Research Article

Highly Efficient and Facile Method for Synthesis of 2-Substituted Benzimidazoles via Reductive Cyclization of *O*-Nitroaniline and Aryl Aldehydes

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A versatile and convenient synthesis of 2-substituted benzimidazoles, using *o*-nitroaniline as starting material with several aryl aldehydes, has been accomplished by using a small amount of a reluctant agent. The reaction was carried out under very mild conditions at room temperature. The yields obtained are very good in reasonably short reaction times.

1. Introduction

Benzimidazoles are very useful intermediates/subunits for the development of molecules of pharmaceutical or biological interest. Substituted benzimidazole derivatives have found applications in diverse therapeutic areas including antihypertensives, antivirals, antifungals, anticancers, and antihistaminics [1]. There are two general methods for the synthesis of 2-substituted benzimidazole. One is coupling of *o*-phenylenediamines and carboxylic acids [2] or their derivatives (nitriles, imidates, or orthoesters) [3], which often require strong acidic conditions, and sometimes combine with very high temperature or the use of microwave irradiation [4]. The other way involves a two-step procedure that is oxidative cyclodehydrogenation of aniline schiff's bases, which are often generated in situ from the condensation of *o*-phenylenediamines and aldehydes. Various oxidative reagents such as tetracyano ethylene [5], nitrobenzene [6], 1,4-benzoquinone [7], DDQ [8], benzofuroxan [9], NaHSO₃ [10], MnO₂ [11], oxone [12], DMP [13], Pb(OAc)₄ [14], and NH₄VO₃ [15] have been employed. However, all of these methods have problems, including drastic reaction conditions, expensive catalyst, low yields, and severe

side-reactions. Therefore, the development of a cost-effective, safe, and inexpensive reagent system is desirable.

In this research, we report a one-pot, high-yield, facile, and inexpensive synthesis of 2-substituted benzimidazoles directly from *o*-nitroanilines and aryl aldehydes via reductive condensation of *o*-nitroanilines at room temperature under mild conditions.

2. Experimental Section

2.1. Materials. All the materials were of commercial reagent grade. The aromatic aldehydes and *o*-nitroaniline were purified by standard procedures and purity determined by thin layer chromatography (TLC).

2.2. Apparatus. IR spectra were recorded as KBr pellets on a Perkin-Elmer 781 spectrophotometer and an Impact 400 Nicolet FT-IR spectrophotometer. ¹H NMR and ¹³C NMR were recorded in DMSO solvent on a Bruker DRX-400 spectrometer with tetramethylsilane as internal reference. Melting points obtained with a Yanagimoto micromelting 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 (from Merck Company).

2.3. General Experimental Procedure for the Tandem Reaction.

This procedure was used for the synthesis of most of the compounds listed in Table 1. A solution of *o*-nitroaniline (0.138 g, 1.0 mmol) and aryl aldehyde (1.0 mmol) in EtOH (4 mL) was prepared. Then 1 M aq Na₂S₂O₄ (0.522 gr, 3.0 mmol) was 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. After completion of the reaction, the resulting solution was poured into ice-water mixture and filtered off, washed with cold water, the crude product was obtained as a solid. The solid product was recrystallized from methanol, and the pure 2-substituted benzimidazole was yielded. The corresponding products were identified by physical and spectroscopic data.

2-Phenyl-benzimidazole (2a) (C₁₃H₁₀N₂). Pale yellow solid; m.p = 289–290°C (m.p = 288–290°C) [16]; IR (KBr)/ν (cm⁻¹) 3446 (NH), 1622 (C=N), 1590, 1445 (C=C, Ar); ¹H NMR (DMSO, 400 MHz)/δ ppm: 7.19 (2H, m, Ar), 7.48–7.64 (5H, m, Ar), 8.17 (2H, m, Ar), 12.9 (1H, s, NH); ¹³C NMR (100 MHz, DMSO)/δ ppm: 111.1, 118.6, 121.9, 126.2, 128.6, 129.5, 130.0, 134.8, 143.5, 151.0; MS: *m/z*: 193 (M–H, 100%).

