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ORIGINAL PAPER

A simple and metal-free one-pot synthesis of 2-substituted-1*H*-4-carboxamide benzimidazole using 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine(PYTZ) as catalyst

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Abstract
In this work, a simple and green method for the convenient synthetic protocol of 2-substituted-1*H*-4-carboxamide benzimidazole was reported from 2,3-diaminobenzamide and a variety of aldehydes by condensation. The results showed that 2,3-diaminobenzamide and aldehydes could react under visible light irradiation at ambient temperature in the presence of PYTZ and pumping air (or other oxidant) to obtain the desired compound with simple workup. The structures of 20 synthesized compounds were determined by NMR, IR and HRMS (new compound) techniques. The method was efficient, metal free, green, and selective.

Keywords 2,3-diaminobenzamide · Visible light irradiation · PYTZ · Air · 2-Substituted-1*H*-4-carboxamide benzimidazole

Introduction

Benzimidazole and its derivatives have the significant importance in medicinal chemistry (Akhtar et al. 2016), such as anti-inflammatory (Monika et al. 2015; Said et al. 2015), analgesic, antifungal, bacterial, antiviral (Carrie et al. 2015), insect repellent, anti-malignant cell proliferation (Mavrova et al. 2013; Marijana et al. 2012), antihypertensive (Mukesh et al. 2013) and so on. Among compounds containing benzimidazole core, many benzimidazole carboxamide derivatives have good biological activity, such as Poly (ADP-Ribose) Polymerase Inhibitor (compounds **1** and **2**, Fig. 1) (Donawho et al. 2007; Penning et al. 2010), inhibition proliferation of human breast cancer cells MX1 (compound **3**, Fig. 1) (Penning et al. 2008).

The multifarious biological applications of substituted benzimidazoles have stimulated the development of numerous methodologies for their synthesis. One method is the condensation of *o*-phenylenediamine with carboxylic acid under the harsh dehydrating conditions (Dudd et al. 2003; Bahrami et al. 2007). The other approach is the condensation of *o*-phenylenediamine with aldehyde in the presence of iodobenzene diacetate (IBD) (Du and Wang 2007), HCl/H_2O_2 (Bahrami et al. 2007), CAN/H_2O_2 (Bahrami et al. 2008), polyethelence glycol (PEG-100) (Mukhopadhyay and Tapaswi 2009), $(NH_4)H_2PW_{12}O_{40}$ (Giri et al. 2007), $CoCl_2{\cdot}6H_2O$ (Khan et al. 2009), PbO_2 (Rege 2010), Cp_2ZrCl_2 (Karhale et al. 2016). In addition, *o*-phenylenediamines and orthoesters could be reacted to obtain benzimidazoles through a condensation reaction under solvent-free conditions using Tungstate sulfuric acid (TSA) as catalyst (Karami and Haghighijou 2012). Mostafavi H used *o*-phenylenediamine and DMF to obtain benzimidazole in the presence of HMDS (Mostafavi et al. 2018). Nevertheless, most of these methodologies were associated with drawbacks such as low yields, heavy metal catalyst used, undesirable products, prolonged reaction time, and tedious workup procedure.

Recently, Samanta reported that 2-substituted benzimidazole derivatives were prepared with high yields between *o*-phenylenediamine and aldehydes under visible light

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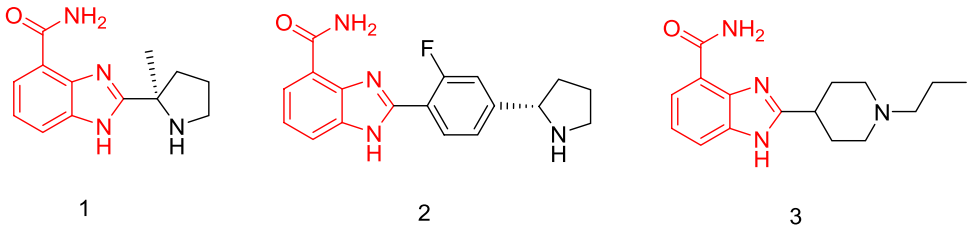
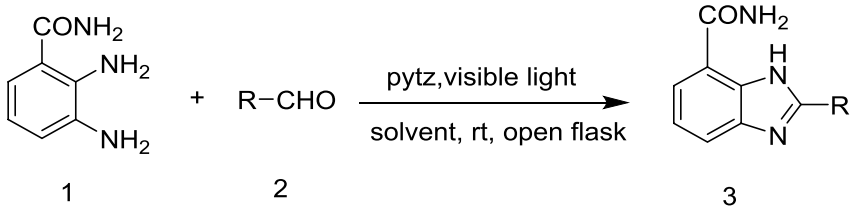


Fig. 1 Representative bioactive of benzimidazole carboxamide derivatives



Scheme 1 PYTZ catalyzed synthesis of 2-substituted-1*H*-4-carboxamide benzimidazole

3a,R=Ph; **3b**,R=2-MePh; **3c**,R=3-MePh; **3d**,R=4-MePh; **3e**,R=2-NO_2Ph; **3f**,R=3-NO_2Ph; **3g**,R=4-NO_2Ph; **3h**,R=2-ClPh; **3i**,R=3-ClPh; **3j**,R=4-ClPh; **3k**,R=2-Py; **3l**,R=3-Py; **3m**,R=4-Py; **3n**,R=n-amyl; **3o**,R=3-FPh **3p**,R=4-FPh; **3q**,R=THF-2-yl; **3r**,R=thiophen-2-yl; **3s**,R=$(CH_2)_2$Ph; **3t**,R=cyclohexyl;

irradiation at ambient temperature in the presence of PYTZ and aerial oxygen (Samanta et al. 2014). The use of a metal-free catalyst and visible light energy, along with the mild reaction conditions, makes this reaction an environmentally benign and energy-saving chemical process. Meanwhile, Park also reported the similar method for benzimidazoles synthesis. The reaction of *o*-phenylenediamine and aldehydes in methanol proceeds at room temperature with only natural sources, molecular oxygen and visible light (LEDs) (Park et al. 2014). Our group has been interested in the bio-activity of benzimidazole derivatives. Therefore, to obtain a wide variety of benzimidazole derivatives for bioactivity evaluation,the following method was adapted to synthesize any 2-substituted-1*H*-7-carb-oxamide benzimidazole effectively (Scheme 1).

