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New strategy for the synthesis of 2-phenylbenzimidazole derivatives with sodium perborate (SPB) as oxidant

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ABSTRACT

A novel strategy for the synthesis of 2-phenylbenzimidazoles with sodium perborate (SPB) as oxidant under mild reaction condition is developed. Excellent chemoselectivity and broad substrate tolerance are the main advantages of this route.

1. Introduction

Benzimidazole units are ubiquitous structural motifs of many pharmaceutically active compounds and exist in a diverse array of therapeutic agents.[1] Selective examples including antiulcers[2] (H^+/K^+-ATPase inhibitors), antihypertensives[3] (AT1 inhibitors), antivirals[4] (virus inhibitors), anticancers[5] (Topo I inhibitors) and antihistaminics[6] (Histamine inhibitors) (Fig. 1). Therefore, facile synthesis of benzimidazoles has gained more and more attentions in recent years, even though the synthesis of benzimidazole has been systematically studied and developed.[7]

Two classical methods are routinely employed to synthesize benzimidazoles. One is through condensation between 1,2-phenylenediamine and carboxylic acid, which usually requires concentrated sulfuric acid, polyphosphoric acid, and high temperature, even with the assistance of microwave irradiation.[8] The other is a two-step sequence involving an initial condensation between 1,2-phenylenediamine and aldehyde followed by an oxidation. Various oxidants have been reported, including nitrobenzene,[9] 1,4-benzoquinone,[10] tetracyanoethylene,[11] benzofuroxan,[12] MnO_2,[13] $Pb(OAc)_4$,[14] Oxone®,[15] aerial oxygen,[16] 2,3-dichloro-5,6-dicyano-benzoquinone (DDQ),[17] (diacetoxyiodo)benzene (IBD),[18] $(NH_4)_2S_2O_8$,[19] and H_2O_2.[20] Although these methods are quite satisfactory, most of them have suffered from certain limitations, like expensive reagents (such as tetracyanoethylene, DDQ and IBD), lengthy reaction time (most organic oxidants and aerial oxygen need hours to complete this reaction), laborious workup and purifications. Heavy metal by-products from oxidant are a serious environmental concern as well.

The synthesis of 2-substituted benzimidazoles generally requires the same equivalent amount of substrates. Unfortunately, even under this condition, many methodologies would generate 1,2-disubstituted benzimidazoles as a byproduct.[21] 1,2-Disubstituted benzimidazoles can be achieved by the N-alkylation of 2-substituted benzimidazoles, which make the diversity of benzimidazoles.[22] And during our research, the results of the 2-(4-chlorophenyl)-6-nitro-1*H*-benzimidazole, which was synthesized from 4-nitro-1,2-phenylenediamine and *p*-chlorobenzaldehyde with the mentioned oxidants and methods, were of dissatisfaction. The strong electron withdrawing substituents on the *o*-phenylenediamine made this reaction more difficult and complex. So it is of great urgency to develop an excellently chemoselective and widely used method for the broad substrate tolerance.

Meanwhile, the environmentally benign and economical organic synthesis is being vigorously pursued, and most of the above oxidants and methods are away from this proposal. But few progresses have been made in this field.[19,20] For the characteristics

