultrasonic technique represented a better procedure in terms of time and yields (Table 2).

The effect of the electron donating group on the aldehyde having gives the better result as compare to the electron withdrawing. The time requires for the completion of reaction for heteroaryl aldehyde as high and yields are low.

Table 2. Optimization of solvent effect on the model reaction

Entry	Solvent	With US[a]		Without US[b]	
		Time (min)	Yield[c] (%)	Time (min)	Yield[c] (%)
1	Solvent free	30	15	150	10
2	Toluene	30	30	150	26
3	Dichloromethane	30	25	150	20
4	Acetonitrile	30	31	150	27
5	Methanol	30	56	150	47
6	Ethanol	30	75	150	70
7	Ethanol-water	30	83	150	67
8	Water	30	93	150	80

[a] Reaction of benzaldehyde with *o*-phenylene diamine in presence of TBAF (5 mol%) under ultrasonic waves for 30 minute. [b] Reaction of benzaldehyde with *o*-phenylene diamine in presence of TBAF (5 mol%) under room temperature condition for 150 minutes. [c] Isolated yield.

Furthermore, effect of catalyst load on reaction time and yield is explored in Table 1. The best result is obtained with 5 mol% of the catalyst. After optimizing the conditions, the generality of this method was examined by the reaction of several substituted aryl aldehydes with *o*-phenylene diamine. The results are shown in Table 3. The newly synthesized compounds were compared (Melting point, MS, NMR, and IR) with literature method.[27] This comparison revealed that the compounds synthesized by this newly developed method were exactly similar in all aspects to the reference compounds.

On investigating the reaction mechanism it was noticed that when aldehyde and *o*-phenylenediamine reacted in presence of TBAF in water under ultrasonication. The reaction led to the formation of intermediates as schiff base. This intermediate was isolated and characterised by spectroscopy method. However, extends of reaction irradiate to gave the mix of product and intermediate (monitor by TLC). After 30 min only product was detected and characterised by spectroscopic method. According to observation the mechanistic part shows TBAF when dissolved in water, which activates the aldehyde towards elctrophillic attack of *o*-phenylenediamine to generate schiff base as intermediate. Later on air oxidation of schiff base furnished desired 2-arylbenzimidazole.

EXPERIMENTAL

Melting points were determined on a Veego apparatus and are uncorrected. Infrared spectra were recorded on a Bruker spectrophotometer in a KBr disc, and the absorption bands are expressed in cm^{-1}. ^1H NMR spectra were recorded on a Varian AS 400 MHz spectrometer in $CDCl_3$/DMSO-d_6, chemical shifts (δ) are in ppm relative to TMS, and coupling constants (*J*) are expressed in Hertz (Hz). Mass spectra were taken on a Macro mass spectrometer (Waters) by electro-spray method (ES). Bandelin Sonorex (with a frequency of 40 KHz and a nominal power 100 W) ultrasonic bath was used for ultrasonic irradiation The reaction vessel placed in side the ultrasonic bath containing

Table 3. Characterization data[a] of 2-substituted benzimidazole **3(a-m)**

Entry	Aldehyde	Time (min)	Isolated yield[a]	M.P. °C
3a	Benzaldehyde	30	94	289-291[31]
3b	Anisaldehyde	40	90	224-226[31]
3c	4-methyl benzaldehyde	40	92	224-225[31]
3d	4-chlorobezaldehyde	45	88	291-293[31]
3e	4-flurobenzaldehyde	45	84	245-246[31]
3f	3-bromobenzaldehyde	50	82	265-266[31]
3g	Furan-2carbaldehyde	60	85	285-287[31]
3h	Piconaldehyde	60	82	218-219[31]
3i	Nicotinaldehyde	60	85	245-248[31]
3j	4-(1*H*-1,2,4-trizol-1-yl)benzaldehyde	60	87	104-106[30]
3k	Napthaldehyde	60	83	270-272[32]
3l	Cinnamaldehyde	65	87	199-201[32]
3m	3-nitrobanzaldehyde	60	85	309-310[32]

[a] Reaction of aldehyde with *o*-phenylene diamine in presence of TBAF (5 mol%) in water under ultrasonic waves. [b] Isolated yield. [c] All the compound characterized by IR. ^1H NMR, Mass and compared with reference compounds.

water.

