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Iodine catalyzed convenient synthesis of 2-Aryl-1-arylmethyl-1 *H*-benzimidazoles in aqueous media

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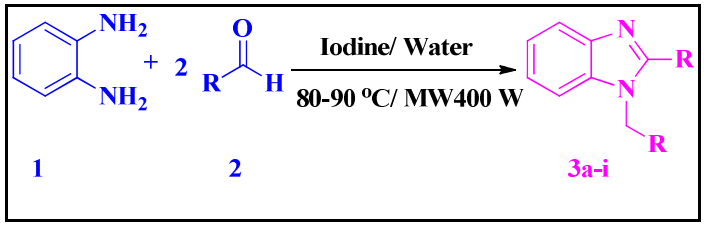
Abstract: Iodine catalyzed synthesis of **2-Aryl-1-arylmethyl-1*H*-benzimidazoles** are demonstrated by using easily available phenylenediamine and aldehydes. New approach is promising and giving moderate yields with high purity and selectively single product in aqueous media.
Keywords: Iodine, Green synthesis, Benzimidazole, Microwave.

1. Introduction

Benzimidazole is an important heterocyclic aromatic organic compound and a privileged structure in medicinal chemistry. The most well-known benzimidazole compound in nature is *N*-ribosyl-dimethylbenz imidazole, which serves as an axial ligand for cobalt in vitamin B_{12}.[1] Due to the structural similarity to purine, antibacterial ability of benzimidazoles is explained by their competition with purines resulting in inhibition of the synthesis of bacterial nucleic acids and proteins.[2,3] It also shows antimicrobial & antibacterial properties,[4] HIV inhibtors,[5] antiparasitic,[6] antiviral,[7] antiprotozoal,[8] antiulcer,[9] antitumor[10] & antiproliferative[11] properties. This shows that benzimidazole containing structures stems from their widespread occurrence in molecules that exhibit significant biological activity. Since benzimidazoles are commonly used as intermediates in synthetic routes and serve as ligands for the asymmetric catalysis.[12]

A literature review reveals a number of methods for synthesis of benzimidazole and its derivatives. In general, it is prepared by the condensation of carboxylic acids or their derivatives with substituted *o*-phenylenediamine with heating at high temperature.[13-15] In last decade use of different transition metal catalysts for the synthesis of benzimidazole has considerably increased. The methods involve preparation of benzimidazoles using activated alcohols, *o*-phenylenediamine and oxygen or manganese(IV) oxide as oxidant.[16] use of palladium catalyzed intermolecular N-arylation reaction.[17-19] An alternative approach is the condensation of aldehydes with *o*-phenylenediamine using catalysts such as triflate salts $Sc(OTf)_3$ and $Yb(OTf)_3$].[20,21] and Lewis acids[22,23]. But on the other hand many of these methods have several drawbacks such as prolonged reaction times, expensive reagents, oxidation processes, tedious workup and low yield. In some cases, 2-substituted and 1, 2-disubstituted benzimidazoles were generated simultaneously with poor selectivity which often requires cumbersome workup and purifications. In connection with our research interest[24] for the development of simple and efficient methods for synthesis disubstituted benzimidazole, we now report an efficient, ecofriendly and practical method for the one-pot synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles selectively by reacting *o*-phenylenediamine and aldehydes in presence of molecular iodine as catalyst in aqueous media (Scheme-1).



2. Results and discussion

As an inexpensive and commercially available reagent iodine has attracted considerable interest due to its non-hazardous nature and efficiency in various organic transformations.[25] Accordingly, we examined the reaction of *o*-phenylenediamine (1) and benzaldehyde (2) in the presence of a catalyst in aqueous media. Since our initial goal was to identify a catalyst which works in aqueous media preferably non-metal a range of relevant agents were examined (Table 1).

