Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2014, 6(11):89-94

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Sonochemical synthesis of 2-arylbenzimidazoles using amberlite IR-120 Resin

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ABSTRACT

A simple, efficient and ecofriendly method for one pot synthesis of 2-arylbenzimidazoles has been developed in acetonitrile using ultrasound and amberlite IR-120 resin at room temperature. Experimental results showed that ultrasound induced amberlite IR-120 resin efficiently synthesized substituted 2-arylbenzimidazoles (96 – 68 %) and recyclable up to five times without loss of activity. The method provides several advantages such as green solvent, simple work-up procedure, shorter reaction time and higher yield.

Keywords: 2-Arylbenzimidazoles; Amberlite IR-120 resin; One-pot reaction; Heterogeneous catalysis; Ultrasound irradiation

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INTRODUCTION

The development of an efficient synthesis of bioactive compounds in an ecologically and economically favorable way is a great challenge in modern chemistry. The ultrasound assisted reaction has become very important in organic synthesis, and replacing the time consuming or low yielding conventional heating method [1]. Benzimidazole moiety is a bicyclic compound having an imidazole ring containing two nitrogen atoms at nonadjacent positions, fused to benzene. It is a structural isostere of naturally occurring nucleotides which allow them to interact easily with the biopolymers of the living system; hence, it has been useful intermediates in the development of molecules of pharmaceutical and biological interest. Substituted benzimidazole derivatives have found applications in diverse therapeutic areas including anti-hepatitis, anti ulcers, antihypertensives, antivirals, antifungals, anticancers, and antihistamines [2, 3, 4].

The widespread interest in benzimidazole containing structures has prompted extensive studies for their synthesis. There are two general synthetic methods for the synthesis of 2-substituted benzimidazoles. One is the coupling of *o*-phenylenediamine and carboxylic acids [5] or their derivatives (nitriles, imidates, or orthoesters) [6], which often require strong acidic conditions and sometimes combines with very high temperatures (i.e., PPA, 180 °C)[7]. The other way involves a two-step procedure that includes the oxidative cyclodehydrogenation of aniline Schiff’s bases, which are often generated in situ from the condensation of *o*-phenylenediamines and aldehydes. Synthesis of 2-arylbenzimidazoles with aldehydes instead of carboxylic acids has attracted attention because it is an environmentally benign reaction leading to the formation of water as the only by-product. Various catalysts, including CAN [8], p-TsOH [9], Ammonium metavanadate [10], Heteropolyacids [11], $Cu_3/2PMo_{12}O_{40}/SiO_2$ [12] and *Mucor miehei* (MML) enzyme [13] have been employed. However, the reported procedures suffer from one or the other disadvantages, such as long reaction duration, low yield of the products, use of excess amount of reagents and tedious work-up procedures. In addition, some of the catalysts and reagents are expensive and toxic in nature. Thus, there is still a need to search for better catalysts and a procedure with operational simplicity. On the other hand, microwave-assisted solvent free organic syntheses [14] and reaction under ultrasound activation [15] have aroused growing interest as efficient, economic, and clean procedures.

Amberlite IR 120 resin (Ion exchange Resin) is a gel type strongly acidic cation exchange resin of the sulfonated polystyrene type. It has excellent physical, chemical and thermal stability and has emerged as an efficient heterogeneous catalyst for various organic reactions like N formylation of amines [16], conversion of aldehyde to nitrile [17], synthesis of various organic compounds like glycosyl dihydro pyridines [18], 1-amidoalkyl-2-naphthols [19] and glycosyl enamines [20].

We previously reported the use of ultrasound for the synthesis of biologically significant 2-aryl-1- arylmethyl-1*H*-benzimidazoles using amberlite IR 120 resin and SiO_2/CCl_3COOH as catalyst [15]. The present communication describes the results of using acetonitrile as switchable solvent under sonication. Switchable solvents make it possible to synthesize 2-arylbenzimidazoles from reactants. Initially, we examined condensation of *o*-phenylenediamine with substituted aromatic aldehydes in the presence of amberlite IR 120 resin and acetonitrile under sonication gives 2-arylbenzimidazoles as shown in Figure 1. The catalyst can be separated from the reaction mixture by simple filtration. Importantly, distillation is not required for separation of the 2-arylbenzimidazoles from the product because all the products are solid and miscible in ethyl acetate.

