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Der Pharma Chemica, 2011, 3 (6):599-605
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

An Efficient, Greener synthesis of 2-Aryl-1-Arylmethyl-1H-Benzimidazoles using Polystyrene Sulfonic acid as a Catalyst

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ABSTRACT

Incorporation of polymer supported PSSA as catalyst renders excellent chemoselectivity in the synthesis of 2-Aryl-1-Arylmethyl-1H-Benzimidazoles from reaction of o-phenylene diamine with several aryl aldehydes. The captivating aspects of this method are the greenness of water mediated system and efficient, selective achievement of desired product within 30 - 40 min.

Key words: Polystyrene sulfonic acid, 2-Aryl-1-Arylmethyl-1H-Benzimidazole, Aqueous media, Chemoselectivity.

INTRODUCTION

Benzimidazoles and their derivatives constitute an important class of compounds in organic chemistry attributing to their enormous application in biological field. Several benzimidazole derivatives have been reported to exhibit biological activities viz anticancer [1], antihypertensive [2], antiviral [3], vasodilator [5] and antimicrobial [6-8]. These compounds have also been reported to act as anti-tumor[4], anthelemintic and antihistaminic[9], anti HIV[10], anti influenza[11], selective neuropeptide YY1 receptor antagonists[12-15], 5-lipoxygenase inhibitors for use as novel anti-allergic agents[16], factor Xa (FXa) inhibitors[17]. Consequently, propelled by these encouraging aspects of the benzimidazole nucleus, today's researchers are driven to delve out innovative methodologies for the synthesis of this vital moiety.

A thorough retrospect over the reported routes for the synthesis of benzimidazoles reveals plenty of preparative methods amongst which the two significant ways involve condensation of o-phenylene diamine with carboxylic acids under dehydrating conditions [18] and condensation of o-phenylene diamine with aryl aldehydes [19]. Amongst all the several reports, the direct condensation-aromatization reaction of o-phenylene diamine with aldehydes under oxidative condition turned out to be the most efficient pattern to synthesize 2-substituted benzimidazoles.

Moreover, these methods encountered simultaneous formation of 1,2-disubstituted benzimidazoles. Therefore, the selectivity in preparing the 1,2-disubstituted benzimidazoles and 2-substituted benzimidazole becomes an issue of high interest. Although abundant routes which avail various catalysts e.g. Laccase [20], NH_4Cl [21], Ytterbium perfluorooctanesulfonates [22], Cu (II) complex [23], LiBr [24] have been reported for the synthesis of 2-substituted benzimidazoles. On the contrary relatively fewer methods have been scripted for the selective synthesis of 1-2 disubstituted benzimidazoles. Survey reveals use of oxalic acid [25], L-Proline [26], Glyoxalic acid [27], $SiO_2/ZnCl_2$ [28], Sodium dodecylsulfate (SDS) [29] as catalyst for the desired selective synthesis of 1,2-disubstituted benzimidazoles. With an overall observation it seems that formation of this selective moiety is likely to furnish in aqueous media [30]. Furthermore, from an environmental view point since water being environmentally benign[31], it is desirable to use it altering the use of organic solvents as a reaction medium, also with tightened regulatory pressure focusing on organic solvents, the search for alternatives has gained an ascending importance. Developing environmentally benign and economical synthesis is an area of research that is being vigorously pursued and avoiding the use of harmful organic solvents is a fundamental strategy for achieving it. In addition, reactions in aqueous media illustrate unique reactivity and selectivity that are not usually observed in organic media [32]. However, the reports in water for synthesizing 1,2-disubstituted benzimidazoles are often limited in scope as they utilize a circuitous route, require longer reaction time and face poor solubility of the organic compounds.

Further, on elaborating the idea of aqueous mediated system, there germinates a need for a special catalyst which homogenizes the water insoluble reactant to uniform phase simultaneously catalyzing the reaction medium with a considerable abridgement of time required. In our ongoing endeavor to establish clean and ecofriendly synthetic methodologies [33], we incorporate polystyrene sulfonic acid depicted by its successful applications catalyzing several selective and non selective water mediated organic reactions [34], as a relatively low toxic, cheap, rapid action catalyst which readily accelerates the reaction abridging the required time to a considerable extent.

