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Cesium Fluoride: A Competent Catalyst for Synthesis of Benzimidazoles Derivatives in Alcoholic Medium

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Abstract: In the present work, successful implementation of greener synthetic protocol and ultrasound irradiations for the rapid synthesis of 2-substituted benzimidazoles derivatives in alcoholic medium is demonstrated. Herein, we describe the one-pot, two component condensation of aryl aldehydes and o-phenylenediamine using cesium fluoride as a catalyst in ethanol under ultrasonic irradiation as well as by conventional technique, which afford 2-substituted benzimidazoles in higher yields within shorter reaction time

I. INTRODUCTION

The heterocyclic benzimidazole scaffold is a useful structural motif for the development of molecules of pharmaceutical or biological interest. The benzimidazole has been an important pharmacophores and privileged structure in medicinal chemistry, encompassing a diverse range of biological activities including antiarrhythmic, antiulcer, anthelmintical, inotropic, antihistamine, antifungal, antiviral, and cytotoxicity. 1 Benzimidazoles are remarkably effective compounds both with respect to their inhibitory activity and their favorable selectivity ratio. Extensive biochemical and pharmacological studies have confirmed that benzimidazole molecules are effective against various strains of microorganisms.2

Benzimidazoles exhibit significant activity as potential antitumor agents,3 antimicrobial agents,4 smooth muscle cell proliferation inhibitors,5 a treatment for intestinal cystitis,6 and in diverse area of chemistry.7 The imidazole core is a common moiety in a large number of natural products and pharmacologically active compounds.8 Recently, there has been considerable amount of progress in imidazole chemistry due to the recognition of importance of the imidazole structure in biological processes and the increasing application of imidazole containing compounds, such as asetomidate, cimetidine, omeprazole and lansoprazole, in drug therapy.9 Therefore the development of facile synthetic routes to achieve access to these molecules is of prime interest.

Benzimidazoles are regarded as a promising class of bioactive heterocyclic compounds that exhibit a range of biological activities. Specifically, this nucleus is a constituent of vitamin-B12.10 This ring system is present in numerous antioxidant, 11–13 antihelmintics,14 antiproliferative,15 anti-HIV,16 anticonvulsant,17 anti-inflammatory,18–21 antineoplastic,22,23 and antitrichinellosis,24 antiparasitic, antiulcer, antihypertensive, antihistaminic, anti-cancer, antiemetic/antipsychotics activities. Owing to the immense importance and varied bioactivities exhibited by benzimidazoles, efforts have been made from time to time to generate libraries of these compounds and screened them for potential biological activities.25-27

Cesium fluoride (CsF) is a useful base in organic chemistry due to the fact that fluoride ion is largely unreactive as a nucleophile.28 Removal of silicon groups (desilylation) is one of the major applications of CsF in the laboratory, as its anhydrous nature allows clean formation of water-sensitive intermediates.29 It is exploited as an efficient catalyst for the synthesis of carboxylic esters,30 trans-α- trifluoromethyl allylic alcohols,31 γ-lactones,32 aromatic esters and ethers,33 thioesters and thioethers,34 and 3,4-dihydropyrimidine-2-(1H)-ones.35 In addition, it has been used for N-alkylation of anilines, carboxamides, and nitrogen heterocyclic compounds,36 and regio- and chemoselective ring opening of epoxides with thiols.37

For many chemical processes, a major adverse effect to the environment is the consumption of energy for heating and cooling. To overcome such problems, it is highly desirable to develop efficient methods that utilize alternative energy sources such as ultrasound and microwave irradiation to facilitate chemical reaction Ultrasound technique has increasingly been used in organic synthesis in the recent years. Ultrasonic irradiation enhances the chemical reaction via the process of acoustic cavitation. The assistance of ultrasonic irradiation efficiently shortens the reaction time. Simple experimental procedure, very high yields, increased selectivity, and clean reaction of many ultrasound induced organic transformations offer additional convenience in the field of synthetic organic chemistry.38-41

