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H_2O_2/HCl as a new and efficient system for synthesis of 2-substituted benzimidazoles

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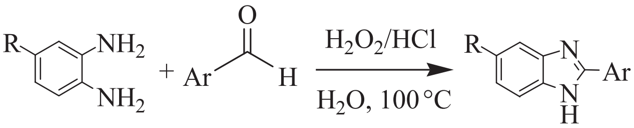
The system, H_2O_2/HCl, oxidises carbon–nitrogen bonds for the synthesis of benzimidazoles from aldehydes and diamines in water at 100°C. Both aryl aldehydes bearing electron-donating and electron-withdrawing substituents afforded desired benzimidazoles in excellent yields. This procedure is also applicable to substituted *o*-phenylenediamines, which produced 2-phenylbenzimidazoles smoothly in excellent yields. The simplicity of the system, the use of water as the solvent, large-scale synthesis and easy work-up are main advantages of this procedure.

Key words: *o*-phenylenediamines, benzimidazoles, aryl aldehydes, hydrogen peroxide

The goal in present day organic synthesis is to perform organic reactions in aqueous medium because of the environmentally benign nature of the solvent.[1] Despite their importance from pharmacological, industrial, and synthetic point of views, comparatively few methods for the preparation of benzimidazoles have been reported. These include the condensation of *o*-aryldiamines and aldehyde using air as the oxidant,[2] the condensation of *o*-aryldiamines with carboxylic acids or their derivatives in the presence of strong acids such as polyphosphoric acid[3] or mineral acids,[4] PS–PPh_3/CCl_3CN[5] and thermal or acid promoted cyclisation of *N*-(*N*-arylbenzimidoyl)-1,4-benzoquinoneimines.[6] However, a number of these methods have some drawbacks such as drastic reaction conditions, long reaction times, tedious work-up procedures, low yields, and co-occurrence of several side reactions. As a consequence, the introduction of new methods and/or further work on technical improvements to overcome the limitations is still an important experimental challenge.

A recent report by Neumann *et al.*[7] on the use of a combination of hydrogen peroxide and hydrohalic acid as a green halogenating agent for arenes inspired us to explore the potential of this system for the synthesis of 2-substituted benzimidazoles by the condensation of *o*-phenylenediamine with aryl aldehydes. We now report a new and efficient method for the synthesis of 2-substituted benzimidazoles by the condensation of *o*-phenylenediamine with aryl aldehydes using aqueous HCl and H_2O_2 as green oxidant system in water at 100°C. The route for the synthesis of 2-substituted benzimidazoles is shown in Scheme 1.



Scheme 1

The applicability of the H_2O_2/HCl system was then examined for the synthesis of 2-substituted benzimidazoles in water at 100°C. To increase the reaction yield in water, LiCl was added in order to increase the dielectric constant of the medium.[8]

A ratio of 1 : 1 : 7 : 3.5 *o*-phenylenediamine/aryl aldehyde/ H_2O_2/HCl was found to be optimum for the coupling of aryl aldehydes and *o*-phenylenediamines and the results are presented in Table 1. As shown, both aldehydes bearing electron-donating (entries 2–5) and electron-withdrawing (entries 6–8) substituents afforded desired benzimidazoles in excellent yields. This procedure is also applicable to substituted *o*-phenylenediamines, which produced 2-phenylbenzimidazoles smoothly in excellent yields. Finally, we have extended this synthetic method for the preparation of additional extended bis-benzimidazoles in a 2 : 1 : 7 : 3.5 molar ratio of *o*-phenylenediamine to aryl dialdehyde to H_2O_2 and HCl (Table 1, entries 15, 16).

Table 1 Reaction of aryl aldehydes with *o*-phenylenediamines in the presence of H_2O_2/HCl system in water[a] at 100°C

Entry	R	Ar	Time/h/Yield/%[b, c]	M.p./°C	Lit. m.p./°C
1	H	C_6H_5–	1.8(92)	293	295[9]
2	H	4-$MeOC_6H_4$–	1.6(96)	225	226[10]
3	H	4-MeC_6H_4–	1.7(95)	269	270[10]
4	H	4-$Me_2NC_6H_4$–	1.6(93)	229	228–229[11]
5	H	2-HOC_6H_4–	1.8(93)	239	242[10]
6	H	4-ClC_6H_4–	1.4(92)	298	301[12]
7	H	4-FC_6H_4–	1.8(93)	250	247–248[13]
8	H	3-$NO_2C_6H_4$–	1.9(90)	205-207	207–208[14]
9	Me	C_6H_5–	1.8(95)	240	240–241[15]
10	Me	4-$MeOC_6H_4$–	1.6(95)	165	169[16]
11	Me	4-MeC_6H_4–	1.6(94)	188	190–191[17]
12	Me	4-ClC_6H_4–	1.5(93)	222	224[9]
13	NO_2	4-ClC_6H_4–	2.0(90)	303	305–308[17]
14	NO_2	C_6H_5–	1.9(90)	208	207–208[17]
15	Me	4-$OHCC_6H_4$–	2.5(85)	175	176–178[18]
16	NO_2	4-$OHCC_6H_4$–	2.9(85)	>300	>300[19]

[a] Reactions were performed in 1M aqueous LiCl.

[b] The products were characterised by comparison of their spectroscopic and physical data with authentic samples synthesised by reported procedures.

[c] Yields refer to pure isolated products.