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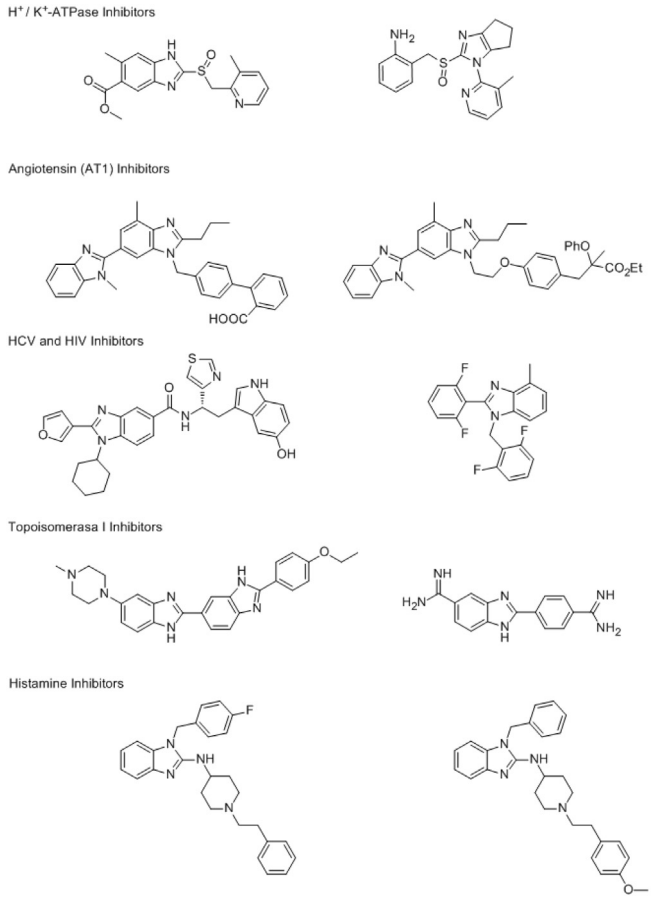
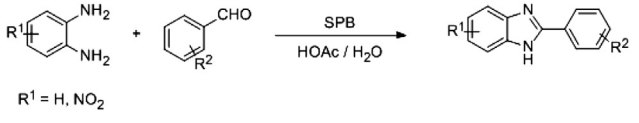


Fig. 1. Biologically active molecules with benzimidazole units.

of inorganic oxides, there is still room for further improvement depending on the safety and efficiency. An inorganic oxide with desired requirements would make a remarkable contribution to the synthesis of benzimidazole.

Hydrogen peroxide is a cheap and environmentally friendly oxidant.[23] However, the use, storage, and transportation of its concentrated solution are hazardous for large-scale uses. Here, we reported a new mild method for the synthesis of 2-(4-chlorophenyl)-6-nitro-1*H*-benzimidazole (compound **1a**) with sodium perborate (SPB) as oxidant. Sodium perborate (SPB) is a commercial detergent additive in chemical industry.[24] At a lower pH value, SPB generates hydrogen peroxide gradually, which carries out the oxidation smoothly. The other advantage of SPB is to generate nontoxic boric acid and water after reaction, which also simplifies the purification. This reagent has been applied for many organic syntheses,[25] such as amides from nitriles,[26] esters from cyclic acetals,[27] and so on. But for the synthesis of benzimidazoles, it has not been reported up to now. Therefore, SPB was selected as an oxidant to synthesize benzimidazoles from phenyl aldehydes and substituted *o*-phenylenediamines in this work (Scheme 1). HOAc was selected as the solvent due to the requirement of an acid to activate SPB.[28] In the control reaction, SPB showed excellent chemoselectivity in synthesis of 2-phenylbenzimidazoles, and the workup of reaction remained convenient. It is believed that SPB has remarkable advantages in this reaction.



Scheme 1. Route for the synthesis of benzimidazole derivatives by using SPB as oxidant.

2. Results and discussion

The experimental conditions were optimized as follows: first, the stoichiometry of SPB needs to be identified on the basis of our initial results. Therefore, the model reaction of condensing 4-nitro-1,2-phenylenediamine and *p*-chlorobenzaldehyde was conducted in HOAc at 50 °C in the presence of various amounts of SPB. The screening results of the reaction were summarized in Table 1, which showed that the yield (up to 93%) was achieved by using 1.1 equiv of SPB. Once the amount of SPB was less or higher than 1.1 equiv, the reaction would give the intermediate Schiff bases or some unidentified by-products.

Table 1
Optimization of the equivalent of SPB for synthesis of 2-phenylbenzimidazole derivatives[a]

Entry	Equivalents of SPB	Yield (%)[b]
1	0.5	54
2	0.8	89
3	1.0	91
4	1.1	93
5	1.2	84
6	1.5	56
7	2.0	57

[a] All reactions were carried out with 1.0 equiv of two substrates and the presence of different equivalents of SPB in HOAc (3 mL) at 50 °C for 8 h.
[b] Isolated yields.

Next, the reaction temperature was optimized. Table 2 implied that the yield was dramatically improved when the temperature increased from 20 °C to 50 °C. However, when the temperature was higher than 50 °C, the yield decreased sharply.