Experimental

Chemistry

Unless specified otherwise, all starting materials and reagents were obtained from commercial suppliers without further purification. All melting points were taken on a METTLEE TOLEDO MP90 melting point apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE III HD 400 MHz instrument using TMS as the internal standard. Abbreviations used for peak multiplicities are s: singlet, d: doublet, t: triplet, q: quadruplet and m: multiplet. Coupling constants *J* are in Hertz and the chemical shifts were given in parts per million (ppm) and calibrated with DMSO-d_6 (residual solvent signals). IR spectra were recorded as KBr pellets on a VERTEX 80/Raman II FTIR spectrometer. Mass spectra were recorded on a Triple TOF™ 5600$^+$ (AB SCIEX USA). The reactions were monitored by thin-layer chromatography (TLC) using silica gel GF254. Photochemical reactor (Phchem III) was obtained from Beijing NBET Technology Co., Ltd.

Synthesis and characterization

General procedure for the synthesis of 2-substituted-1*H*-4-carboxamide benzimidazole derivatives 3*a*–*t*

In a dark environment, a mixture of 2,3-diaminobenzamide (1.51 g, 10 mmol), PYTZ (20 mg), and ethanol (200 mL) was taken in an open pear-shaped bottle, stirred magnetically at room temperature, and then aldehyde (10 mmol) was added slowly in 2 min. The bottle was exposed to visible light (Xenon, 10 A) under stirring condition. The reaction was monitored by TLC. After the reaction completed, the reaction mixture was transferred to a three-neck bottle outside of the photochemical reactor and air was introduced to ensure that the intermediate was completely oxidized. Then, the solvent was evaporated in vacuum to 40 mL until the solid appeared. The mixture was cooled down in an ice bath for crystallization, filtration. The crude solid was recrystallized from 25 mL ethanol (30 °C) to get the target products.

Result and discussion

In our previous work, we had synthesized a lot of 2-substituted benzimidazoles to evaluate their biological activity by Samanta's method. To further carry out our project, we

Table 1 Optimization of the reaction conditions using different reaction conditions

Entry	Catalyst	Light source	Reaction time (h)	Yield (%)[a]
1	–	Dark	3	39
2	–	Electric current: 5 A (Xenon lamp)	2.5	62
3	–	Electric current: 10 A (Xenon lamp)	2	64
4[b]	–	LEDs (7 W)	2.5	54
5	PYTZ	Dark	2.5	63
6	PYTZ	Electric current: 5 A (Xenon lamp)	2.5	77
7	PYTZ	Electric current: 10 A (Xenon lamp)	1	75
8	PYTZ	LEDs (7 W)	2.5	64
9	PYTZ	Filter glass[c]	3.5	46
10[d]	PYTZ	Electric current: 10 A (Xenon lamp)	1[e]	75

Reaction conditions: 2,3-diaminobenzamide (1 mmol), 4-chlorobenzaldehyde (1 mmol), and PYTZ (2 mg) in ethanol (20 mL) were stirred at room temperature in an open flask

[a]Isolated yield after recrystallization

[b]Reaction conditions: 2,3-diaminobenzamide (1 mmol), 4-chlorobenzaldehyde (1.05 mmol), in MeOH (10 mL) were stirred at room temperature in an open flask under blue LEDs(7 W) (Park et al. 2014)

[c]The glass blocking ultraviolet light

[d]2,3-diaminobenzamide (10 mmol), 4-chlorobenzaldehyde (10 mmol), and PYTZ (20 mg) in ethanol (200 mL) were stirred at room temperature in an open flask

[e]Need additional oxidation time

decided to introduce the amido group to benzene ring to synthesize more 2-substituted-1*H*-4-carboxamide benzimidazole derivatives based on the previous experiences and using similar reaction sequence.

Our initial efforts were focused on optimization of reaction conditions based on the literatures (Samanta et al. 2014; Park et al. 2014). But there was a difference in their methods. In Samanta's method, the visible light and PYTZ were dispensable to synthesize 2-substituted benzimidazole using *o*-phenylenediamine and aldehyde. In the absence of visible light, PYTZ showed no catalytic activity; and in the absence of PYTZ, the reaction did not proceed under identical conditions. But Park reported that PYTZ was not necessary in this reaction. To demonstrate the role of visible light and PYTZ in our research, the reaction between 3,4-toluylenediamine and 4-chlorobenzaldehyde was considered as the model reaction for investigating and several experiments were conducted in Table 1.

At first, the protocol reaction was carried out with free catalyst under dark condition. To our surprise, the reaction could occurr to provide the product with 39% in 3 h (Table 1, entry 1), which was contrary to the conclusions reported in the literature (Samanta et al. 2014). We speculated that amide group, an electron-withdrawing group, at 2,3-diaminobenzamide ring, could promote the reaction easily. To increase the reaction yield, we considered to change the light intensity in our research. It was found that the yield gradually increased with the light intensity increasing (Table 1, entries 1–3). When the electron current was increased from 5 to 10 A (Table 1, entries 2–3, entries 6–7), the intensity of the Xenon light was increased. The reaction time was shortened, but the final yield was not greatly affected. Under the same reaction time, the yield was decreased from 62 to 54% using LEDs (Park et al. 2014) as the light source (Table 1, entry 4).