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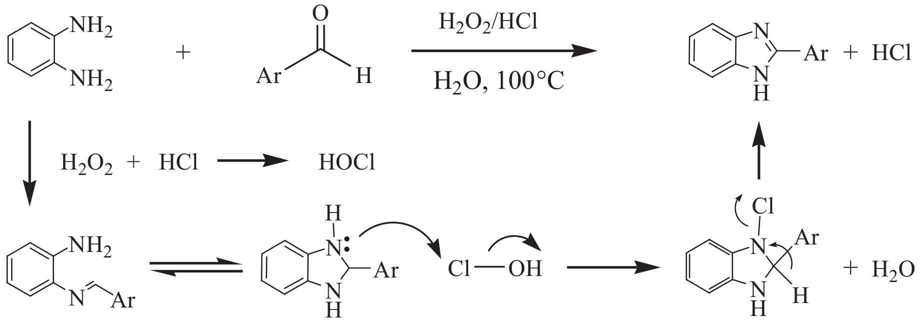

1 2

Scheme 2 Possible mechanism and tentative intermediates in the synthesis of benzimidazoles

To access the feasibility of applying this method in a preparative scale, we carried out the coupling of 4-methyl-*o*-phenylenediamine with benzaldehyde in 50 mmol scale. As expected, the reaction proceeded smoothly, similar to the case in a smaller scale (entry 9, Table 1), and the desired 2-phenyl-5-methylbenzimidazole was obtained in 96% isolated yield.

Regarding the mechanism of the oxidation step, the reaction probably involves the formation of hypochlorous acid by the reaction of aqueous hydrogen peroxide with hydrochloric acid,[7] which then reacts with the cyclic hydrobenzimidazoles **1** to afford intermediate **2** followed by the elimination of hydrogen chloride to yield the corresponding benzimidazoles (Scheme 2).

In conclusion, we have developed a new and efficient method for the synthesis of 2-substituted benzimidazoles and bis-benzimidazoles. The use of water as the solvent, large scale synthesis, easy work-up and excellent yields are main advantages of this procedure which make the H_2O_2/HCl system an attractive, metal-free, synthetic tool to the present methodologies.

Experimental

All chemicals were purchased from Merck chemical company and used without further purification. All of the products were characterised by comparison of their spectral and physical data with those of authentic samples. Yields refer to isolated products.

General experimental procedure for synthesis of benzimidazoles

In a round-bottomed flask (50 ml) equipped with a magnetic stirrer, a solution of *o*-phenylenediamine (1 mmol), aryl adehyde (1 mmol) and 0.02 g of LiCl in H_2O (5 ml) were prepared. 30% H_2O_2 (7 mmol) and 37% HCl (3.5 mmol) were added and the mixture was stirred at 100°C for the time indicated in Table 1. The progress of the reaction was monitored by TLC (eluent: *n*-hexane/ethyl acetate: 7/3). The reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 × 10 ml). The extract dried with anhydrous $MgSO_4$. The filtrate was evaporated and the resulting crude material was purified by column chromatography on silica gel to afford the pure benzimidazole in 85–96% yields (Table 1). An identical procedure was employed using *o*-phenylenediamine (2 mmol), terephthalaldehyde (134.1 mg, 1 mmol) in the presence of 30% H_2O_2 (7 mmol) and 37% HCl (3.5 mmol) for the synthesis of bis-benzimidazoles (Table 1).

Selected characterisation data

2-Phenyl-1H-benzimidazole (Table 1, entry 1): IR (KBr): 3248, 1683, 1648, 1580, 1523, 1302 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-*d6*): δ = 7.54 (m, 2H), 7,75 (m, 3H), 7.85 (m, 2H), 8.3 (m, 2H). ^{13}C NMR (50 MHz, DMSO-*d6*): δ = 114.2, 123.9, 125.7, 128, 129.8, 132.5, 133, 149.5.

2-(4-N,N-dimethylaminopheyl)-1H-benzimidazole (Table 1, entry 4): IR (KBr): 3380, 1618, 1590,, 1484, 1456, 1420 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-*d6*): δ = 3.1 (s, 3H), 6.9 (d, 2H, *J* = 9.2 Hz), 7.5 (m, 2H), 7.2 (m, 2H), 8.06 (d, 2H, *J* = 9.2 Hz). ^{13}C NMR (50 MHz, DMSO-*d6*): δ = 39.5, 107.8, 111.8, 113.2, 125.1, 129.1, 131.5, 149.8, 153.2.

5-Methyl-2-phenyl-1H-benzimidazole (Table 1, entry 9): IR (KBr): 3376, 1619, 1596, 1488, 1456, 1356, 1340 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-*d6*): δ = 2.5 (s, 3H), 7.4 (m, 1H), 7.6 (s, 1H), 7.75 (m, 4H), 8.25 (m, 2H). ^{13}C NMR (50 MHz, DMSO-*d6*): δ = 21.2, 113.4, 113.7, 123.5, 127.4, 127.8, 129.6, 130.3, 132.4, 133, 134, 148.7.

2,2'-Phenylenebis(5-nitro-1H-benzimidazole) (Table 1, entry 16): IR (KBr): 3250, 1630, 1513, 1342 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-*d6*, TFA) δ = 8.45 (s, 2H), 8.2 (d, *J* = 8.4 Hz, 2H), 8.1 (m, 2H), 7.9 (m, 2H), 7.7 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (50 MHz, DMSO-*d6*, TFA) δ = 150.8, 111.4, 135.7, 122.1, 115.5; 146.5, 131.8, 122.6, 133.4, 134.6.

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