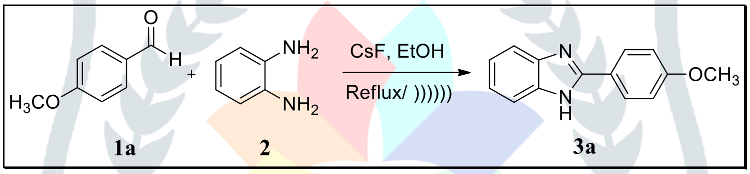
As the benzimidazoles have various therapeutic utility, a number of synthetic protocols for this type of derivatives have been developed. The first benzimidazole was prepared in 1872 by Hoebrecker42, furthermore several methods have been reported for synthesis of benzimidazoles such as cupric acetate43,

Numerous methods have been reported in the literature for the synthesis of benzimidazoles. A range of methods are available for the synthesis of 2- substituted benzimidazoles includes condensation-dehydration of o-phenylenediamines with carboxylic acids, acid anhydrides, esters, amides, lactones, nitriles, imino-ethers and imino-thioethers, amidines and guanidines, acid chlorides and esters.44 Ample of catalysts have been disclosed for achieving this transformation. Some of them are hypervalent iodine as oxidant,45 oxalic acid,46 H2O2/HCl,47 TiCl4,48 PPA,49 SOCl2/SiO2,50 silica-sulfuric acid,51 L-proline,52 sulphamic acid,53 zeolite54 and CuCl/TMEDA.55

Considering the increasing environmental pollution and its drastic impact on living systems, emerging area of green chemistry demands eco-friendly organic chemical processes that utilize biocompatible, inexpensive and readily available catalysts. In this regard, implementation of CsF as a catalyst is playing very attractive role to build up eco-friendly routes for the construction of various heterocyclic molecules. Therefore, it was thought to develop a new, greener and efficient method for such type of cyclocondensation reactions by means of easily available catalyst.

Results and Discussion

Initially, in order to optimize the reaction conditions, we have chosen the reaction of p-methoxy benzaldehyde (1a), and o-phenylene diamine (2) as a standard model reaction. In addition, ultrasound irradiation technique is successfully implemented to carry out the reactions.



Scheme:- Standard model reaction.

The effect of various catalysts on the model reaction was conducted (Table 4.1.1). The results indicated that the catalyst had a significant effect on the product yield. According to literature, it has become apparent that formation of benzimidazoles does not take place in the absence of catalyst. In an order to evaluate the effect of catalyst, various catalysts were used for performing the model reaction. Intentionally, fluoride containing compounds, i.e., tetra-n-butyl ammonium fluoride (TBAF), KF and CsF were utilized for our purpose. When the reaction was carried out in the absence of catalyst the product formed in very trace amount (Table 1, Entry 1).

Our attempts started with the use of KF and NH4F (Table 1, Entries 2, 3) as catalysts, however yields of the product in those case were found to be moderate. With these results, tetra-n-butyl ammonium fluoride and CsF have been used for our further study and it was observed that when we utilize TBAF and CsF reaction seems to proceed smoothly and yields of the product in each case were found to be good. (Table 1, Entries 4, 5).

Table 1. Screening of the catalysts[a]

Entry	Catalyst	Time (min)	Yield[b] (%)
1	----	120	Trace
2	KF	120	52
3	NH_4F	120	60
4	TBAF	120	84
5	**CsF**	**120**	**90**

[a]*Reaction conditions*: **1a** (1 mmol), **2** (1 mmol), CsF (15 mol%), in ethanol (10 mL) at Reflux temp.; [b]Isolated yields.

In an order to evaluate the effect of solvent various solvents such as acetonitrile (MeCN), tetrahydrofuran (THF), methanol (MeOH), ethanol (EtOH), chloroform (CHCl3), dichloromethane (DCM), water (H2O) have been used for the model reaction (Table 2). The use of different solvents like CHCl3, THF and DCM afforded the desired product in very low yields, (Table 2, Entries 1-3). However, the use of MeCN, water and MeOH gave the product in slightly higher yields (Table 2, Entries 4-6).