Table 1 Effect of reaction conditions for the preparation of (3a)[a]

Entry	Catalyst (mmol %)	Solvent	Time	Yield (%)[b]
1	p-TSA (0.1)	H_2O	12 h	55
2	CF_3SO_3H (0.1)	H_2O	11 h	43
3	$NaHSO_3$-SiO_2 (0.1)	H_2O	16 h	25
4	$(CO_2H)_2$ (0.1)	H_2O	6 h	60
5	TFA (0.1)	H_2O	9 h	51
6	I_2 (0.1)	H_2O	1.3 h	95
7	I_2 (0.05)	H_2O	2.5 h	84
8	I_2 (0.2)	H_2O	1.3 h	95
9	Without catalyst	H_2O	24 h[c]	00
10	I_2 (0.1)	THF	3 h	71
11	I_2 (0.1)	MeCN	3 h	79
12	I_2 (0.1)	EtOH	3 h	84
13	I_2 (0.1)	DMF	3 h	77
14	I_2 (0.1)	H_2O	6 min (MW, 70^{0}C 400W)	94

[a] all reactions carried out at 80-90^{0}C.
[b] Isolated yield
[c] No product was observed

All the Reactions were generally carried out at 80-90^{0}C using water as solvent. The use of p-toluenesulfonic acid (p-TSA) (entry 1, Table 1), CF_3SO_3H (entry 2, Table 1) and solid supported catalyst such as $NaHSO_3$-SiO_2 (entry 3, Table 1), Oxalic acid (entry 4, Table 1) and TFA (entry 5, Table 1) was examined but found to be less effective in water. The desired product 3a was isolated only in 25–60% yield. The use of iodine however accelerated the reaction and increased the product yield significantly (entry 6, Table 1) affording compound 3a in 95% yield. The reaction was carried out using 0.1 mmol of iodine. The yield of the product was decreased when 0.05 mmol of iodine was used (entry 7, Table 1). No change was observed in yields or reaction time when 0.2 mmol of iodine was used for the reaction (entry 8, Table 1). Further it was observed that there is no reaction up to 24 h in absence of iodine (entry 9, Table 1). The effect of solvent e.g. tetrahydrofuran (THF), acetonitrile (MeCN), ethanol (EtOH) & dimethylformamide (DMF) (entry 10-13, Table 1) was also examined and found to be counter productive.

As it is well known that use of microwave (MW)[26] reduce reaction time remarkably. The present reaction also gave excellent results under microwave irradiations (entry 14, Table 1).

To our delight we have observed the formation of 3a (Table 1) with 95% isolated yield with conventional method (entry 6, Table 1) and 94% isolated yield under microwave irradiation (entry 14, Table 1). To expand the scope & the generality of this method, various aromatic and heterocyclic aldehydes were used to synthesize a range of 1, 2-disubstituted benzimidazoles (3a-i) (Table 2). This reaction was very clean and free from side reactions, such as formation of 2-substituted benzimidazoles, which are normally observed as minor product during 1, 2- disubstituted benzimidazole synthesis, which help us to predict the mechanistic approach.

The reaction seems to proceed via the path shown in Scheme 2, which may involve the iminium catalyzed formation of an *N*, *N*'-dibenzylidene-*o*-phenylenediamine and ring closure to give a five membered ring (Scheme 2).

All derivatives are producible by traditional method as well as by using MW conditions, MW conditions shows advantage over reaction time (Table 2). Yield wise both approaches are at par. Both approaches exclusively delivered only one product i.e. 1, 2-disubstituted benzimidazoles.

Table 2: Molecular iodine-catalyzed synthesis of 1, 2-disubstituted bezimidazoles.

Entry	R	Product	Time required in traditional approach[a] (h)	Yield [b] (%)	Time required in microwave (min)[c]	Yield [b] (%)
1	Ph	**3a**	1.3	95	6	94
2	4-ClC_6H_4	**3b**	1.5	91	9	90
3	3-$O_2NC_6H_4$	**3c**	1.2	84	7	85
4	4- MeC_6H_4	**3d**	1.5	90	7	92
5	4- FC_6H_4	**3e**	1.3	92	6	90
6	4-CNC_6H_4	**3f**	1.3	61	6	98
7	4-$MeOC_6H_4$	**3g**	1.5	91	7	94
8	4-$Me_2NC_6H_4$	**3h**	1.2	91	8	88
9	2-furyl	**3i**	1.5	88	7	92

[a] All reactions carried out at 80-90^{0}C.
[b] Isolated yield
[c] All reactions carried out at 70^{0}C, using 400 W.