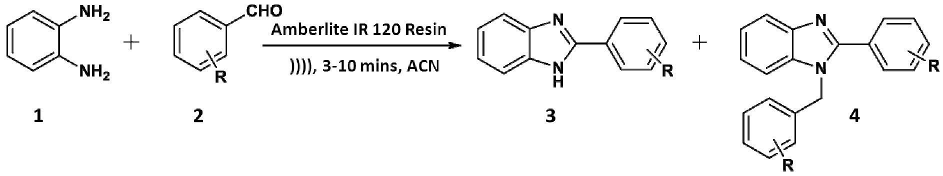


Figure. 1 General scheme for synthesis of 2-arylbenzimidazoles

EXPERIMENTAL SECTION

All reagents were obtained from commercial sources and used without further purification. ^1H and ^{13}C NMR spectra of $CDCl_3$ solutions were obtained with an Advance 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, F^{254}. The solvent for the development of the TLC plate was hexane: ethyl acetate (7:3).

General procedure for the synthesis of 2-arylbenzimidazoles derivatives:

A mixture of the corresponding aldehyde (1mmol), Amberlite IR 120 resin (100 mg), *o*-phenylenediamine (1mmol) and acetonitrile (10 ml) was irradiated in a sonicator for a given time. The progress of the reaction was monitored by TLC. After cooling to room temperature, the residue was purified by chromatography on silica gel using ethyl acetate as eluent. The products were identified by comparing their spectral parameters and physical constants with those reported in [9-10].

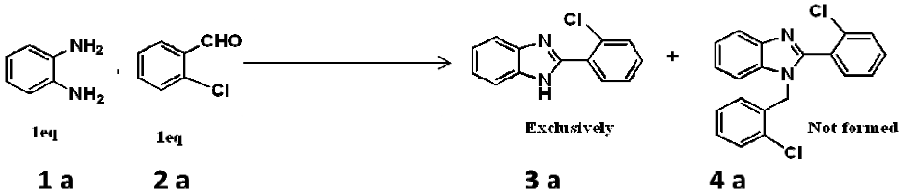
2-(2-Chlorophenyl) -1H-benzimidazole (3a)

$C_{13}H_9ClN_2$; White solid (~95%); mp 230 – 232°C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.40 (dd, 1H, J = 7.5 Hz), 7.68 (br, 2H), 7.48 (dd, 1H, J= 7.55 Hz), 7.40 (m, 2H, J = 7.5 Hz), 7.31 (m, 2H, J = 7.2 Hz); ^{13}C NMR (125MHz, $CDCl_3$): 149.23, 132.45, 131.28, 131.16, 130.90, 128.53, 127.79, 123.43, 77.49, 77.23, 76.98, 51.01; ESI-MS: m/z = 227.1 (M-1).

RESULTS AND DISCUSSION

We report here the selectivity of acetonitrile as solvent for the synthesis of 2-arylbenzimidazoles, followed by the recycle of the amberlite IR 120 resin as catalyst by reaction medium. The optimal conditions for synthesizing 2-arylbenzimidazoles using *o*-phenylenediamine and substituted aromatic aldehyde in acetonitrile gave a 96% yield at room temperature (Table 1, entry 14 and 7) but the synthesis in dichloromethane resulted in a poor yield (35%). The optimal amount of catalyst for the reaction is 100 mg, which is associated with clean and efficient conversion to 2-arylbenzimidazoles within 5 min. Sonication is a critical factor in the efficiency of the reaction, and at 72% amplitude, the reaction proceeds to completion within a short time.