2-(2,3-Dichlorophenyl)-benzimidazole (2b) (C₁₃H₈Cl₂N₂). Yellow solid; m.p = 224–226°C [17]; IR (KBr)/ν (cm⁻¹) 3095 (NH), 1624 (C=N), 1540, 1433 (C=C, Ar); ¹H NMR (DMSO, 400 MHz)/δ ppm: 7.2 (2H, m, Ar), 7.53 (1H, m, Ar), 7.64 (2H, m, Ar), 7.82 (2H, m, Ar), 12.8 (1H, s, NH); ¹³C NMR (100 MHz, DMSO)/δ ppm: 115.93, 122.90, 128.91, 130.53, 131.27, 132.12, 132.89, 133.23, 139.30, 149.08.

2-(4-Methylphenyl)-benzimidazole (2c) (C₁₄H₁₂N₂). White solid; m.p = 260–261°C, (m.p = 261–263°C) [18]; IR (KBr)/ν (cm⁻¹) 3429 (NH), 1620 (C=N), 1587, 1433 (C=C, Ar); ¹H NMR (DMSO, 400 MHz)/δ ppm: 2.36 (3, s, Me) 7.18 (2H, m, Ar, *J* = 3.2 Hz), 7.34 (2H, d, Ar, *J* = 8 Hz), 7.57 (2H, m, Ar, *J* = 3.2 Hz), 8.06 (2H, d, Ar, *J* = 8 Hz), 12.8 (1H, s, NH); ¹³C NMR (100 MHz, DMSO)/δ ppm: 21.41, 115.50, 122.43, 125.89, 127.93, 129.97, 139, 140.03, 151.90.

2-(4-Bromophenyl)-benzimidazole (2d) (C₁₃H₉BrN₂). Pale yellow solid; m.p = 292–293°C (m.p = 250–252°C) [19]; IR (KBr)/ν (cm⁻¹) 3449 (NH), 1628 (C=N), 1598, 1456 (C=C, Ar); ¹H NMR (DMSO, 400 MHz)/δ ppm: 7.53 (2H, m, Ar, *J* = 8.2 Hz), 7.83 (2H, m, Ar, *J* = 8.2 Hz), 7.95 (2H, d, Ar, *J* = 4.8 Hz), 8.28 (2H, d, Ar, *J* = 4.8 Hz); ¹³C NMR (100 MHz, DMSO)/δ ppm: 102.5, 121.5, 141.6, 127, 128.1, 130.4, 138.2, 150.2.

2-(2-Chlorophenyl)-benzimidazole (2e) (C₁₃H₉ClN₂). Yellow solid; m.p = 231–233°C, (m.p = 232–234°C) [18]; IR (KBr)/ν (cm⁻¹) 3444 (NH), 1591 (C=N), 1575, 1440 (C=C, Ar); ¹H NMR (DMSO, 400 MHz)/δ ppm: 7.2 (2H, m, Ar), 7.50–7.89 (6H, m, Ar), 12.9 (1H, s, NH); ¹³C NMR

(100 MHz, DMSO)/δ ppm: 116.02, 122.72, 127.87, 130.40, 130.80, 131.64, 132.16, 132.54, 139.50, 149.64; MS: *m/z*: 228.5 (M+).

2-(4-Chlorophenyl)-benzimidazole (2f) (C₁₃H₉ClN₂). Yellow solid; m.p = 290–291°C, (m.p = 291–293°C) [20]; IR (KBr)/ν (cm⁻¹) 3442 (NH), 1598 (C=N), 1580, 1429 (C=C, Ar); ¹H NMR (DMSO, 400 MHz)/δ ppm: 7.2 (2H, m, Ar), 7.50–7.89 (6H, m, Ar), 13 (1H, s, NH); ¹³C NMR (100 MHz, DMSO)/δ ppm: 113.5, 123.7, 127.6, 128.3, 129.4, 133.4, 138.9, 151.8; MS: *m/z*: 229.0 (M + H)+.

2-(2-Hydroxyphenyl)-benzimidazole (2g) (C₁₃H₁₀N₂O). White solid; m.p = 238–240°C (m.p = 240–242°C) [21]; IR (KBr)/ν (cm⁻¹) 3325 (OH), 3055 (NH), 1593 (C=N), 1530, 1491 (C=C, Ar); ¹H NMR (DMSO, 400 MHz)/δ ppm: 6.99–7.05 (2H, m, Ar, *J* = 8 Hz), 7.27 (2H, m, Ar, *J* = 8 Hz), 7.37 (1H, t, Ar), 7.66 (2H, m, Ar), 8.06 (1H, d, Ar), 13.19 (1H, s, OH), 13.19 (1H, s, NH); ¹³C NMR (100 MHz, DMSO)/δ ppm: 112.10, 113.11, 117.67, 119.56, 123.26, 126.68, 132.16, 141.21, 152.22, 158.56; MS: *m/z*: 210 (M+).