General procedure for the synthesis of benzimidazole

A mixture of aldehyde (10 mmol), *o*-phenylene diamine (10 mmol) and TBAF (5 mol%) was dissolved in minimum quantity of water with constant stirring. Further the reaction mass was irradiated under ultrasonic irradiation at ambient temperature for appropriate time (Table 3). The progress of reaction was monitored by TLC. After the completion of reaction, mixture was extract with ethyl acetate (2 × 25 mL) and dried under vacuum. The residue was subjected to column chromatography (60-120 mesh size silica gel, eluted with hexane-ethyl acetate (80:20) to obtain the pure product. The compounds **3(a-j)** were prepared by following the above procedure and their percentage yield and physical constants were recorded in Table 3. Their structures have been confirmed by ^{1}H NMR, IR and Mass spectra.

Spectral data of representative compounds

Compound (3d): ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 12.55 (br s, -NH), 8.14 (d, 2H), 7.61 (m, 1H), 7.23-7.28 (m, 3H), 7.12-7.04 (m 2H); IR (KBr): 3053 (NH), 1682 (C=N), cm^{-1}; MS: *m/z*: 229.0 (M+1), 231 (M+3); *Anal. Calcd* for $C_{13}H_9N_2Cl$: C, 68.28; H, 3.97; N, 12.25. Found: C, 68.40; H, 3.89; N, 12.48%.

Compound (3e): ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 12.98 (s, 1H, -NH), 8.05 (d, *J* = 8.50 Hz, 2H), 7.29 (m, 4H), 7.17 (m, 1H); MS (EI): *m/z* = 213 (M+); IR (KBr, cm^{-1}): 3447 (NH), 1624 (C=N); *Anal. Calcd* $C_{13}H_9FN_2$: C, 73.57; H, 4.27; N, 13.20. Found: C, 73.92; H, 4.48; N, 13.19%.

Compound (3h): ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): δ 12.83 (br s, -NH), 8.09-8.11 (d, 1H), 7.85 (t, 1H), 7.65-7.69 (d, 1H), 7.53-7.55 (d, 1H), 7.34-7.36 (d, 2H), 7.18 (m, 2H); MS (EI): *m/z* = 210 (M+1); IR (KBr, cm^{-1}): 3445 (NH), 3054, 2431, 1611 (C=N); *Anal. Calcd* for $C_{15}H_{11}N_5$: C, 74.62; H, 5.30; N, 20.08; Found: C, 74.82; H, 5.58; N, 20.18%.

Compound (3k): ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 11.86 (s, 1H, -NH), 8.75 (brs, 1H), 8.39 (dd, 1H, *J* = 8.0 & 2.2 Hz), 8.02-790 (m, 3H), 7.26 (m, 2H, Ar-H); MS (EI): *m/z* = 245 (M+1); IR (KBr, cm^{-1}): 3055, 2925, 1654 (C=N), *Anal. Calcd* for $C_{13}H_9FN_2$: C, 83.61; H, 4.92; N, 11.47; Found: C, 83.87; H, 4.88; N, 11.01%.

CONCLUSIONS

In conclusion, the present procedure using TBAF as catalyst provides an efficient one-pot synthesis of 2-substituted benzimidazole in water under ultrasonic irradiation. The advantages of this procedure are operational simplicity, wide substrate scope, availability of catalyst, cost effective and high yields. In many cases, the products crystallized directly from the reaction mixture in high purity. We believe that this method presents a practical alternative to existing procedures for the synthesis of 2-substituted benzimidazole.

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