Table 1 Optimization of reaction conditions by using the *o*-phenylenediamine and *o*-chlorobenzaldehyde at room temperature

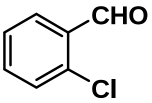
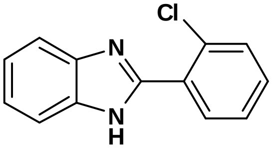
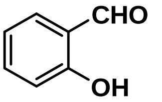
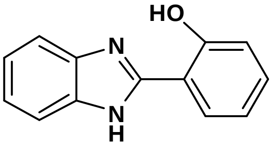
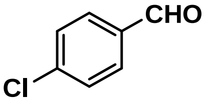
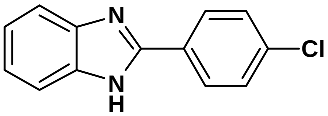
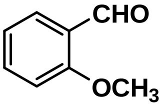
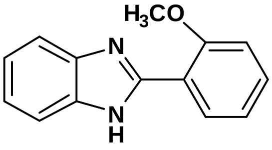
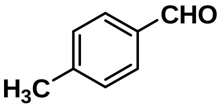
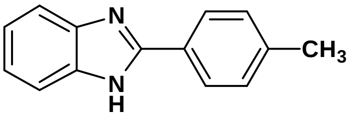
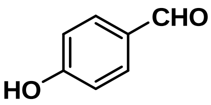
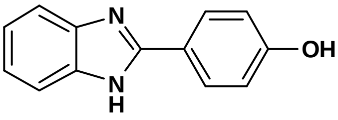
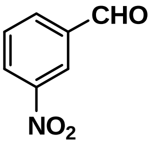
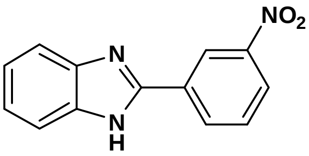
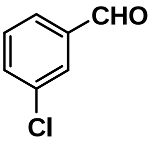
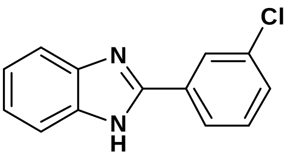


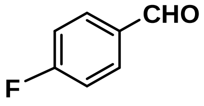
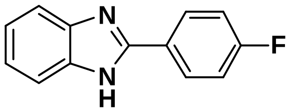
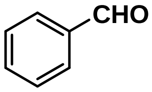
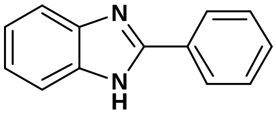
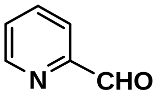
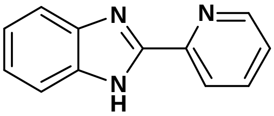
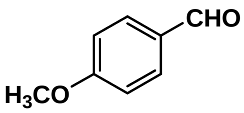
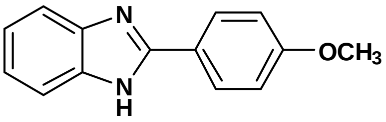
Entry	Catalyst	Catalyst load (g)	Solvent (10 mL)	Ultrasound irradiation time (min)	Yield (3a)^{a} (%)
1.	Amberlite IR 120 resin	-	H_2O	5	44
2.	Amberlite IR 120resin	0.1	EtOH	5	16
3.	Amberlite IR 120 resin	0.1	MeOH	5	14
4.	Amberlite IR 120 resin	0.1	$EtOH/H_2O$ (2/1)^{c}	5	11
5.	Amberlite IR 120 resin	0.1	THF	5	30
6.	Amberlite IR 120 resin	0.1	Acetone	5	50
7.	Amberlite IR 120 resin	0.1	Acetonitrile	5	96
8.	$HClO_4$	0.1^{b}	EtOH	5	25
9.	$HClO_4$	0.1^{b}	$EtOH/H_2O$ (2/1) ^{c}	5	22
10.	$HClO_4$	0.1^{b}	Acetone	5	16
11.	Silica	0.1	$EtOH/H_2O$ (2/1) ^{c}	5	40
12.	Silica	0.1	EtOH	5	47
13.	Amberlite IR 120	0.1	Chloroform	5	43
14.	Amberlite IR 120	0.1	Dichloromethane	5	35
15.	TFA	0.1^{b}	$EtOH/H_2O$ (2/1) ^{c}	5	44
16.	TFA	0.1^{b}	-	12	50
17.	$FeCl_3$	0.1	EtOH/ H_2O	12	52
18.	TCA	0.1	$EtOH/H_2O$ (2/1) ^{c}	12	62