Table 2
The effect of reaction temperature on this reaction[a]

Entry	Reaction temperature (°C)	Reaction time (h)[c]	Yield (%)[b]
1	20	Overnight	Trace
2	30	2	39
3	40	1.5	73
4	50	1	92
5	60	0.7	62
6	80	1	Trace

[a] All reactions were carried out with 1.0 equiv of two substrates and 1.1 equiv of SPB in HOAc (3 mL).
[b] Isolated yields.
[c] The reaction was monitored by TLC (eluent: 2/1, v/v, *n*-hexane/ethyl acetate).

As SPB didn't dissolve in HOAc well, HOAc/H_2O mixture was tried as solvent and different ratios of HOAc with H_2O were tested. The results showed that a mixture of H_2O/HOAc=1/2 (v/v) was the most effective solvent system (Table 3) based on the comparison of reaction time.

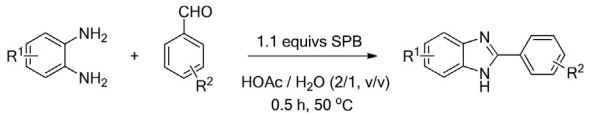
Table 3
The different ratio of H_2O and HOAc as a solvent[a]

Entry	Solvent	Time (h)[c]	Yield (%)[b]
1	3 mL HOAc	1	93
2	2 mL HOAc+1 mL H_2O	0.5	93
3	1 mL HOAc+2 mL H_2O	2	76
4	3 mL H_2O	2	Trace

[a] All reactions were carried out with 1.0 equiv of two substrates and 1.1 equiv of SPB at 50 °C.
[b] Isolated yields.
[c] The reaction was monitored by TLC (eluent: 2/1, v/v, *n*-hexane/ethyl acetate).

Then the scopes and limitations of this protocol were investigated starting from *o*-phenylenediamine bearing 4-nitro-, 3-nitro- and itself, reacted with phenyl aldehydes (Table 4) using the optimized reaction condition.

Table 4
The reactions between substituted *o*-phenylenediamine and phenyl aldehydes[a]

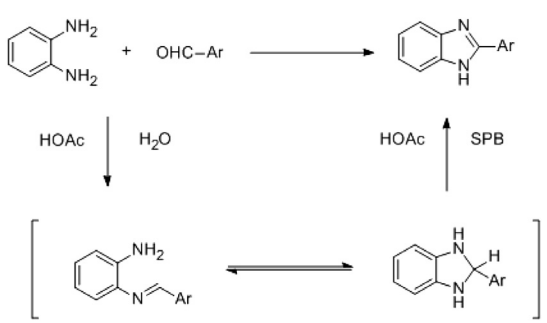


Entry	R^1	R^2	Yield (%)[b]	Compound
1	4-Nitro	4-Nitro	90	**1b**
2	4-Nitro	2-Nitro	92	**1c**
3	4-Nitro	3-Nitro	90	**1d**
4	4-Nitro	4-Methoxy	93	**1e**
5	4-Nitro	3-Methoxy	90	**1f**
6	4-Nitro	3,4-Dimethoxy	92	**1g**
7	4-Nitro	2-Hydroxy	92	**1h**
8	H	4-Nitro	95	**2a**
9	H	2-Nitro	96	**2b**
10	H	3-Nitro	95	**2c**
11	3-Nitro	2-Hydroxy	98	**3a**
12	3-Nitro	2,6-Dimethyl	99	**3b**
13	3-Nitro	4-Dimethylamino	95	**3c**
14	3-Nitro	3,4-Dimethoxy	95	**3d**

[a] All reactions were carried out with 1.0 equiv of two substrates and 1.1 equiv of SPB in H_2O/HOAc=1:2 (v/v, 3 mL) at 50 °C for 0.5 h.
[b] Isolated yields. Characterized by ^{1}H NMR, ESI-MS.