Table 2. Screening of solvents[a]

Entry	Solvent	Temperature (°C)	Time (min)	Yield[b] (%)
1	$CHCl_3$	Reflux	120	28
2	THF	Reflux	120	36
3	DCM	Reflux	120	46
4	ACN	Reflux	120	68
5	Water	Reflux	120	74
6	MeOH	Reflux	120	75
7	**EtOH**	**Reflux**	**120**	**90**

[a]*Reaction conditions*: **1a** (1 mmol), **2** (1 mmol), CsF (15 mol%), in solvent (10 mL); [b]Isolated yields.

Whereas, use of ethanol brought the reaction to completion efficiently and obtain the product in excellent yield. The reaction proceeds smoothly at reflux temperature with 15 mol% of CsF and completes within 2 h (Table 2, Entry 7). In order to know the reaction condition, we have used CsF in ethanol at room temperature. It was noted that, the reaction leads to formation of product in trace amount, (Table 3, Entry 1). Therefore, in an attempt to reduce reaction time and increase product yields, model reaction tested at higher temperature. To evaluate the appropriate temperature we carried out the model reaction at 40°C, 60°C and reflux condition, (Table 3, Entries, 2, 3, 4) however increasing the temperature enhances the reaction rate substantially with respective 57%, 70% and 90% yield.

To evaluate the appropriate concentration of the catalyst for the model reaction, we investigate the model reaction at different concentration of CsF such as 5, 10, 15 and 20 mol%. The product was formed in 60, 72, 90 and 90% yield, respectively, (Table 3, entries 4-7). This shows that 15% of CsF is sufficient to carry out the reaction efficiently. With these satisfactory results in hand, it was decided to use CsF for further studies. To generalize the optimized reaction condition, some substituted aldehydes were allowed to undergo this two-component reaction.

Table 3. Effect of the concentration of catalyst and temperature.[a]

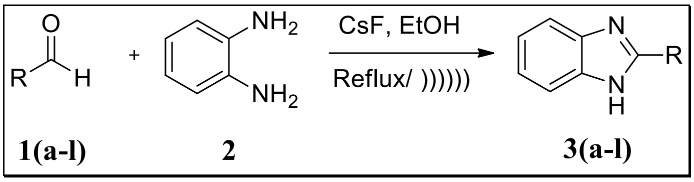
Entry	Temperature(°C)	Catalyst (mol %)	Yield[b] (%)
1	R.T.	15	Trace
2	40	15	57
3	60	15	70
4	**Reflux**	**15**	**90**
5	Reflux	5	60
6	Reflux	10	72
7	Reflux	20	90

[a]*Reaction conditions*: **1a** (1 mmol), **2** (1 mmol) and CsF in ethanol (10 mL) for 2 h; [b]Isolated yields.

The model reaction was further investigated under ultrasound irradiation in the presence of CsF with a view to explore whether (i) the reaction could be expedited, and (ii) the product yield could be enhanced. In this case, no significant improvement in the product yield was observed, but the reaction time enormously reduced to 30 min as compared to conventional method (2 h). It is a well-established fact that fluoride ion is capable of forming strong hydrogen bonding with a variety of hydrogen bond acceptor compounds.56 On the basis of that, it is proposed that CsF forms hydrogen bond between fluoride anion and amine, which results in the transfer of electron density from fluoride anion to amine, and ultimately enhances the nucleophilicity of amine, while at the same time it reduces the nucleophilicity of the fluoride.57 This accelerates the rate of reaction enormously and affords the desired product in shorter reaction time.

For assessing the generality of optimized reaction condition, wide range of substituted aldehydes were allowed to undergo this two-component condensation reaction. Aromatic aldehydes with several functionalities were found to be compatible under the optimized reaction conditions.