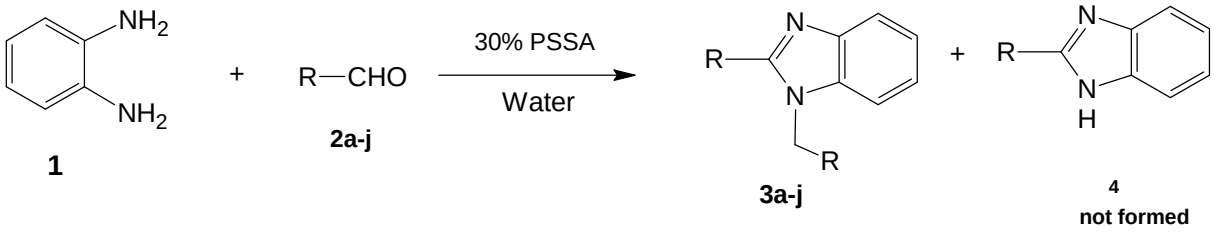
MATERIALS AND METHODS

All chemicals and solvents were reagent grade and used as purchased without any further purification. Analytical thin-layer chromatography was performed on percolated silica gel 60-F 254 plates. The data found were in consistent with the proposed structure. IR spectra on KBr disks were recorded on a Schimazdu IR-470 FT-IR spectrophotometer. The routine nuclear magnetic resonance spectra were taken in $CDCl_3$ using a Bruker 300 MHz spectrophotometer with TMS as an internal standard. Chemical shift δ was given in ppm relative to TMS and compared with reported literature values. Elemental analysis was done using EURO Vector Elemental Analyzer. Melting points were determined in an open capillary tube and were found to be uncorrected.

1-Aryl-2-arylmethyl-1H-Benzimidazoles 3; General Procedure

A mixture 1.0 mmol of aldehyde **2** and 0.5 mmol of o-phenylene diamine were placed in 10mL glass tube bearing 5mL of water. To this 0.1mL of 30% PSSA w/v was added and the reaction was subjected at room temperature. The completion of the reaction was confirmed by TLC (Ethyl acetate: Pet Ether). After the completion precipitated product was easily separated with simple filtration process. The obtained product was washed with H_2O and dried to yield the corresponding 1,2 disubstituted benzimidazole.

Scheme I



Spectroscopic data of representative compounds:

1-benzyl-2-phenyl-1H-benzimidazole (3a):

White solid; mp 132–134 ^{0}C; IR (KBr cm^{-1}): 3031(C–H stretching of aromatic ring), 2918(C–H stretching of aliphatic) 1395 (C–N stretching of imidazole ring), 1510, 1440 (C=C stretching of aromatic ring); ^{1}H NMR ($CDCl_3$, 300 MHz,): 5.25 (2H, s, CH_2), 7.15-7.7 (14H, m, Ar-H); Elemental analysis, Molecular Weight: 284.35, Calculated: C, 84.50; H, 5.63; N, 9.85 Found : C, 84.51; H, 5.69; N, 9.80.

1-(4-Nitrobenzyl)-2-(4-nitrophenyl)-1H-benzimidazole (3d):

Pale Yellow solid; mp 195 $_0$C; IR (KBr,cm–1): 3075 (C–H stretching of aromatic ring), 2922 (C–H stretching of aliphatic), 1614 (C=N stretching of imidazole ring), 1526, 1350 (NO_2 stretching of aromatic ring), 1507, 1455 (C=C stretching of aromatic ring), 1381 (C–N stretching of imidazole ring); ^{1}H-NMR ($CDCl_3$, 300 MHz,): 5.50 (2H, s, CH_2), 7.22–8.37 (12H, m, Ar–H); Elemental analysis, Molecular Weight: 374.34, Calculated: C, 64.17; H, 3.74; N, 14.97, Found : C, 64.20; H, 3.68; N, 14.91.

1-(4-Hydroxybenzyl)-2-(4-hydroxyphenyl)-1H-benzimidazole (3h):

White solid; mp 258 ^{0}C; IR (KBr, cm–1): 3060 (C–H stretching of aromatic ring), 3425(O–H stretching), 2935 (C–H stretching of aliphatic), 1546 (C=N stretching of imidazole ring), 1522, 1441 (C=C stretching of aromatic ring), 1346 (C–N stretching of imidazole ring); ^{1}H NMR ($CDCl_3$,300MHz): 5.49 (2H, s, CH_2), 7.14–8.19 (12H, m, Ar–H) 9.3 - 9.8(2H, OH); Elemental analysis, Molecular Weight: 316.35, Calculated: C, 75.94; H, 5.06; N, 8.86, Found : C, 75.88; H, 5.04; N, 8.80.