Based on the above experiments, the catalyst, PYTZ, was added in reaction mixture and the reactions were carried out under different light intensities (Table 1, entries 5–8). It was found that PYTZ could promote the reaction with higher yield and short reaction time. The addition of PYTZ as the catalyst in the dark increased the yield from 39 to 63% (Table 1, entries 1 and 5). In addition, the yield was increased from 62 to 77% when the electric current was 5 A using Xenon lamp as light source (Table 1, entries 2 and 6), and the yield was increased from 64 to 75% when the electric current was 10 A with reducing time for from 2 to 1 h (Table 1, entries 3 and 7). According to Park's procedure LEDs as light source (Park et al. 2014), the addition of PYTZ also made the yield increase from 54 to 64% (Table 1, entries 4 and 8). In addition, blocking ultraviolet light using filter glass when the electric current was 10 A using Xenon lamp as light source, the action also could proceed with 46% yield (Table 1, entry 9). Therefore, it was believed that Xenon lamp was a more suitable light source and PYTZ was a good catalyst for this reaction.

As reported in the literatures, oxygen can be used as an oxidant (Chen et al. 2013) or as a co-oxidant (Nagasawa et al. 2014; Lee et al. 2015) in the reactions by opening the flask (Park et al. 2014; Lee et al. 2015) or pumping in air (Chen et al. 2013). In our research, when the amount of 2,3-diaminobenzamide was 1 mmol (Table 1, entries 1–9), the oxygen in the air could meet the needs to complete the oxidation process by opening the flask. When the reaction was scaled up from 1 to 10 mmol, the oxidation process

was very difficult to occur completely. For example, when 10 mmol of 2,3-diaminobenzamide was used in the reaction (Table 1, entry 10), 2,3-diaminobenzamide and 4-chlorobenzaldehyde were disappeared to form two new spots on TLC after 1 h (R_f = 0.55, 0.45, hex/EtOAc, 2:3).After the air was continuously bubbled into the reaction mixture by a small pump at a speed of 100 bubbles per minute on average, one spot on TLC disappeared, and another spot turned into big one on TLC(R_f = 0.45, hex/EtOAc, 2:3), which was verified by NMR as the target compound.

After investigating the influence of different reaction parameters on the model reaction, we turned our attention towards the synthesis of benzimidazole derivatives using 2,3-diaminobenzamide and a variety of aldehydes, and the results are summarized in Table 2.

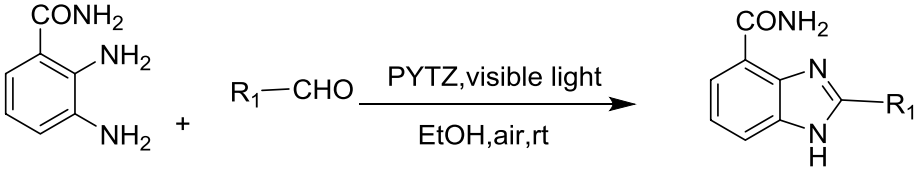


Table 2 PYTZ catalyzed reaction of 2,3-diaminobenzamide and aldehydes to synthesis of 2,4-disubstituted benzimidazole derivatives

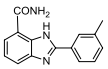
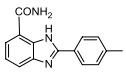
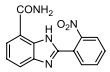
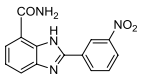
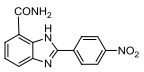
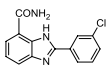
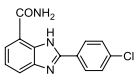
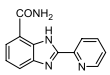
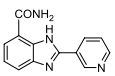
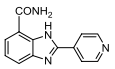
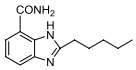
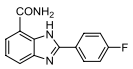
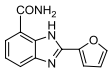
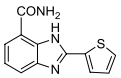
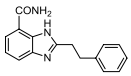
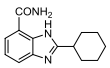
Entry	Product	R_1	Product[a]	Time(h)[b]	Yield(%)[c]	M.p.(Obs)/°C	M.p.(Lit)/ °C
1	3a	Ph		4(1.5)	54	239.3	239-241 (Jeans F et al. 2015)
2	3b	2-MePh		6.5(3)	48	195.0	Present work
3	3c*	3-MePh		10.5(4)	95	309.2	Present work
4	3d	4-MePh		15(6.5)	45	295.2	Present work
5	3e	2-NO_2Ph		11.5(3)	72	252.8	Present work
6	3f	3-NO_2Ph		20（11）	77	252.8	Present work
7	3g	4-NO_2Ph		21(10.5)	81	252.8	Present work
8	3h	2-ClPh		9(6)	72	271.7	Present work
9	3i	3-ClPh		11(4)	65	259.5-261.2	Present work
10	3j	4-ClPh		10(4)	65	297.8	Present work
11	3k	2-Py		5(3)	36	263.3-264.5	Present work
12	3l	3-Py		7(4.5)	89	298.6-301.5	Present work

Table 2 (continued)

Entry	Product	R_1	Product[a]	Time(h)[b]	Yield(%)[c]	M.p.(Obs)/°C	M.p.(Lit)/ °C
13	3m	4-Py		6.5(3)	83	320.4-321.3	Present work
14	3n*	n-amyl		6(0)	15	329.3	Present work
15	3o	3-FPh		8.5(3)	79	268.3	Present work
16	3p	4-FPh		10(4.5)	56	305.5	Present work
17	3q	THF-2-yl		16.5(6.5)	78	272.9	Present work
18	3r	thiophen-2-yl		20(8)	65	272.3	Present work
19	3s	$(CH_2)_2Ph$		9(3)	27	298.1	Present work
20	3t	cyclohexyl		10(4)	90	290.1	Present work

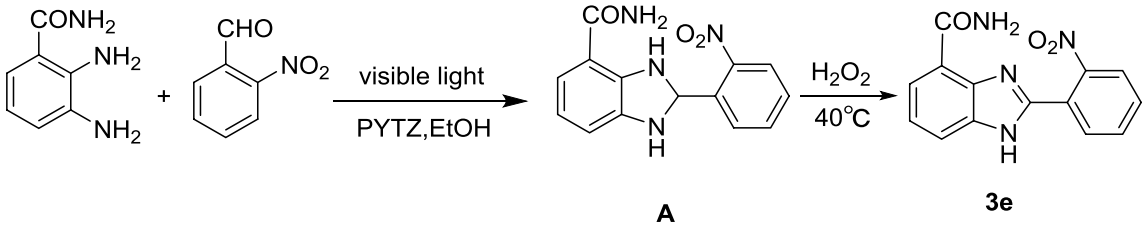
Reaction conditions: 2,3-diaminobenzamide (10 mmol), aryl aldehyde (10 mmol), and PYTZ (20 mg) in ethanol (200 mL) were stirred at room temperature

*New compound;

[a]All products were identified by their IR and ^{1}H NMR,^{13}C NMR spectra.

