Efficient, rapid and one pot synthesis of 2-substituted benzimidazoles using the NaOH/I_2 system as an oxidant under mild conditions

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A one-pot efficient synthesis of benzimidazole derivatives has been achieved from aryl aldehydes and *o*-phenylenediamine in the presence of the NaOH/I_2 system at room temperature in acetonitrile. The simplicity of the procedure and work-up, larger scale synthesis, high yields and short reaction times are the advantages of this method.

Keywords: *o*-phenylenediamine, benzimidazoles, aryl aldehydes, sodium hydroxide, iodine, acetonitrile

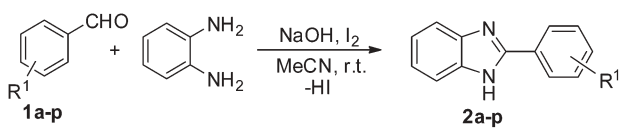
The benzimidazole scaffold is a useful structural motif for displaying chemical functionality in biologically and pharmacologically active molecules. Optimisation of benzimidazole-based structures has resulted in marketed medicines such as Omeprazole[1] and Pimobendan[2] and lead compounds in a wide range of therapeutic areas (*e.g.*,hepatitis C virus,[3] casein kinas 2,[4] factor Xa[5]). Medicinal chemists consider these heterocycles privileged structures. Indeed, the development of new synthetic methods, which could render accessible chemical space currently not attainable by existing methods, would be of considerable importance to the chemistry community.

Moreover, these fused heterocycles have been studied as new non-nucleoside topoisomerase-I poisons, human immunodeficiency virus-1 reverse transcriptase inhibitors, and/or potent DNA gyrase inhibitors.[6–8] They can act as ligands to transition metals for modelling biological systems.[9,10] In addition, benzimidazoles are very important intermediates in organic reactions.[11,12]

The most popular synthetic approaches generally include the coupling of *o*-phenylenediamines and carboxylic acids or various derivatives.[13,14] Various catalysed syntheses of benzimidazole derivatives by condensation of *o*-phenylenediamine with aldehydes in the presence of sodium hydrogen sulfite[15] or oxone[16] are known. Condensation of *o*-phenylenediamine with orthoesters in the presence of various Lewis acid catalysts are also known *viz.* $ZrCl_4$, $SnCl_4.5H_2O$, $TiCl_4$, $BF_3.Et_2O$, $ZrOCl_2.8H_2O$ and $HfCl_4$.[17,18] Phthalic acid attached to polyethylene glycol ether and polymer supported 4-fluoro-3-nitrobenzoic acid in solid phase have been used as precursors for 2-substituted benzimidazoles.[19,20] However, many of the synthetic protocols reported so far suffer from disadvantages, such as needing anhydrous conditions,[21] harsh reaction conditions, use of metals and expensive reagents,[22] and prolonged reaction times.[23] Therefore, the development of a cost effective, safe and inexpensive reagent system is desirable.

Results and discussion

We now report the results of our studies describing the development of an efficient method for the synthesis of benzimidazoles in one step, whereby aryl aldehydes were condensed with *o*-phenylenediamine using solid I_2 and NaOH as an efficient oxidant system in the presence of acetonitrile at room temperature without the need for the preparation or isolation of any intermediate agents (Scheme 1).



Scheme 1 Synthesis of 2-substituted benzimidazoles from o-phenylenediamine and aryl aldehydes in the presence NaOH/I_2.

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Firstly, in order to find the effect of solvent on this reaction, several solvents including acetonitrile, dichloromethane, acetone, and ethanol were investigated during the course of this study. After screening different solvents, it was found that acetonitrile was best (Table 1). A ratio of 5:2:1:1 of NaOH/I_2/aryl aldehyde/*o*-phenylendiamine was found to be optimum for the reaction.

In order to ascertain of the limitation of this method, the reaction of *o*-phenylenediamine with various aromatic aldehydes with the NaOH/I_2 system under optimised conditions in acetonitrile solvent were carried out. The results are summarised in Table 2. In all entries, the benzimidazoles were obtained as products in excellent yield after short reaction times.

With regard to the mechanism of the oxidation step, the reaction probably involves the formation of NaOI by the reaction of sodium hydroxide with iodine which then reacts with the initially formed hydrobenzimidazoles to afford intermediate **3** followed by the elimination of hydrogen iodide to yield the corresponding benzimidazoles **2** (Scheme 2).

Table 1 Optimisation of solvent effect on the reaction[a]

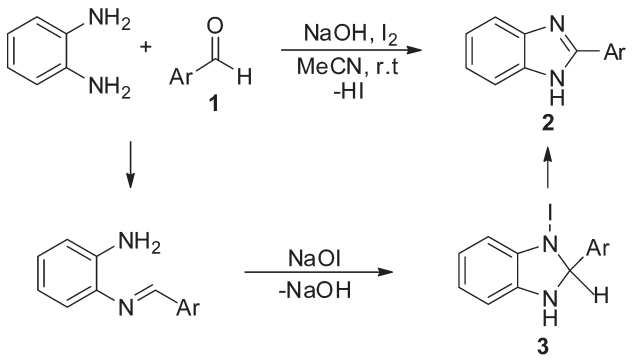
Entry	Solvent	Time/min	Yield/%
1	Acetonitrile	33	93
2	Ethanol	58	39
3	Acetone	45	32
4	Dichloromethane	60	28

[a] Reaction of benzaldehyde with *o*-phenylenediamine in a variety of different solvents.