Compared the results of compounds **1b** with **2a**, **1c** with **2b**, and **1d** with **2c**, it seems that the yield was reduced slightly by the introduction of strong electron withdrawing 4-nitro group, which decreases the nucleophilicity of *o*-phenylenediamine. From **1b** to **1h**, the substituents on aldehyde moiety had little influence on the reaction either electron withdrawing groups or electron donating groups. Comparing **1e** to **1h** with **3a** to **3d**, *m*-nitro- on *o*-phenylenediamine had higher yield than that of *p*-nitro. For **1h** and **3a**, this method could tolerate easily oxidized groups like hydroxyl. The influences of steric hindrance of the substrates were also considered, **3b** was tested and the results were still satisfied. As can be seen, this procedure had great substrate tolerance as the yields were all greater than 90%.

The oxidative capacity of SPB is due to the generation of H_2O_2 with the proceeding of reaction.[28] It was speculated that when diamine interacted with aldehyde, forming the Schiff bases, the generated hydrogen peroxide finished the oxidation of cyclic intermediates (Scheme 2).[20b,c] The advantages of SPB natural properties, such as easy soluble in water, mild reaction condition, nonhazardous, and extremely cheap, made this method match green chemistry requirements. In this work, it makes this reaction excellent chemoselectivity and broad substrate tolerances.



Scheme 2. A possible pathway for the synthesis of 2-phenylbenzimidazoles.

3. Conclusions

A novel strategy of benzimidazole synthesis using sodium perborate (SPB) as oxidant was developed. Mild reaction conditions, convenient synthesis and workup, excellent substrate tolerance were the highlights of this procedure. In addition, low cost and ready availability of reagents, an environmentally benign procedure and good chemoselectivity made this methodology a useful contribution to the existing procedures available for the synthesis of 2-phenylbenzimidazoles.

4. Experimental section

4.1. General experimental details

All chemical reagents and solvent were commercial products without further purification. Thin-layer chromatography (TLC) was performed on silica gel plates. Column chromatography was performed using silica gel (Hailang, Qingdao) 200–300 mesh. ^{1}H and ^{13}C NMR spectra were recorded employing a Bruker AV-400 spectrometer with chemical shifts expressed in parts per million (in DMSO-d_6, Me_4Si as internal standard). Electrospray ionization (ESI) mass spectrometry was performed in a HP 1100 LC-MS spectrometry. Melting points were determined by an X-6 micro-melting point apparatus and were uncorrected.

4.2. General procedure for the synthesis of 2-phenylbenzimidazoles

*4.2.1. Exemplified with 2-(4-chlorophenyl)-6-nitro-1H-benzimidazole (compound **1a**).* The 4-nitro-1,2-phenylenediamine (50.0 mg, 0.30 mmol), *p*-chlorobenzaldehyde (45.9 mg, 0.30 mmol), and SPB (55.3 mg, 0.33 mmol) were added to a solution of H_2O/HOAc=1:2 (v/v, 3 mL) at 50 °C for 0.5 h (Table 3). The progress of the reaction was monitored by TLC (eluent: 2/1, v/v, *n*-hexane/ethyl acetate). After completion of the reaction, the solution was poured into a beaker containing 20 mL of water. Many solid precipitated. It was filtered, washed with water (10 mL×2), and then purified by quick column chromatography (eluent: 4/1, v/v, *n*-hexane/ethyl acetate). Yellow solid; yield: 83.1 mg, 93%; mp 304.7–304.9 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.67 (d, J=8.0 Hz, 2H), 7.75 (d, J=8.8 Hz, 2H), 8.12 (d, J=8.8 Hz, 1H), 8.20 (d, J=8.0 Hz, 1H), 8.45 (s, 1H); HRMS (ESI): calcd for $C_{13}H_9ClN_3O_2$ $[M+H]^+$ 274.0383, found 274.0378.

*4.2.2. 2-(4-Nitrophenyl)-6-nitro-1H-benzimidazole (Table 4, compound **1b**).* Yellow solid; yield: 83.5 mg, 90%; mp 289.2–289.9 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (s, 1H), 8.15 (s, 1H), 8.41–8.45 (m, 4H), 8.59 (s, 1H), 13.92 (s, 1H); HRMS (ESI): calcd for $C_{13}H_7N_4O_4$ $[M-H]^-$ 283.0467, found 283.0467.