[b]The numbers in parentheses were the oxidation time.

[c]Isolates yields of purified products.



Scheme 2 The synthesis route of compound **3e**

Reaction of both electron-rich or -poor aromatic aldehydes provided the corresponding benzimidazoles in good yields (Table 2, entries 1–13, 15–16). In addition, aliphatic aldehydes (Table 2, entries 14,19 and 20) and five-membered heterocyclic aldehydes (Table 2, entries 17 and 18) were also the suitable substrates for the process, which proves the reaction efficiency. The simple and metal-free one-pot mild conditions allowed the reaction of aldehydes that contain a range of functional groups. As was evident from Table 2, when 2,3-diaminobenzamide reacted with *o*-nitrobenzaldehyde (Table 2, entry 5), oxygen in the pumping air could not oxidize the C–N single bond to C=N, and the obtained compound was 2-(2-nitrophenyl)-2,3-dihydrogen-1*H*-benzo[*d*]imidazole-4-carboxamide (Scheme 2, **A**). The nuclear magnetic data of **A** were as follows: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (s, 1H, $CONH_2$), 8.36 (dd, J = 7.7, 1.5 Hz, 1H, $CONH_2$), 8.09 (dd, J = 8.1, 1.2 Hz, 1H, Ar–H), 7.91–7.82 (m, 2H, NH),