2-(3-Hydroxyphenyl)-benzimidazole (2h) (C₁₃H₁₀N₂O). Yellow solid; m.p = 245–247°C [17]; IR (KBr)/ν (cm⁻¹) 3434 (OH), 3243 (NH), 1588 (C=N), 1541, 1445 (C=C, Ar); ¹H NMR (DMSO, 400 MHz)/δ ppm: 6.9 (1H, d, Ar), 7.18 (2H, m, Ar), 7.33 (1H, t, Ar), 7.59 (4H, d, Ar), 12.9 (1H, s, NH); ¹³C NMR (DMSO, 100 MHz)/δ ppm: 113.93, 115.55, 117.55, 117.80, 122.59, 130.51, 131.86, 139.87, 151.93, 158.30.

2-(4-Hydroxyphenyl)-benzimidazole (2i) (C₁₃H₁₀N₂O). White solid; m.p = 254–255°C (m.p = 254.1–256.6°C) [22]; IR (KBr)/ν (cm⁻¹) 3383 (OH), 3202 (NH), 1668 (C=N), 1600, 1457 (C=C, Ar); ¹H NMR (DMSO, 400 MHz)/δ ppm: 6.91–7.50 (4H, m, Ar), 7.73–8.21 (4H, m, Ar), 9.7 (1H, s, OH), 15.2 (1H, s, NH); ¹³C NMR (100 MHz, DMSO)/δ ppm: 113.06, 114.04, 116.83, 126.03, 131.62, 132, 149.93, 160.71.

2-(3-Methoxyphenyl)-benzimidazole (2j) (C₁₄H₁₂N₂O). Yellow solid; m.p = 200–202°C (m.p = 205–206°C) [19]; IR (KBr)/ν (cm⁻¹) 3437 (NH), 1596 (C=N), 1541, 1464 (C=C, Ar); ¹H NMR (DMSO, 400 MHz)/δ ppm: 3.9 (3H, s, Me), 7.05 (1H, m, Ar), 7.19 (2H, m, Ar), 7.45 (1H, s, Ar), 7.59 (2H, m, Ar, *J* = 8 Hz), 7.74 (2H, m, Ar, *J* = 8 Hz), 12.9 (1H, s, NH); ¹³C NMR (100 MHz, DMSO)/δ ppm: 56.01, 114.03, 115.25, 116.50, 117.80, 124.49, 130.47, 132.63, 138.99, 152.23, 159.10.

2-(2,5-Dimethoxyphenyl)-benzimidazole (2k) (C₁₅H₁₄N₂O₂). Yellow solid; m.p. 197–198°C [17]; IR (KBr)/ν (cm⁻¹) 3408 (NH), 1622 (C=N), 1511, 1458 (C=C, Ar); ¹H NMR (DMSO, 400 MHz)/δ ppm: 4.02 (3H, s, Me), 3.85 (3H, s, Me) 7.33 (2H, d, Ar), 7.55 (2H, m, Ar), 7.89 (2H, m, Ar), 8.02 (1H, s, Ar), 15 (1H, s, NH); ¹³C NMR (DMSO, 100 MHz)/δ ppm: 56.69, 57.05, 11.24, 114.41, 114.55, 114.65, 122.19, 126.30, 131.68, 146.07, 152.58, 153.72.

TABLE 1: Reaction of various aryl aldehydes with *o*-nitroaniline.

Entry	Substrate Ar	Product ^a	Time (hour)	Yield (%) ^b
1		2a	2	95
2		2b	1.8	95
3		2c	2	94
4		2d	1.8	92
5		2e	2.2	91
6		2f	1.5	94
7		2g	1.8	90
8		2h	1.7	93
9		2i	1.8	91
10		2j	1.6	92
11		2k	1.2	94
12		2l	1.9	91
13		2m	1.7	92

^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.

