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Molecular Iodine Assisted Green Synthesis of Benzimidazoles

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Abstract: *Green synthesis of 2-substituted Benzimidazoles in the presence of molecular iodine(10mol%) the mixture of o-phenylenediamine in I_2 was added benzoyl chloride at room temperature and reaction mixture was grind at room temperature after 20 minutes reaction was completed. The reaction gives high yield. The short reaction time, clean reaction, and easy workup make this protocol green and efficient.*

Keywords: Benzimidazoles, molecular iodine, room temperature, green synthesis

I. INTRODUCTION

Substituted Benzimidazole is a bicyclic compound having imidazole ring fused to benzene. The compounds that exhibit the functionality of benzimidazole have been extensively employed in the area of pharmaceuticals. Benzimidazole nucleus is a part of the nucleotide portion of vitamin $B_{12,}$ in some drugs such as proton pump inhibitors, anthelmintics agents[1] and antirhino/enteroviral agents[2], Benzimidazoles also exhibit significant activity against several viruses including HIV[3], herpes (HSV-1)[4], RNA[5], influenza[6] and human cytomegalovirus (HCMV). In recent years benzimidazoles have been reported to act as topoisomerase I inhibitors[7], selective neuropeptide Y Y1 receptor antagonists[8], angiotensin II (AII) inhibitors[9], inhibitors of HCMV replication, potential antitumour agents[10], antimicrobial agents[11], smooth muscle cell proliferation inhibitors[12], a treatment for interstitial cystitis[13], antihistamine (astemiazole)[14], antifungal (chlorfenazol), anti-ulcerative (omeprazole)[15],anti-inflammatory activity[16] and in diverse areas of chemistry[17].

Interest in these structures stems from their widespread occurrence in molecules that display a wide range of useful biological properties. Widely used traditional methods for their preparation involve the reaction of a carboxylic acid or its derivative with an appropriate *o*-phenylenediamine, *o*-aminophenol or *o*-aminothiophenol in the presence of a strong acid or cyclodehydration of mono-acylated product under acidic condition or by pyrolysis at 200–350 ^{0}C.2-substituted benzimidazoles by condensing a variety of carboxylic acids with *o*-aminophenols or *o*-phenylenediamines in presence of PS-PPh_3 resin[18] , Zeolite[19], trifluoroacetic acid and difluoro acetic acid[20] and by Lewis acids in ethanol[21].Recently *Siddiqui et al* [22-23] reported the method of the synthesis of these heterocycles by using ionic liquids as a part of green chemistry.

Survey of literature reveals that methods for the synthesis of above heterocycles have been suffer from several drawbacks such as low yield, more reaction steps, tedious manipulations in the isolation of products and utilization of toxic reagents. These reactions require harsh dehydration conditions such as strong mineral acids, which have limited the viability of many starting materials. The development of simple, efficient and environmentally benign chemical processes or methodologies for widely used organic compounds from readily available reagents is one of the major challenges for chemists in organic synthesis.

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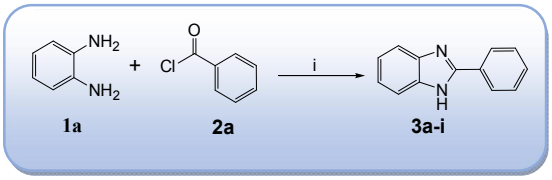
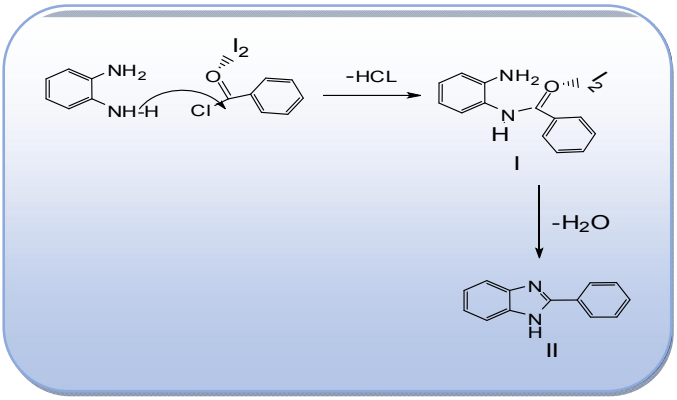
II. METHODOLOGY



Scheme 1. Reaction conditions; I_2 (10 mol%) , RT

Molecular iodine reagent has found broad application in organic chemistry and now a days frequently used in synthesis[109]. Therefore, the development of simple, efficient, inexpensive, nontoxic and readily available reagents providing convenient procedure with improved yield. Owing to its unique catalytic properties iodine has been extensively used for an organic reaction [110-112].From previous study we found that I_2 gives the best result compare to other catalyst. To a clean mixture of *o*-phenylenediamine **1a** in I_2 was added benzoyl chloride **2a** at room temperature and reaction mixture was vigorously stirred, after addition is over reaction mixture was precipitate out as a solid product (reaction was completed in 20 min. which was checked by TLC). After completion of reaction, mixture was diluted with water and filtered and wash with sodium thiosulphate iodine remove with filtrate. The isolated product was further purified by column chromatography give pure product **3a** in 93% yield which was fully characterized. The IR spectrum of **3a** shows absorption at 1640 & 3420 cm^{-1} corresponds to C=N and –NH functional group respectively. The ^{1}H-NMR spectrum of **3a** showed broad singlet at δ 4.5 for –N*H* and multiplet of nine protons in the region of 7.32-8.19 for aromatic region. The elemental analysis and physical constant concerned with the literature values of **3a**.