*4.2.3. 2-(2-Nitrophenyl)-6-nitro-1H-benzimidazole (Table 4, compound **1c**).* Yellow solid; yield: 85.4 mg, 92%; mp 219.9–220.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81–7.84 (m, 2H), 7.92–7.96 (m, 1H), 8.02 (dd, J_1=7.6 Hz, J_2=1.6 Hz, 1H), 8.13 (dd, J_1=8.0 Hz, J_2=2.4 Hz, 1H), 8.18 (dd, J_1=8.8 Hz, J_2=1.2 Hz, 1H), 8.54 (s, 1H), 13.77 (s, 1H); HRMS (ESI): calcd for $C_{13}H_7N_4O_4$ $[M-H]^-$ 283.0467, found 283.0463.

*4.2.4. 2-(3-Nitrophenyl)-6-nitro-1H-benzimidazole (Table 4, compound **1d**).* Yellow solid; yield: 83.5 mg, 90%; mp 282.7–283.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (d, J=8.0 Hz, 1H), 7.90 (t, J=8.0 Hz, 1H), 8.17 (s, 1H), 8.40 (dd, J_1=8.0 Hz, J_2=1.6 Hz, 1H), 8.52–8.56 (m, 1H), 8.63 (d, J=8.0 Hz, 1H), 9.03 (d, J=1.6 Hz, 1H),

13.98 (s, 1H); HRMS (ESI): calcd for $C_{13}H_7N_4O_4$ $[M-H]^-$ 283.0467, found 283.0472.

*4.2.5. 2-(4-Methoxyphenyl)-6-nitro-1H-benzimidazole (Table 4, compound **1e**).* Yellow solid; yield: 81.8 mg, 93%; mp 234.6–235.3 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.86 (s, 3H), 7.16 (d, J=8.4 Hz, 2H), 7.71–7.75 (m, 1H), 8.08–8.17 (m, 3H), 8.49 (s, 1H), 13.43 (s, 1H); HRMS (ESI): calcd for $C_{14}H_{10}N_3O_3$ $[M-H]^-$ 268.0722, found 268.0723.

*4.2.6. 2-(3-Methoxyphenyl)-6-1H-nitro-benzimidazole (Table 4, compound **1f**).* Yellow solid; yield: 79.1 mg, 90%; mp 138.8–139.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.88 (s, 3H), 7.13–7.17 (m, 1H), 7.52 (t, J=8.0 Hz, 1H), 7.77–7.81 (m, 3H), 8.12–8.16 (m, 1H), 8.50 (s, 1H), 13.60 (s, 1H); HRMS (ESI): calcd for $C_{14}H_{12}N_3O_3$ $[M+H]^+$ 270.0879, found 270.0873.

*4.2.7. 2-(3,4-Dimethoxyphenyl)-6-nitro-1H-benzimidazole (Table 4, compound **1g**).* Red solid; yield: 89.9 mg, 92%; mp 173.4–175.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.86 (s, 3H), 3.90 (s, 3H), 5.68 (s, 1H), 7.16 (d, J=8.8 Hz, 1H), 7.71 (s, 1H), 7.79 (d, J=8.8 Hz, 2H), 8.09 (d, J=8.4 Hz, 1H), 8.54 (s, 1H), 13.42 (s, 1H); HRMS (ESI): calcd for $C_{15}H_{12}N_3O_4$ $[M-H]^-$ 298.0828, found 298.0825.

*4.2.8. 2-(2-Hydroxyl-phenyl)-6-nitro-1H-benzimidazole (Table 4, compound **1h**).* Yellow solid; yield: 76.7 mg, 92%; mp 279.6–280.1 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.02–7.09 (m, 3H), 7.43 (t, J=7.6 Hz, 1H), 7.77 (d, J=8.8 Hz, 1H), 8.11 (t, J=8.8 Hz, 2H), 8.49 (s, 1H); HRMS (ESI): calcd for $C_{13}H_{10}N_3O_3$ $[M+H]^+$ 256.0722, found 256.0717.

*4.2.9. 2-(4-Nitrophenyl)-1H-benzimidazole (Table 4, compound **2a**).* Yellow solid; yield: 105.1 mg, 95%; mp 310.9–311.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.27 (dd, J_1=8.0 Hz, J_2=2.8 Hz, 2H), 7.64–7.67 (m, 2H), 8.40–8.45 (m, 4H); HRMS (ESI): calcd for $C_{13}H_8N_3O_2$ $[M-H]^-$ 238.0617, found 238.0622.