Table 3 Characterization data of synthesized compounds **5a–u**

Compound	Characterizing data
3a	Yellow solid, yield 54%, m.p. 239.3 °C [Lit. 239–241 °C (Jeans et al. 2015)]; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.42 (s, 1H, NH), 9.37 (s, 1H, Ar–H), 8.27 (d, J = 1.8 Hz, 1H, $CONH_2$), 8.26–8.22 (m, 1H, $CONH_2$), 7.88 (d, J = 7.6 Hz, 1H, Ar–H), 7.79 (s, 1H, Ar–H), 7.76 (d, J = 7.9 Hz, 1H, Ar–H), 7.64–7.53 (m, 3H, Ar–H), 7.36 (t, J = 7.8 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.62 ($CONH_2$), 152.37 (C-2), 141.92 (C-8a), 135.80 (C-1′), 131.09 (C-4′), 129.62 (2C, C-3′, C-5′), 129.57 (2C, C-2′, C-6′), 127.36 (9a), 123.42 (C-6), 122.93 (C-5), 122.84 (C-4), 115.49 (C-7); IR (KBr) (ν_{max}, cm^{-1}): 3349 (N–H), 3175 (C–H),1649 (C=C),1575
3b	Yellow solid, yield 48%, m.p. 195.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.37 (s, 1H, NH), 9.37 (d, J = 3.4 Hz, 1H, Ar–H), 8.08 (d, J = 1.8 Hz, 1H, $CONH_2$), 8.04 (d, J = 7.9 Hz, 1H, $CONH_2$), 7.88 (dd, J = 7.6, 1.2 Hz, 1H, Ar–H), 7.79 (d, J = 3.5 Hz, 1H, Ar–H), 7.74 (dd, J = 8.0, 1.2 Hz, 1H, Ar–H), 7.49 (t, J = 7.7 Hz, 1H, Ar–H), 7.41–7.33 (m, 2H, Ar–H), 2.45 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.66 ($CONH_2$), 152.95 (C-2), 141.79 (C-8a), 137.63 (C-1′), 135.10 (C-2′), 132.04 (C-6′), 130.47 (C-5′), 130.03 (C-3′), 129.38 (C-4′), 126.70 (C-9a), 123.18 (C-6), 122.93 (C-5), 122.76 (C-4), 115.49 (C-7), 21.63 (CH_3); IR (KBr) (ν_{max}, cm^{-1}): 3357 (N–H), 3157 (C–H), 2957, 2923, 1671 (C=O), 1478 (C=N), 1142, 901, 753
3c	Yellow solid, yield 95%, m.p. 309.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.15 (s, 1H, NH), 9.34 (d, J = 3.5 Hz, 1H, Ar–H), 7.90 (dd, J = 7.6, 1.1 Hz, 1H, $CONH_2$), 7.84 (dt, J = 7.3, 1.1 Hz, 1H, $CONH_2$), 7.76 (d, J = 1.1 Hz, 1H, Ar–H), 7.76–7.72 (m, 1H, Ar–H), 7.50–7.45 (m, 1H, Ar–H), 7.45–7.44 (m, 1H, Ar–H), 7.44–7.40 (m, 1H, Ar–H), 7.38 (t, J = 7.8 Hz, 1H, Ar–H), 2.65 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.65 ($CONH_2$), 152.95 (C-2), 141.79 (C-8a), 137.63 (C-1′), 135.10 (C-2′), 132.03 (C-3′), 130.46 (C-5′), 130.03 (C-4′), 129.39 (C-6′), 126.70 (C-9a), 123.17 (C-6), 122.94 (C-5), 122.75 (C-4), 115.47 (C-7), 21.61 (CH_3); IR (KBr) (ν_{max}, cm^{-1}): 3326 (N–H), 2908, 2804, 1712 (C=O), 1577 (C=C), 1134, 872, 789; HRMS calcd for $C_{15}H_{13}N_3O$ $[M+H]^+$ 252.1137, found 252.1132
3d	Brown solid, yield 45%, m.p. 295.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.32 (s, 1H, NH), 9.38 (d, J = 3.3 Hz, 1H, Ar–H), 8.15 (s, 1H, $CONH_2$), 8.13 (d, J = 1.7 Hz, 1H, $CONH_2$), 7.87 (dd, J = 7.6, 1.2 Hz, 1H, Ar–H), 7.80–7.75 (m, 1H, Ar–H), 7.73 (dd, J = 7.9, 1.2 Hz, 1H, Ar–H), 7.42 (s, 1H, Ar–H), 7.41 (s, 1H, Ar–H), 7.34 (t, J = 7.8 Hz, 1H, Ar–H), 2.41 (s, 3H,CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.67 ($CONH_2$), 152.53 (C-2), 140.98 (C-8a), 135.74 (2C, C-1′,C-4′), 130.18 (2C, C-3′,C-5′), 127.31 (2C, C-2′,C-6′), 126.83 (C-9a), 123.30 (C-6), 122.77 (C-5), 122.64 (C-4), 115.33 (C-7), 21.52 (CH_3); IR (KBr) (ν_{max}, cm^{-1}): 3319 (N–H), 3176, 1675, 1599 (C=C), 1480, 1048, 850,727