III. RESULT AND DISCUSSION



Scheme:-2 Systematic mechanism of the synthesis of Benzimidazoles

Generally, the synthesis of benzimidazole is proceeding through two step process. First is the acylation followed by cyclization .In first step hydrochloric acid is liberated as by product during the reaction, we thought that this liberated hydrochloric acid may facilated the further cyclization to delivered the target 2-phenyl benzimidazole **3a (II)**, to check this we performed the reaction of **3a** in molecular solvent (acetonitrile) without any added catalyst, we got mono-acylated product exclusively with no sign of benzimidazole, this indicates that librated hydrochloric acid is not taking part for further cyclization.

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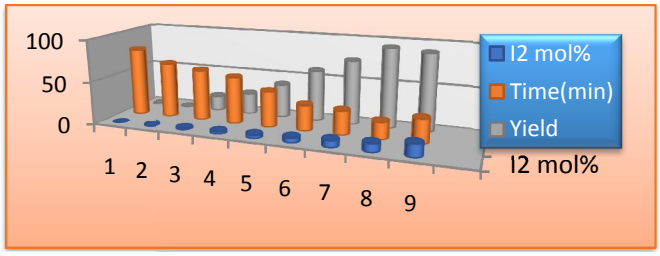
Table 1. Catalytic study of I_2 for formation of 3a

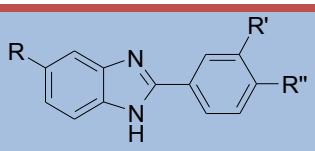
Entry	I_2 (mol %)	Time (min.)	Yield [a] (%)
1	No iodine	80	00
2	1	65	traces
3	2	60	18
4	3	55	25
5	4	42	40
6	6	30	60
7	8	28	75
8	10	20	95
9	15	28	92



[a] **Isolated yield after column chromatography**

The effect of mole ratio of the I_2 with respect to the formation of **3a** was investigated (Table 1). It can be observed that a minimum of equimolar proportion of the I_2 is required for optimum result. As we wish to explore here the I_2 as promoter for this heterocyclization, A mixture of *o*-phenylenediamine (4.6 mmol) and benzoyl chloride (4.6 mmol),by addition of iodine however reaction proceed to gave the 2-phenyl benzimidazole as sole product. These results confirmed that I_2 due to its large electrochemical window promoted this heterocyclization for the formation of target molecule 2-phenyl benzimidazole in excellent yield in short span of reaction time. It becomes evident from above results (Table 1), the I_2 afforded the best results. Consequently, all further studies were conducted at room temperature using I_2 to synthesize different 2-susbtituted benzimidazole.

Table 2. Synthesis of Benzimidazoles **3a-i**

Entry	 3a-i			Time (min.)	Yield [a] (%)
	R	**R'**	**R''**		
3a	**H**	H	**H**	**12**	92
3b	**H**	H	**NO_2**	**21**	88
3c	**H**	F	**CF_3**	**17**	90
3d	**Me**	H	**H**	**14**	92
3e	**Me**	H	**NO_2**	**20**	93
3f	**Me**	F	**CF_3**	**18**	95
3g	**CoPh**	H	**H**	**20**	94
3h	**CoPh**	H	**NO_2**	**22**	89
3i	**CoPh**	F	**CF_3**	**24**	92

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IV. EXPERIMENTAL

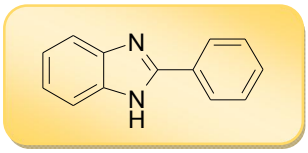
Typical procedure for synthesis of 2-phenyl benzimidazole (3a) in I_2 :

A mixture of *o*-phenylenediamine (4.6 mmol) and benzoyl chloride (4.6 mmol) in I_2 (10 mol%) was stirred at room temperature. After completion of the reaction (progress of reaction was monitored by TLC). Reaction mixture was diluted with water (10 mL) and the separated product was filtered and washes with sodium thiosulphate. The product, thus isolated, was pure enough. It was subjected to further purification by column chromatography using 20% EtOAc in petroleum ether as eluent and fully characterized.

Conclusion: -In conclusion we have synthesized substituted Benzimidazoles in the presence of molecular iodine at room temperature. The reaction gives high yield. The short reaction time, clean reaction, and easy workup make this protocol green and efficient.

Acknowledgment: -Author is thankful to Department of Chemistry, B. Raghunath ACS College, Parbhani.

Characterization data for Compound:-



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

M. P. (^{0}C) : 294-295

IR ($CHCl_3$, cm^{-1}): υ_{max} 735, 810, 1035, 1140, 1310, 1463, 1643, 3420.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.3 (brs, 1H), 7.32-8.19 (m, 9H).

^{13}C NMR : δ 112, 115.3, 121.7, 122.5, 126.4, 129, 130, 130.3, 134.9, 143.6, **(50 MHz, $CDCl_3$)** 151.6.

Elemental Analysis : $C_{13}H_{10}N_2$

Calcd. C, 80.39; H, 5.19; N, 14.42.

Found C, 80.19; H, 5.05; N, 14.23.

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