^{a} *Isolated yields based on the aromatic aldehyde*
^{b} *Quantity of catalyst in mL*
^{c} *amount of reactants (in equivalents)*

The scope of application of the presented method is demonstrated by using the various substituted aromatic and heteroaromatic aldehyde compounds to react with *o*-phenylenediamine. The results that are summarized in Table 2, clearly reveal the scope of the sonochemical reaction in the presence of amberlite IR 120 in acetonitrile at room temperature. Amberlite IR- 120 is able to catalyze the reaction and recycle from the reaction medium easily because it has an acidic surface and immiscible in acetonitrile. Acetonitrile has high polarity (dielectric constants being 35.94) and converts the reactant to 2-arylbenzimidazoles under sonication efficiently. Aromatic aldehydes with substituents such as *o, p, m-* chloro performed well in this reaction without the formation of any side products. The interesting features of the *o, p-* methoxy, *p*-methyl and *o, p-* hydroxy substituents are that, it performed moderate whereas nitro substituents reaction was worse. The reaction conditions were mild enough to prevent damage to the acid-sensitive moieties, such as methoxy which commonly undergoes cleavage under strongly acidic reaction conditions. The progress of this reaction was inspected by measuring the concentration of intermediate and benzimidazole with TLC.

Table 2 Amberlite IR 120 catalyzed selective synthesis of 2-arylbenzimidazole at room temperature. The literature melting points is given in parentheses

Entry	Aldehyde (**2**)	Product (**3**)	Ultrasonic irradiation time (min)	Yield (%) [a]	mp ,°C (Obs.)
1.		 **3a**	05	96	230-232
2.		 **3b**	06	75	225-227
3.		 **3c**	07	93	289-291
4.		 **3d**	04	80	232-234
5.		 **3e**	03	82	263-265
6.		 **3f**	09	82	257-259
7.		 **3g**	10	68	204-207
8.		 **3h**	07	89	209-211

9.		 **3i**	08	88	290-293
10.		 **3j**	07	93	288-290
11.		 **3k**	07	85	oil
12.		 **3l**	03	80	224-226

[a] Isolated yield based on the aromatic aldehyde
3a was characterized by ^1H, ^{13}C NMR and ESI-MS spectral analysis, 3b- 3i, 3l were characterized by ESI–MS spectral analysis, 3a-3l were characterized by comparison of their melting points with reported values, and on TLC with authentic samples prepared by the reported [9-10].

In view of a greener chemistry, efficient recovery and reuse of the catalyst is highly desirable. Thus the recovery and reusability of amberlite IR 120 resin were investigated. After the reaction was completed, ethyl acetate was added until the solid crude product was dissolved. Then, amberlite IR 120 resin as the catalyst was isolated from the mixture of the reaction by simple filtration and reused again after washing with water. The reusability of amberlite IR 120 resin was examined efficiently without any activation by using *o*-chlorobenzaldehyde as a model substrate in the above experimental procedure. The recovered amberlite IR 120 resin was reused directly for five consecutive condensation reactions of *o*-phenylenediamine with *o*-chlorobenzaldehyde affording 98%, 96%, 95%, 93%, 92% yields respectively.

CONCLUSION

In conclusion, we have developed an efficient and highly selective procedures for the synthesis of 2-arylbenzimidazoles (96 – 68 %) via one-step condensation–aromatization reaction of *o*-phenylenediamine with electronically divergent aldehydes under sonication promoted over the surface of amberlite IR 120 resin. The presented new method requires only inexpensive eco-friendly reagents and the catalytic system is recyclable.

Acknowledgments

This scientific work has been funded by the TATA College, Kolhan University, Chaibasa, Jharkhand, INDIA and Prometeo Project of the National Secretariat of Higher Education, Science, Technology and Innovation (SENESCYT), Ecuador.

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