1-(2-Chlorobenzyl)-2-(2-chlorophenyl)-1H-benzimidazole(3b):

Pale yellow solid; mp 160 ^{0}C;IR (KBr, cm–1): 3060 (C–H stretching of aromatic ring), 2924 (C–H stretching of aliphatic), 1621 (C=N stretching of imidazole ring), 1535, 1449 (C=C stretching of aromatic ring), 1396 (C–N stretching of imidazole ring); ^{1}H NMR ($CDCl_3$,300MHz) 5.35 (2 H, s, CH_2) 7.12- 7.76 (12H, m, Ar–H); Elemental analysis, Molecular Weight: 353.24, Calculated: C, 67.98; H, 3.96; N, 7.93, Found : C, 67.89; H, 3.90; N, 7.90.

1-(6-Methoxy-2-ChloroQuinolyl)-2-(2-[6-Methoxy-2-ChloroQuinolyl])-1H-benzimidazole (3j):

Off-white solid; mp 206 ^{0}C;IR (KBr, cm–1): 3075 (C–H stretching of aromatic ring), 2924 (C–H stretching of aliphatic), 1620 (C=N stretching of imidazole ring), 1495, 1450 (C=C stretching of aromatic ring), 1394 (C–N stretching of imidazole ring); ^{1}H NMR ($CDCl_3$,300MHz) 5.43 (2 H, s, CH_2), 3.96 (6H, OCH_3), 7.21- 7.81(12H, m, Ar–H); Elemental analysis, Molecular Weight: 515.39, Calculated: C, 65.24; H, 3.88; N, 10.87, Found : C, 65.20; H, 3.85; N, 10.81.

RESULTS AND DISCUSSION

Initially we employed 1:1 mol *o*-phenylene diamine and benzaldehyde reaction in water in the presence of 30% polystyrene sulfonic w/v acid at reflux condition. Astonishingly, instead of

forming the 2-substituted benzimidazole as expected it yielded 1,2-disustituted benzimidazole to a considerable quantity. This excellent chemoselectivity mediated by this aqueous system led us to further investigate this conversion as a major goal of interest. Further in the same case introduction of 2:1 mol of aldehyde and *o*-phenylene diamine respectively, resulted in exclusive formation of the expected 1,2- disubstituted benzimidazole with no formation of 2-substituted benzimidazole. To optimize the reaction conditions and the quantity of 30% PSSA, we employed a model reaction using o-phenylene diamine **1** and benzaldehyde **2a**, with variation in solvents, temperature conditions and volume (in mL) of 30% PSSA (**Table I**). Summarizing the observations (from **Table 1**) the results were found optimum in water at room temperature with 0.1ml of 30% PSSA **Scheme 1**. Although the yield and time aspects were same for organic solvents, yet water proved to be vital due to its serene ecofriendly nature.

Table I - Optimization of reaction conditions for synthesis of 1-Benzyl-2-Phenyl-1H-benzimidazole (3a)

Solvents	30% PSSA(in mL)	Time(min)	Temp(^{0}C)	Yield (%)
EtOH	0.2	30	Reflux	90
MeOH	0.2	40	Reflux	90
Ethylene Glycol	0.2	40	70-80	89
Water	0.2	35	70-80	86
Water	0.2	35	r.t	90
Water	0.1	35	r.t	90
Water	0.01	55	70-80	86

The most meritorious aspect of this method is its greenness and rapid formation of the expected product at room temperature in merely 30-40 min, which readily outwits the prolonged time procedures that have been reported in the literature.

Optimum conditions and versatility of the scaffold was examined by subjecting different aryl aldehydes with o-phenylene diamine and 1,2-disubstituted benzimidazoles 3a-j with various functional groups were obtained in excellent selectivity and yields **(Table II)**.