Table 4. Synthesis of 2-substituted benzimidazols[a].



Product	R	With US[a]		Without US[b]		M. P. (°C)
		Time (Min)	Yield[c] (%)	Time (hrs)	Yield[c] (%)	
3a	4-OMe-Ph	30	91	2	90	260-266
3b	Ph	30	88	2	87	280-282
3c	4-Cl-Ph	30	85	2	85	292-294
3d	4-OH-Ph	30	92	2	90	296-298
3e	Piperonyl	30	84	2	82	259-262
3f	4-OH-3-OMe-Ph	30	82	2	80	235-237
3g	3,4-(OMe)$_2$-Ph	30	85	2	84	270-272
3h	2-Cl-Ph	30	84	2	82	245-246
3i	4-NO$_2$-Ph	30	87	2	85	255-256
3j	4-Me-Ph	30	85	2	83	278-281
3k	Acetaldehyde	60	--	5	--	--
3l	Propionaldehyde	60	--	5	--	--

[a]*Reaction conditions*: **1a** (1 mmol), **2** (1 mmol), Catalyst (15 mol%), in ethanol (10 mL) under ultrasonic waves. [b]Reaction conditions: **1a** (1 mmol), **2** (1 mmol), Catalyst (15 mol%), in solvent (10 mL) at reflux condition. [c]Isolated yield.

Conclusion

In conclusion, we have developed an expeditious, greener and efficient one pot two component protocol for the synthesis of benzimidazoles using aldehydes and ortho phenylenediamine in the presence of cesium fluoride as an easily available reaction accelerator. CsF has been proved to be an efficient catalyst for the synthesis of benzimidazoles in ethanol by classical as well as non-classical methods. This method offers remarkable advantages such as simple experimental procedure, mild reaction conditions, lower reaction time, and higher product yields, avoiding hazardous organic solvent.

Experimental

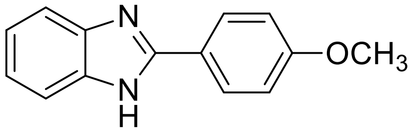
General experimental procedure for the synthesis of benzimidazoles (3a-l)

Conventional method: To a mixture of aldehyde 1 (1 mmol) and o-phenylenediamine 2 (1 mmol) in 10 mL ethanol, catalytic amount of cesium fluoride (CsF) (15 mol %) was added and reaction mass was refluxed for time specified in Table 3, until the complete conversion of the starting materials was achieved. Progress of the reactions was monitored with the help of TLC. After 2 h heating reaction mixture was poured on crushed ice, solid compound thus obtained was stirred well and collected by simple filtration, which was further washed with water (10 mL) to afford crude product 3. This crude product was purified by recrystallization technique from ethanol as a solvent.

Ultrasound method: To a mixture of aldehyde 1 (1 mmol) and o-phenylenediamine 2 (1 mmol) in 10 mL ethanol, catalytic amount of cesium fluoride (CsF) (15 mol %) was added and it was subjected to ultrasound irradiation for 30 min., until the complete conversion of the starting materials was achieved. Reaction progress was monitored by TLC (ethyl acetate/n-hexane: 1:9). After 30 min. the reaction mixture mass was poured on crushed ice, solid compound thus obtained was stirred well and collected by simple filtration, which was further washed with water (10 mL) to afford crude product. This crude product was purified by recrystallization technique from ethanol as a solvent.

Spectral data for representative compound

2-(4-methoxyphenyl)-1H-benzo[d]imidazole (3a)

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.85 (s, 3H, OCH_3), 5.40 (s, 1H, -NH), 6.94-6.69 (d, 2H, Ar-H), 7.21-7.24 (d, 2H, Ar-H), 7.56-7.61 (t, 2H, Ar-H), 8.04 (d, 2H, Ar-H). **Mass (ES-MS)** m/z 225.0 (M+).	 **(3a)**

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