3e	Orange solid, yield 72%, m.p. 252.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (s, 1H, Ar–H), 8.36 (dd, J = 7.7, 1.5 Hz, 1H, Ar–H), 8.09 (dd, J = 8.1, 1.2 Hz, 1H, Ar–H), 7.91 – 7.82 (m, 2H, $CONH_2$), 7.76 (td, J = 7.7, 1.4 Hz, 1H, Ar–H), 7.56 (dt, J = 8.0, 1.5 Hz, 1H, Ar–H), 7.24 (d, J = 1.3 Hz, 1H, Ar–H), 7.22 (d, J = 1.2 Hz, 1H, Ar–H), 6.67 (s, 2H, Ar–H), 6.59 (td, J = 7.8, 0.8 Hz, 1H, Ar–H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.43 ($CONH_2$), 153.99 (C-2), 149.60 (C-2′), 146.01 (C-8a), 136.81 (C-5′), 133.93 (C-6′), 132.07 (C-4′), 130.67 (C-9a), 130.55 (C-1′), 128.63 (C-3′), 124.80 (C-6), 120.32 (C-5), 115.20 (C-4), 114.67 (C-7); IR (KBr) (ν_{max}, cm^{-1}): 3360 (N–H), 3167, 1668 (C=O), 1517 (C–NO_2), 1191, 1120, 745
3f	Brown red solid, yield 77%, m.p. 252.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.80 (s, 1H, NH), 9.25 (s, 1H,$CONH_2$), 9.07 (s, 1H, $CONH_2$), 8.72 (d, J = 7.8 Hz, 1H, Ar–H), 8.39 (dd, J = 8.0, 2.3 Hz, 1H, Ar–H), 7.93 (d, J = 7.0 Hz, 1H, Ar–H), 7.89 (d, J = 7.9 Hz, 1H, Ar–H), 7.87–7.84 (m, 1H, Ar–H), 7.81 (d, J = 8.0 Hz, 1H, Ar–H), 7.42 (t, J = 7.8 Hz, 1H, Ar–H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.39 ($CONH_2$), 150.19 (C-2), 148.89 (C-3′), 141.64 (C-8a), 135.88 (C-6′), 133.59 (C-1′), 131.36 (C-5′), 131.19 (C-9a), 125.42 (C-4′), 123.92 (C-6), 123.55 (C-2′), 123.32 (C-5), 121.73 (C-4), 115.89 (C-7); IR (KBr) (ν_{max}, cm^{-1}): 3448 (N–H), 3166, 3066, 1655 (C=O), 1524 (C–NO_2), 1498, 1253, 855, 753, 708
3g	Yellow solid, yield 81%, m.p. 252.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.80 (s, 1H, NH), 9.25 (d, J = 3.2 Hz, 1H, Ar–H), 8.52 (d, J = 6.6 Hz, 1H, Ar–H), 8.51 (s, 1H, $CONH_2$), 8.47 (s, 1H, $CONH_2$), 8.46 (d, J = 6.7 Hz, 1H, Ar–H), 7.94 (dd, J = 7.5, 1.1 Hz, 1H, Ar–H), 7.89 (d, J = 3.4 Hz, 1H, Ar–H), 7.82 (dd, J = 8.0, 1.1 Hz, 1H, Ar–H), 7.43 (t, J = 7.8 Hz, 1H, Ar–H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.39 ($CONH_2$), 150.19 (C-2), 148.89 (C-4′), 141.64 (C-8a), 135.88 (C-1′), 133.59 (C-2′), 131.36 (C-6′), 131.19 (C-9a), 125.42 (C-3′), 123.92 (C-5′), 123.55 (C-6), 123.32 (C-5), 121.73 (C-4), 115.89 (C-7); IR (KBr) (ν_{max}, cm^{-1}): 3456 (N–H), 3151, 3072, 1597 (C=C), 1512 (C–NO_2), 1100, 953, 855
3h	Yellow solid, yield 72%, m.p. 271.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.28 (s, 1H, NH), 9.29 (d, J = 3.4 Hz, 1H, Ar–H), 8.00 (dd, J = 7.1, 2.3 Hz, 1H, $CONH_2$), 7.94–7.90 (m, 1H, $CONH_2$), 7.83–7.79 (m, 1H, Ar–H), 7.79–7.76 (m, 1H, Ar–H), 7.71 (dd, J = 7.4, 1.8 Hz, 1H, Ar–H), 7.61 (dd, J = 7.2, 5.1 Hz, 1H, Ar–H), 7.57 (dd, J = 7.0, 5.4 Hz, 1H, Ar–H), 7.41 (t, J = 7.8 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.48 ($CONH_2$), 150.10 (C-2), 148 (C-8a), 141.31 (C-1′), 135.31 (C-2′), 132.60 (C-4′), 132.27 (C-3′), 131.11 (C-6′), 129.28 (C-5′), 128.14 (C-9a), 123.50 (C-6), 123.18 (C-5), 121.73 (C-4), 115.92 (C-7); IR (KBr) (ν_{max}, cm^{-1}): 3387 (N–H), 3066, 1662 (C=O), 1603, 1494, 1206, 874, 762 (C–Cl)

Table 3 (continued)