Table 2 Synthesis of 2-substituted benzimidazoles using NaOH/I_2

Entry	Substrate	Product[a]	Time/min	Yield/%[b]	M.p./°C[Ref.]
1	Ph	**2a**	33	93	289–290[24]
2	3-$MeOC_6H_4$	**2b**	39	94	200–202[25]
3	4-BrC_6H_4	**2c**	38	92	292–293[25]
4	4-ClC_6H_4	**2d**	32	94	290–291[26]
5	2,3-$Cl_2C_6H_3$	**2e**	30	95	224–226[27]
6	2-ClC_6H_4	**2f**	39	90	231–233[28]
7	4-MeC_6H_4	**2g**	45	94	260–261[28]
8	2-HOC_6H_4	**2h**	41	93	238–240[29]
9	4-$O_2NC_6H_4$	**2i**	33	97	307–309[30]
10	4-HOC_6H_4	**2j**	39	93	254–255[31]
11	3-$O_2NC_6H_4$	**2k**	32	95	309–310[32]
12	4-$Me_2NC_6H_4$	**2l**	38	93	293–295[31]
13	4-$MeOC_6H_4$	**2m**	37	95	229–230[31]
14	2,3-$(MeO)_2C_6H_3$	**2n**	42	94	197–198[27]
15	3-HOC_6H_4	**2o**	40	93	245–247[27]
16	2-$O_2NC_6H_4$	**2p**	35	92	212–214[30]

[a] All compounds are known and their physical and spectroscopic data were in good agreement with those of authentic samples.
[b] Yields refer to pure isolated products.



Scheme 2 Proposed mechanism for synthesis of 2-substituted benzimidazole derivatives using the $NaOH/I_2$ system.

The structure of the products has been confirmed by physical and spectroscopic data such as; IR, ^{1}H NMR and ^{13}C NMR. In the ^{1}H NMR spectra, the N-H proton has a chemical shift in the range δ 7.10–15.20. The signals in the region δ 6.84–9.10 are assigned to the aromatic ring protons. In the ^{13}C NMR spectra, the benzimidazole C=N (C-2) carbon has a chemical shift of 148.9–151 ppm.

Conclusions

In this research, we have developed a simple, highly efficient and convenient, one-pot synthetic method for the synthesis of biologically important benzimidazole derivatives by the condensation of *o*-phenylenediamine with aryl aldehydes at room temperature. Features such as; reduced reaction times and high yields make it a useful and attractive strategy for the preparation of various benzimidazole derivatives. The operational simplicity of the procedure is also attractive and offers wide scope in organic synthesis.

Experimental

All the materials were of commercial reagent grade. The aromatic aldehydes, and *o*-phenylenediamine were purified by standard procedures and their purity determined by TLC. IR spectra were recorded as KBr pellets on a Perkin-Elmer 781 spectrophotometer and an Impact 400 Nicolet FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded for DMSO-d_6 solutions on a Bruker DRX-400 spectrometer with tetramethylsilane as internal reference. Melting points were obtained with a Yanagimoto micro melting point apparatus are uncorrected. The purity determination of the substrates and reaction monitoring were accomplished by TLC on silica-gel Polygram SILG/UV 254 plates.

Synthesis of benzimidazoles; general procedure

In a round-bottomed flask (50 mL) equipped with a magnetic stirrer, a solution of *o*-phenylenediamine (1.0 mmol), and an aryl aldehyde (1.0 mmol) in MeCN (4 mL) was prepared. NaOH (5.0 mmol) and solid I_2 (2.0 mmol) were added and the mixture was stirred at room temperature for the time indicated in Table 1. The progress of the reaction was monitored by TLC (eluent: ether–EtOAc, 7:3). When the starting materials had completely disappeared, the mixture was quenched with H_2O (14 mL), extracted with CH_2Cl_2 (4 × 10 mL), and the combined extracts were dried over $MgSO_4$. The filtrate was evaporated and the corresponding benzimidazole was obtained as the only product (Table 1). Finally, the structure of the product was identified and characterised by spectroscopic and physical data.

2-(4-Methylphenyl)benzimidazole (**2g**): White solid; m.p. 260–261 °C, (lit.[28] 261–263 °C); IR (KBr); ν_{max}/cm^{-1}; 3429 (NH), 1620 (C=N), 1587, 1433 (C = C, Ar); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.36 (3, s, Me) 7.18 (2H, m, ArH), 7.34 (2H, d, ArH, *J* = 8.0 Hz), 7.57 (2H, m, ArH), 8.06 (2H, d, ArH, *J* = 8.0 Hz), 12.80 (1H, s, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 21.4, 115.5, 122.4, 125.9, 127.9, 130, 139, 140.0, 151.9.

2-(4-Dimethylaminophenyl)benzimidazole (**2l**): Yellow solid; m.p. 293–295 °C (lit.[31] 294.2–296.3 °C); IR (KBr); ν_{max}/cm^{-1}; 3391 (NH), 1605 (C=N), 1518, 1459 (C = C, Ar); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.84 (2H, d, ArH, *J* = 7.8Hz), 7.43 (2H, m, ArH), 7.70 (2H, m, ArH), 8.21 (2H, d, ArH, *J* = 7.8 Hz), 15.20 (1H, s, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 39.5, 107.8, 111.8, 113.2, 125.1, 129.1, 131.5, 149.8, 153.2.

Electronic Supplementary Information

IR and ^{1}H NMR spectra of the compounds listed in Table 1 are provided as electronic supplementary information available through stl.publisher.ingentaconnect.com/content/stl/jcr/suppdata.

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