3. Conclusion

In conclusion, a facile and efficient synthesis of derivatives has been developed via iodine mediated conditions in water. The methodology employs readily available and inexpensive catalyst under organic solvent free conditions. For all the presented reactions water was used as solvent, which is environmentally benign and supporting 'green chemistry' and alternative to present methods. The methodology should find wide usage both in academia and pharmaceutical industries.

4. Experimental Section

Unless stated otherwise, reactions were performed under open air. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (230–400 mesh) using distilled hexane-ethyl acetate. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d6 solution by using Varian 300 MHz spectrometers. Proton chemical shifts (d) are relative to tetramethylsilane (TMS, d = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Infrared spectra were recorded on Bruker Alpha E FTIR spectrophotometer. Melting points were recorded on optimelt digital melting point apparatus and are uncorrected. All the readily available chemicals & solvents were used from Alfa & Sigma-Aldrich chemicals.

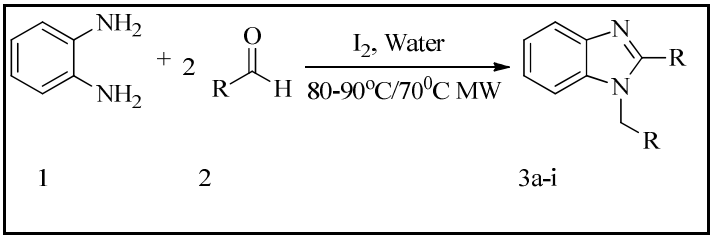
General procedure for the synthesis of compound 3a-i

General procedure for traditional approach

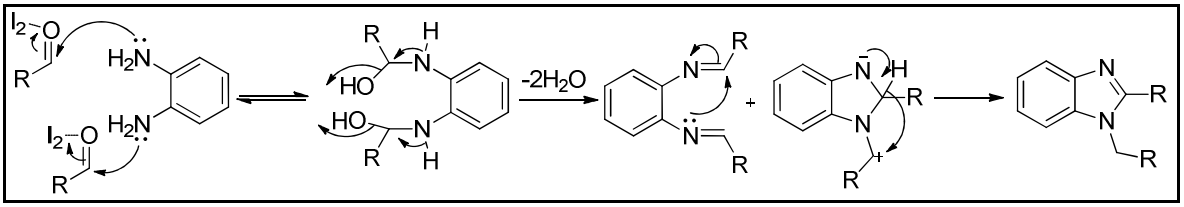
A mixture of o-phenylenediamine (10 mmol) and aromatic aldehyde (20 mmol) was added in H_2O (20 ml) followed by iodine (0.1 mmol) at room temp. The mixture was then stirred at 80–90^{0}C and the progress were monitored by TLC. After completion of the reaction (1.2 - 1.5 h), the mixture was cooled to room temperature and diluted with ice cold water (50 ml). A solid precipitated was collected by filtration and washed with cold water and then dried to give the corresponding crude 1, 2-disubstituted benzimidazole, which was further purified by column chromatography on silica gel using 1:9 – 4:6 ethyl acetate–petroleum ether to afford the desired compound **(3a-i).**

General procedure for Microwave Approach

A mixture of o-phenylenediamine (10 mmol) and aromatic aldehyde (20 mmol) was added in H_2O (20 ml) followed by iodine (0.1 mmol) at room temperature, resultant mixture was stirred at 70^0C in microwave and the progress was monitored by TLC. The mixture was cooled to room, temperature and poured into ice-water (50 ml). A solid precipitated that was collected by filtration and washed with water and then dried to give crude corresponding 1, 2-disubstituted benzimidazole. Which was further purified by column chromatography on silica gel using 1:9 – 4:6 ethyl acetate–petroleum ether to afford the desired compound.



Scheme 1



Scheme-2 Proposed mechanism for the formation of disubstituted benzimidazoles

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