Compound	Characterizing data
3i	Bright yellow solid, yield 65%, m.p. 259.5-261.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.53 (s, 1H, NH), 9.28 (d, J = 3.2 Hz, 1H, Ar–H), 8.32 (q, J = 1.4 Hz, 1H, $CONH_2$), 8.23 (ddd, J = 5.6, 4.4, 2.8 Hz, 1H, $CONH_2$), 7.91 (dd, J = 7.6, 1.1 Hz, 1H, Ar–H), 7.78 (s, 1H, Ar–H), 7.76 (d, J = 1.1 Hz, 1H, Ar–H), 7.64 (d, J = 1.3 Hz, 1H, Ar–H), 7.64–7.62 (m, 1H, Ar–H), 7.39 (t, J = 7.8 Hz, 1H, Ar–H) ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.47 ($CONH_2$), 150.85 (C-2), 141.72 (C-1′), 135.78 (C-8a), 134.39 (C-3′), 131.64 (C-2′), 131.59 (C-6′), 130.77 (C-5′), 126.93 (C-4′), 126.01 (C-9a), 123.71 (C-6), 123.25 (C-5), 123.17 (C-4), 115.68 (C-7); IR (KBr) (ν_{max}, cm^{-1}): 3333 (N–H), 3152, 2928 (C–N), 1655 (C=O), 1525, 1492, 1132, 855, 813, 753 (C–Cl), 631
3j	Yellow solid, yield 65%, m.p. 297.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.49 (s, 1H, NH), 9.31 (d, J = 3.4 Hz, 1H, Ar–H), 8.28 (s, 1H, $CONH_2$), 8.26 (s, 1H, $CONH_2$), 7.90 (d, J = 7.5 Hz, 1H, Ar–H), 7.82 (d, J = 3.4 Hz, 1H, Ar–H), 7.76 (d, J = 7.9 Hz, 1H, Ar–H), 7.69 (s, 1H, Ar–H), 7.67 (s, 1H, Ar–H), 7.38 (t, J = 7.8 Hz, 1H, Ar–H) ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.55($CONH_2$), 151.29 (C-2), 141.83 (C-8a), 135.82 (C-4′), 135.74 (C-1′), 129.73 (2C, C-3′, C-5′), 129.10 (2C, C-2′, C-6′), 128.47 (C-9a), 123.60 (C-6), 123.07 (C-5), 123.02 (C-4), 115.58 (C-7); IR (KBr) (ν_{max}, cm^{-1}): 3362 (N–H), 3173, 1666 (C=O), 1498, 1153, 1085, 904, 865,760 (C–Cl)
3k	Light gray solid, yield 36%, m.p. 263.3-264.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.61 (s, 1H, NH), 9.30 (d, J = 3.3 Hz, 1H, Ar–H), 8.88–8.70 (m, 1H, $CONH_2$), 8.47 (d, J = 7.9 Hz, 1H, $CONH_2$), 8.05 (td, J = 7.8, 1.8 Hz, 1H, Ar–H), 7.91 (dd, J = 7.6, 1.1 Hz, 1H, Ar–H), 7.85 (d, J = 3.4 Hz, 1H, Ar–H), 7.80–7.69 (m, 1H, Ar–H), 7.66–7.51 (m, 1H, Ar–H), 7.39 (t, J = 7.8 Hz, 1H, Ar–H) ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.51 ($CONH_2$), 151.66 (C-1′), 150.09 (C-2), 148.00 (C-3′), 141.93 (C-8a), 138.26 (C-5′), 135.70 (C-9a), 125.83 (C-6′), 123.74 (C-4′), 123.42 (C-6), 123.36 (C-5), 122.61 (C-4), 116.20 (C-7); IR (KBr) (ν_{max}, cm^{-1}): 3300 (N–H), 3070, 1664, 1569 (C=O), 1498,1120, 1034, 869
3l	Yellow solid, yield 89%, m.p. 298.6-301.5; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.61 (s, 1H, NH), 9.43 (d, J = 2.2 Hz, 1H, $CONH_2$), 9.29 (s, 1H, $CONH_2$), 8.74 (d, J = 4.7 Hz, 1H, Ar–H), 8.60 (d, J = 8.0 Hz, 1H, Ar–H), 7.92 (d, J = 7.6 Hz, 1H, Ar–H), 7.87–7.81 (m, 1H, Ar–H), 7.78 (s, 1H, Ar–H), 7.63 (dd, J = 8.0, 4.8 Hz, 1H, Ar–H), 7.40 (t, J = 7.8 Hz, 1H, Ar–H) ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.48 ($CONH_2$), 151.61 (C-2), 150.06 (C-2′), 148.38 (C-4′), 141.77 (C-8a), 135.75 (C-6′), 134.82 (C-1′), 125.75 (C-9a), 124.59 (C-5′), 123.73 (C-6), 123.26 (C-5), 123.16 (C-4), 115.70 (C-7); IR(KBr)(ν_{max},cm^{-1}): 3430 (N–H), 3045, 1794, 1617, 1495 (C=C), 1245, 864, 750
3m	Brown solid, yield 83%, m.p. 320.4-321.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.77 (s, 1H, NH), 9.33 – 9.10 (m, 1H, Ar–H), 8.82 (d, J = 1.7 Hz, 1H, Ar–H, $CONH_2$), 8.81 (d, J = 1.6 Hz, 1H, $CONH_2$), 8.19 (d, J = 1.7 Hz, 1H, Ar–H), 8.18 (d, J = 1.7 Hz, 1H, Ar–H), 7.97–7.91 (m, 1H, Ar–H), 7.89–7.84 (m, 1H, Ar–H), 7.84–7.79 (m, 1H, Ar–H), 7.44 (t, J = 7.8 Hz, 1H, Ar–H) ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.34 ($CONH_2$), 151.15 (C-2), 149.90 (2C, C-3′, C-5′), 141.65 (C-1′), 136.63 (C-8a), 135.81 (C-9a), 124.06 (C-6), 123.84 (C-5), 123.49 (2C, C-2′, C-6′), 121.16 (C-4), 116.02 (C-7); IR (KBr) (ν_{max}, cm^{-1}): 3341 (N–H), 3164, 1690, 1605, 1500, 1474 (C=C), 1249, 833
3n	Yellow solid, yield 15%, m.p. 329.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.73 (s, 1H, NH), 9.40 (s, 1H), 7.85 (d, J = 7.3 Hz, 1H, Ar–H), 7.72 (s, 1H, $CONH_2$), 7.68 (d, J = 8.1 Hz, 1H, $CONH_2$), 7.31 (t, J = 7.8 Hz, 1H, Ar–H), 2.94 (t, J = 7.6 Hz, 2H, H-1), 1.89–1.82 (m, 2H, H-2), 1.40 (d, J = 3.5 Hz, 2H, H-3), 1.38 (d, J = 4.0 Hz, 2H, H-4), 0.95–0.91 (m,3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.81 ($CONH_2$), 156.79 (C-2), 141.56 (C-8a), 134.98 (C-9a), 122.47 (C-6), 122.26 (C-5), 121.71 (C-4), 114.90(C-7), 31.33 (C-3′), 28.85 (C-1′), 27.60 (C-4′), 22.28 (C-2′), 14.32 (C-5′) IR (KBr) (ν_{max}, cm^{-1}): 3330 (N–H), 3177, 2952, 2862, 1662 (C=O), 1604, 1490, 1000, 757; HRMS calcd for $C_{13}H_{17}N_3O$ $[M+H]^+$ 232.1450, found 232.1445
3o	Yellow solid, yield 79%, m.p. 268.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.53 (s, 1H, NH), 9.28 (d, J = 3.2 Hz, 1H, Ar–H), 8.32 (q, J = 1.4 Hz, 1H, $CONH_2$), 8.23 (ddd, J = 5.6, 4.4, 2.8 Hz, 1H, $CONH_2$), 7.91 (dd, J = 7.6, 1.1 Hz, 1H, Ar–H), 7.78 (s, 1H, Ar–H), 7.76 (d, J = 1.1 Hz, 1H, Ar–H), 7.64 (d, J = 1.3 Hz, 1H, Ar–H), 7.64–7.62 (m, 1H, Ar–H), 7.39 (t, J = 7.8 Hz, 1H, Ar–H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.48 ($CONH_2$), 161.73 (C-3′), 151.08 (C-2), 141.72 (C-8a), 135.76 (C-1′), 131.85 (C-5′), 123.69 (C-9a), 123.50 (C-6′), 123.21 (C–6), 117.95 (C-5), 117.74 (C-4), 115.66 (C-7), 114.18 (C-2′), 113.94 (C-4′); IR (KBr) (ν_{max}, cm^{-1}): 3336 (N–H), 3072, 2928, 1658 (C=O), 1595, 1467, 1200, 1033 (C–F), 798, 750; HRMS calcd for $C_{14}H_{10}FN_3O$ $[M-1]^-$ 254.0808, found 254.0868
3p	Yellow solid, yield 56%, m.p. 305.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.49 (s, 1H, NH), 9.31 (d, J = 3.4 Hz, 1H, Ar–H), 8.28 (s, 1H, $CONH_2$), 8.26 (s, 1H, $CONH_2$), 7.90 (d, J = 7.5 Hz, 1H, Ar–H), 7.82 (d, J = 3.4 Hz, 1H, Ar–H), 7.76 (d, J = 7.9 Hz, 1H, Ar–H), 7.69 (s, 1H, Ar–H), 7.67 (s, 1H, Ar–H), 7.38 (t, J = 7.8 Hz, 1H, Ar–H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.58 ($CONH_2$), 161.99 (C-4′), 151.53 (C-2), 141.88 (C-8a), 135.82 (C-1′), 129.85 (C-2′), 129.77 (C-6′), 126.26 (C-9a), 123.46 (C-6), 122.93 (C-5), 122.86 (C-4), 116.83 (C-7), 116.60 (C-3′), 115.48 (C-5′); IR (KBr) (ν_{max}, cm^{-1}): 3484 (N–H), 3086, 1662 (C=O), 1601, 1486, 1448, 1223, 1007 (C–F), 842