*4.2.10. 2-(2-Nitrophenyl)-1H-benzimidazole (Table 4, compound **2b**).* Yellow solid; yield: 106.2 mg, 96%; mp 239.4–240.1 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.24–7.27 (m, 2H), 7.58 (d, J=8.0 Hz, 1H), 7.67 (t, J=8.0 Hz, 1H), 7.74–7.72 (m, 1H), 7.85–7.89 (m, 1H), 7.97–7.80 (m, 1H), 8.04 (dd, J_1=8.0 Hz, J_2=1.2 Hz, 1H), 13.06 (s, 1H); HRMS (ESI): calcd for $C_{13}H_8N_3O_2$ $[M-H]^-$ 238.0617, found 238.0617.

*4.2.11. 2-(3-Nitrophenyl)-1H-benzimidazole (Table 4, compound **2c**).* Yellow solid; yield: 105.1 mg, 95%; mp 203.5–204.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.25–7.29 (m, 2H), 7.66 (s, 2H), 7.86 (t, J=8.0 Hz, 1H), 8.33–8.36 (m, 1H), 8.62 (d, J=8.0 Hz, 1H), 9.00–9.03 (m, 1H); HRMS (ESI): calcd for $C_{13}H_8N_3O_2$ $[M-H]^-$ 238.0617, found 238.0620.

*4.2.12. 2-(2-Hydroxyl-phenyl)-4-nitro-1H-benzimidazole (Table 4, compound **3a**).* Yellow solid; yield: 81.7 mg, 98%; mp 259.5–260.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.02–7.09 (m, 2H), 7.42–7.49 (t, J=8.8 Hz, 2H), 8.10–8.15 (m, 2H), 8.30 (s, 1H), 8.80 (s, 1H); HRMS (ESI): calcd for $C_{13}H_{10}N_3O_3$ $[M+H]^+$ 256.0722, found 256.0719.

*4.2.13. 2-(2,6-Dimethylphenyl)-4-nitro-1H-benzimidazole (Table 4, compound **3b**).* Orange solid; yield: 86.4 mg, 99%; mp 74.3–74.8 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.10 (s, 6H), 7.21 (d, J=7.6 Hz, 2H), 7.36 (t, J=7.6 Hz, 1H), 7.45 (t, J=8.0 Hz 1H), 8.17–8.20 (m, 2H), 13.42 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.2, 119.1, 121.6, 127.2, 127.6, 128.7, 129.9, 131.3, 133.5, 137.9, 146.9, 155.2; HRMS (ESI): calcd for $C_{15}H_{12}N_3O_2$ $[M-H]^-$ 266.0930, found 266.0930.

*4.2.14. 2-(4-N,N-Dimethyl-aniline)-4-nitro-1H-benzimidazole (Table 4, compound **3c**).* Red solid; yield: 87.6 mg, 95%; mp 272.1–272.3 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.04 (s, 6H), 6.84 (d, J=8.0 Hz, 2H), 7.36 (s, 1H), 8.03–8.05 (m, 2H), 8.22–8.25 (m, 2H), 12.80 (s, 1H); HRMS (ESI): calcd for $C_{15}H_{15}N_4O_2$ $[M+H]^+$ 283.1195, found 283.1192.

*4.2.15. 2-(3,4-Dimethoxyphenyl)-4-nitro-1H-benzimidazole (Table 4, compound **3d**).* Yellow solid; yield: 92.8 mg, 95%; mp 190.0–190.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.85 (s, 3H), 3.91 (s, 3H), 7.10 (d, J=8.4 Hz, 1H), 7.36 (t, J=8.0 Hz, 1H), 7.95 (s, 1H), 8.01 (d, J=8.4 Hz, 1H), 8.06 (t, J=8.0 Hz, 2H), 12.94 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 56.0, 56.2, 111.4, 111.9, 118.8, 121.7, 121.8, 126.5, 129.6, 133.3, 147.1, 149.1, 151.4, 155.3; HRMS (ESI): calcd for $C_{15}H_{14}N_3O_4$ $[M+H]^+$ 300.0984, found 300.0985.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.06.045.

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