2-(4-Methoxyphenyl)-benzimidazole (**2l**) (C₁₄H₁₂N₂O). Yellow solid; m.p = 229–230°C, (m.p = 229.2–231.1°C) [22]; IR (KBr)/ν (cm⁻¹) 3344 (NH), 1608 (C=N), 1506, 1461 (C=C, Ar); ¹H NMR (DMSO, 400 MHz)/δ ppm: 3.89 (3H, s, Me), 7.2 (2H, d, Ar, *J* = 8 Hz), 7.52 (2H, m, Ar, *J* = 4 Hz), 7.79 (2H, m, Ar, *J* = 4 Hz), 8.38 (2H, d, Ar, *J* = 8 Hz), 15.3 (1H,

s, NH); ¹³C NMR (DMSO, 100 MHz)/δ ppm: 56.24, 114.06, 115.34, 115.53, 126.03, 130.62, 132, 148.91, 163.61.

2-(*N,N*-Dimethylphenyl)-benzimidazole (**2m**) (C₁₅H₁₅N₃). Yellow solid; m.p = 277–279°C (m.p = 294.2–296.3°C) [22]; IR (KBr)/ν (cm⁻¹) 3391 (NH), 1605 (C=N), 1518, 1459

SCHEME 1: Synthesis of 2-substituted benzimidazoles from *o*-nitroanilines and aryl aldehydes via an in situ nitro reduction.

SCHEME 2: Possible mechanism and tentative intermediates in the synthesis of benzimidazoles.

(C=C, Ar); ¹H NMR (DMSO, 400 MHz)/ δ ppm: 6.84 (2H, d, Ar, J = 7.8 Hz), 7.43 (2H, m, Ar, J = 4 Hz), 7.70 (2H, m, Ar, J = 4 Hz), 8.21 (2H, d, Ar, J = 7.8 Hz), 15.2 (1H, s, NH); ¹³C NMR (DMSO, 100 MHz)/ δ ppm: 39.5, 107.8, 111.8, 113.2, 125.1, 129.1, 131.5, 149.8, 153.2.

3. Results and Discussion

In order to synthesis of 2-substituted benzimidazoles, *o*-nitroanilines and aryl aldehydes were reacted together in mole ratio 1 : 1 in the presence of sodium dithionite at room temperature (Scheme 1). In this reaction, the corresponding benzimidazoles were obtained as benefit and significant products.

We have studied the different reaction conditions on model reaction. The results revealed that, when the reaction was carried out at room temperature, it has got the excellent yields of product in short reaction times. We hypothesized that the formation of the 2-substituted benzimidazoles could be achieved by two mechanisms (Scheme 2).

In order to test our initial hypothesis postulating a rather controlled aryl nitro reduction during the reductive cyclization step and in order to explain the observed reaction outcome, it was attempted some comparison experiments with two different routes which have been widely used in the aryl nitro group reduction. When the reaction between *o*-nitroaniline and 4-methylbenzaldehyde was conducted, the desired monosubstituted benzimidazole was generated as the sole product in high yield. On the contrary, when the same reaction was subjected to the Na₂S₂O₄ conditions, a mixture of monosubstituted and 1,2-disubstituted benzimidazoles

was formed with the disubstituted analog as the major component.

In order to ascertain the limitation of the reaction, the reaction of *o*-nitro aniline with several aryl aldehydes in the presence of sodium dithionite was occurred. The obtained results are indicated in Table 1. As can be seen in this table, the reaction with all aryl aldehydes, the 2-substituted benzimidazoles were obtained in excellent yields as only product and short reaction times. It seems that the order of addition of substrates together influenced on the quality and yield of the reaction product.

The structure of products has been confirmed by physical and spectroscopic data such as IR, ¹H NMR, and ¹³C NMR. In the IR spectra, the stretching frequency of aromatic C=C is formed in the region between ν = 1429–1600 cm⁻¹. The stretching vibration of C–H in the alkyl groups appeared at region between ν = 2903–3059 cm⁻¹. In the ¹H NMR spectra, one proton of N–H has chemical shift in δ = 12.72–15.2 ppm. The signals around δ = 6.84–8.38 are assigned by protons of CH=CH of aromatic rings. In the ¹³C NMR spectra, the carbon of C=N has chemical shift in δ = 148.9–151 ppm.

4. Conclusion

In this study, we have developed an efficient method for the synthesis of benzimidazoles and other derivatives. Using of Na₂S₂O₄ as a highly efficient, inexpensive, easy handling, and nontoxic reducing reagent makes the present procedure ecofriendly and economically acceptable. Furthermore, high yields of products, short reaction times, mild reaction

conditions, and easy workup are other noteworthy advantages which make this method a valid contribution to the existing methodologies.

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