Table 3 (continued)

Compound	Characterizing data
3q	Brown solid, yield 78%, m.p. 272.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.43 (s, 1H, NH), 9.39-9.00 (m, 1H,H-5), 8.07–7.97 (m, 1H, $CONH_2$), 7.87 (d, J = 7.6 Hz, 1H, $CONH_2$), 7.79 (s, 1H, Ar–H), 7.71 (d, J = 7.9 Hz, 1H, Ar–H), 7.37 (d, J = 2.9 Hz, 1H, Ar–H), 7.34 (d, J = 7.8 Hz, 1H, H-3), 6.79 (dd, J = 3.5, 1.8 Hz, 1H, H-4) ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.50 ($CONH_2$), 145.97 (C-2′), 145.03 (C-5′), 144.54 (C-2), 141.83 (C-8a), 135.06 (C-9a), 123.50 (C-6), 122.93 (C-5), 115.46 (C-4), 113.05 (C-7), 112.55 (C-4′), 107.11 (C-3′); IR (KBr) (ν_{max}, cm^{-1}): 3337(N–H), 3020, 1665 (C=O), 1507, 1257, 1155 (C–O), 1012, 898
3r	Yellow solid, yield 65%, m.p. 272.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.45 (s, 1H, NH), 9.15 (s, 1H, H-5), 7.95 (d, J = 3.6 Hz, 1H, H- 3), 7.85 (dd, J = 8.8, 6.4 Hz, 2H, $CONH_2$), 7.79 (s, 1H, Ar–H), 7.72 (d, J = 7.9 Hz, 1H, Ar–H), 7.35 (t, J = 7.8 Hz, 1H, Ar–H), 7.29 (t, J = 4.4 Hz, 1H, H-4) ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.51 ($CONH_2$), 148.09 (C-2′), 141.78 (C-2), 135.50 (C-8a), 132.82 (C-3′), 130.38 (C-5′), 129.10 (C-4′), 128.50 (C-9a), 123.44 (C-6), 122.91 (C-5), 22.62 (C-4), 115.26 (C-7); IR (KBr) (ν_{max}, cm^{-1}): 3342 (N–H), 3076, 1659 (C=O), 1607, 1506, 1428 (S–C), 1257, 700
3s	Yellow solid, yield 27%, m.p.298.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.75 (s, 1H, NH), 9.33 (s, 1H, Ar–H), 7.80 (d, J = 7.6 Hz, 1H, $CONH_2$), 7.68 (s, 1H, $CONH_2$), 7.64 (d, J = 7.8 Hz, 1H, Ar–H), 7.33–7.23 (m, 5H, Ar–H), 7.19 (ddd, J = 8.7, 5.0, 3.6 Hz, 1H, Ar–H), 3.26–3.19 (m, 2H, H-1), 3.19–3.12 (m, 2H, H-2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.76 ($CONH_2$), 155.92 (C-2), 141.47 (C-8a), 141.23 (C-3′), 134.93 (2C, C-4′, C-8′), 128.83 (2C, C-5′, C-7′), 128.77 (C-9a), 126.59 (C-6′), 122.55 (C-6), 122.35 (C-5), 121.84 (C-4), 114.97 (C-7), 33.56 (C-1′), 30.68 (C-2′); IR (KBr) (ν_{max}, cm^{-1}): 3301 (N–H), 3143, 2927, 2789, 1657(C=O), 1597, 1495
3t	Dark brown solid, yield 90%, m.p. 290.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.62 (s, 1H, NH), 9.38 (d, J = 3.6 Hz, 1H, Ar–H), 7.80 (dd, J = 7.7, 1.2 Hz, 1H, $CONH_2$), 7.67 (d, J = 3.9 Hz, 1H, $CONH_2$), 7.62 (dd, J = 7.9, 1.2 Hz, 1H, Ar–H), 7.26 (t, J = 7.8 Hz, 1H, Ar–H), 2.94 (tt, J = 11.5, 3.6 Hz, 1H, H-1), 2.12–2.07 (m, 1H), 2.05 (d, J = 3.8 Hz, 1H), 1.83 (q, J = 3.8 Hz, 1H), 1.79 (q, J = 3.5 Hz, 1H), 1.74 – 1.69 (m, 1H), 1.66 (d, J = 3.4 Hz, 1H), 1.63 (d, J = 3.3 Hz, 1H), 1.44 (dt, J = 12.2, 3.4 Hz, 1H), 1.38 (dt, J = 12.2, 3.2 Hz, 1H), 1.30 (tt, J = 12.2, 3.2 Hz, 1H) ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.83 ($CONH_2$), 160.38 (C-2), 141.27 (C-8a), 134.91 (C-9a), 122.46 (C-6), 122.38 (C-5), 121.75 (C-4), 114.96 (C-7), 37.98 (C-1′), 31.56 (2C, C-2′, C-6′), 25.93 (C-4′), 25.84 (2C, C-3′, C-5′); IR (KBr) (ν_{max}, cm^{-1}): 3383 (N–H), 3073, 2975, 2854, 1655 (C=O), 1605, 1490, 1235, 851, 540

7.76 (td, J = 7.7, 1.4 Hz, 1H, Ar–H), 7.56 (dt, J = 8.0, 1.5 Hz, 1H, Ar–H), 7.24 (d, J = 1.3 Hz, 1H, Ar–H), 7.22 (d, J = 1.2 Hz, 1H, Ar–H), 6.67 (s, 2H, Ar–H), 6.59 (td, J = 7.8, 0.8 Hz, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.43 ($CONH_2$), 153.99 (C-2′), 149.60 (C-1′), 146.01 (C-8a), 136.81 (C-5′), 133.93 (C-6′), 132.07 (C-4′), 130.67 (C-9a), 130.55 (C-3′), 128.63 (C-6), 124.80 (C-7), 120.32 (C-5), 115.20 (C-4), 114.67 (C-2). HRMS calcd for $C_{14}H_{12}N_4O_3$ $[M+1]^+$ 285.0988, found 285.0982. When the reaction temperature raised to 40 °C, and 30% H_2O_2 (4 mL) was added to the reaction solution, compound **A** was oxidized to the desired product after 0.5 h (Scheme 2, **3e**). [R_f (**A**) = 0.7, R_f (**3e**) = 0.6, hex/EtOAc, 1:2] This was consistent with the proposed reaction mechanism of PYTZ-catalyzed synthesis of benzimidazole (Samanta et al. 2014). It was possible that the electron cloud density of the benzimidazole ring was lowered due to the presence of a strong electron-withdrawing group –NO_2, making the entire structure more stable and difficult to be oxidized. When 2,3-diaminobenzamide reacted with *n*-hexanal (Table 2, entry 14), it produced many by-products without any oxidation time, resulting in a lower yield, which is probably because the activity of *n*-hexanal was too high to occur the side reactions more easily.

From the data in Table 2, it was found that the reaction time was longer than that reported in the literature (Samanta et al. 2014). It was possible that the amide group –$CONH_2$ at the benzene ring affected the reactivity of the amino group with aldehyde. The mechanism needs further study. Comparing the corresponding 2-disubstituted benzimidazoles under the same reaction of Table 2, it was found that, when the reaction was scaled up, there was no difference in the reaction time, (Support information, Table 1, entries 1,7,10 and 11). However, the yield of target product could increase by pumping air (Support information, Table 1, entry 11). In other words, our method was very mature and simple. Furthermore, the structures of the synthesized 2,4-disubstituted benzimidazole derivatives were confirmed by IR, ^{1}H and ^{13}C NMR and HRMS analysis (Table 3).

Conclusions

We describe a one-pot, simple, and efficient for the synthesis of benzimidazole derivatives using 2,3-diaminobenzamide and a variety of aldehydes, not only aryl aldehydes, at ambient temperature by using PYTZ. The amide group –$CONH_2$ at the benzene ring affected the reactivity of the amino group

with aldehyde,which made the reaction time longer and the oxidation more difficult. The present protocol offers several advantages such as operational simplicity, mild reaction conditions, green and metal free, a simple experimental and workup procedure.

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