Table II – Synthesis of 2-Aryl-1-Arylmethyl-1*H*-benzimidazoles using 0.1 mL of 30% PSSA in water at Room temperature

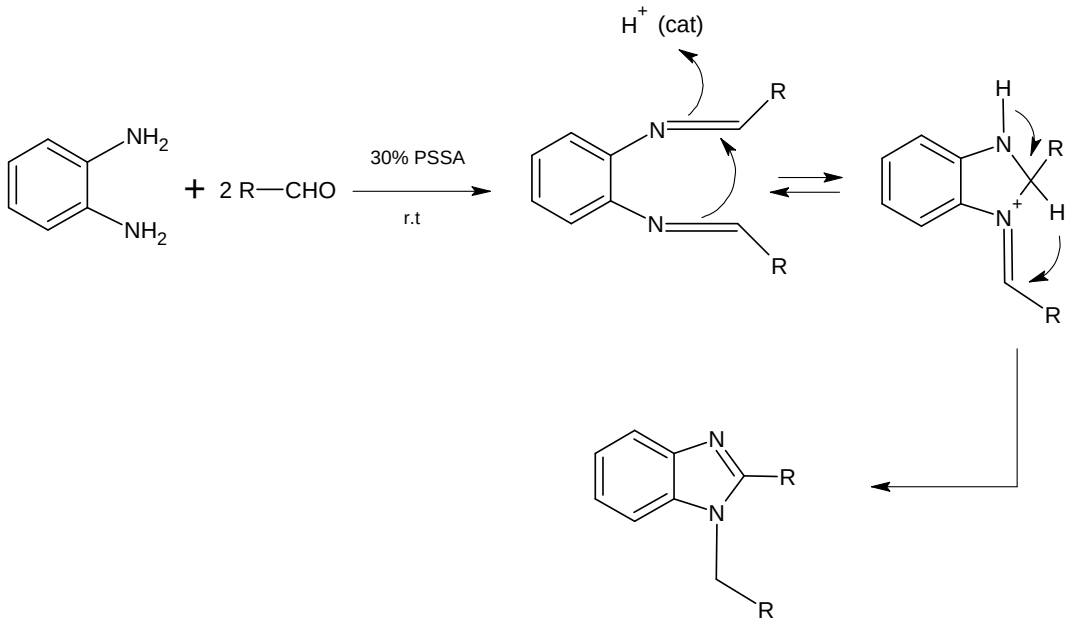
Entry	Ar	Time(min)	Product[b]	Yield(%)[a]	Mp(^{0}C)	Lit
1	Ph (**2a**)	35	**3a**	90	132-134	134[25]
2	2-ClC_6H_4(**2b**)	40	**3b**	87	160	158-159[25]
3	4-ClC_6H_4 (**2c**)	40	**3c**	87	137	137-138[35]
4	4-$NO_2C_6H_4$ (**2d**)	40	**3d**	90	195	192[36]
5	3-$NO_2C_6H_4$(**2e**)	35	**3e**	86	120-121	120[25]
6	4-$MeOC_6H_4$ (**2f**)	40	**3f**	85	128	129[37]
8	4-OHC_6H_4(**2h**)	35	**3h**	88	225	226[29]
9	4-$Me_2NC_6H_4$(**2i**)	40	**3i**	89	255	255[25]
10	6-methoxy-2-chloro quinoline(**2j**)	50	**3j**	86	210	--

[a] *All the yields in this section were obtained by recrystallized isolated products for accurate evaluation on the effect of reaction conditions.*
[b] *All compounds are known and their physical and spectroscopic data were in good agreement with those of authentic samples.(Except **3j**)*

Moreover this method was applicable readily for several aromatic aldehydes. Among the reaction of varied aryl aldehydes there was no significant change in the yield and time aspect regardless of the diversity of the substituted functional groups of aldehydes. The reaction proved to be equally efficient for both electron donating (**Table II 2h**) as well as electron withdrawing (**Table II 2d, 2e**) substituents.

The plausible mechanism for the synthesis of 1,2-disubstituted benzimidazoles **3** may involve formation of N,N'- dibenzylidene-o-phenylenediamine proceeded with successive protonation and ring closure concluded with aromatization via deprotonation and 1,3 hydride transfer **Scheme II**.

Scheme II



CONCLUSION

In conclusion, we have developed a greener and efficient approach for the selective synthesis of 1,2-disubstituted benzimidazoles, which attains completion in 30-40 min in aqueous medium and may provide an useful route for rapid drug discovery. The use of polystyrene supported, relatively low toxic, and inexpensive PSSA as a catalyst and the water as a reaction medium are additional eco-friendly attributes of this synthetic protocol.

Acknowledgment
One of the authors (PPP) is thankful to DST-PURSE for providing JRF. Department of Chemistry for providing Spectral analysis.

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