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GREEN AND EFFICINET,ONE-POT SYNTHESES OF 2-(1H-BENZO[D]IMIDAZOL-2-YL)-N-(PYRIDIN-4-YL)BENZAMIDE

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ABSTRACT
Green and efficient, one-pot three component syntheses of 2-(1H-benzo[d]imidazol-2-yl)-N-(pyridin-4-yl)benzamides have been developed by combining benzene-1,2-diamine with diethyl phthalate & pyridin-4-amine in the presence of phosphoric acid in water at 95-100 ^{o}C. These reactions provide excellent yields, involve easy workup and use water as solvent which are the merits of this preparation.

KEYWORDS: Water, diethyl phthalate, pyridin-4-amine and benzene-1,2-diamine.

INTRODUCTION
Development of efficient and environmentally friendly methods is an important challenge in modern organic syntheses.[I] In many synthetic organic processes, solvents represent a severe pollution problem. Thus, the replacement of hazardous solvents with relatively green solvents or the altogether elimination of use of hazardous solvents in chemical processes has been one of the key achievements of green chemistry.[II] Based on the principles of green chemistry, a green solvent should meet numerous criteria such as low toxicity, non-volatility, non-mutagenicity, non-flammability and widespread availability.[III] In the past decade, water,[IV] glycerol,[V] polyethylene glycol[VI]and ionic liquids[VII] have been used as green solvents in organic reactions. As a result, serious efforts are being made to develop water as a solvent for most of the organic syntheses and processes wherever possible.

On the other hand, benzimidazole derivatives bear versatile pharmacological properties[VIII] based on their presence in both clinical medicines[IX] and compounds of broad biological functions.[X] In addition, the treatment potency of benzimidazoles in diseases such as ischemia-reperfusion injury,[XI] hypertension,[XII] obesity[XIII] etc. have been recently reported.

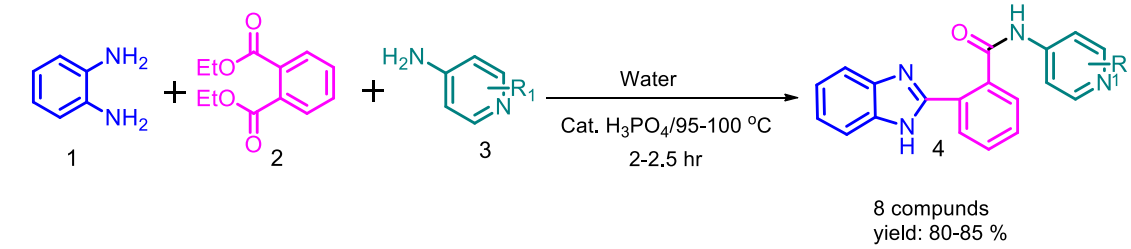
Keeping the above results in mind , we now wish to report our synthetic studies on reactions of benzene-1,2-diamine with diethyl phthalate & pyridin-4-amine. This is probably first report to prepare 2-(1H-benzo[d]imidazol-2-yl)-N-(pyridin-4-yl)benzamides in water.

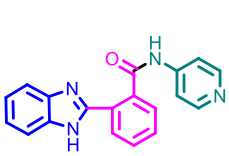
RESULTS AND DISCUSSION

As illustrated in **SCHEME 1**, the one-pot three component reaction was initiated with Benzene-1,2-diamine **1** with diethyl phthalate **2** & pyridin-4-amines **3** to get 2-(1H-benzo[d]imidazol-2-yl)-N-(pyridin-4-yl)benzamide in the presence of various solvents and acid catalysts. For this purpose, Benzene-1,2-diamine **1** (1 mmol) with diethyl phthalate **2** (1 mmol) & pyridin-4-amine **3a** (1 mmol) were charged for the synthesis of **4a** using various solvents like PEG-600, ethylene glycol, DMF, DMSO and water at different temperature as a simple model reaction in the presence of different acid catalyst (20 mol%) like HCl, H_3PO_4 and H_2SO_4 (**Table-1).** The foremost results were produced in the presence of H_3PO_4 as catalyst at 95-100 ^oC for 2-2.5 hr to form **4a** with good yields 85 % by using **1 , 2 & 3a**. Compound **4a structure** was confirmed by ^{1}H-NMR, ^{13}C-NMR and Mass.

In continuation of the protocol, a model one-pot reaction was carried out in the presence of different amount of catalyst H_3PO_4 (10, 20 and 30 mol%) with reference to compound **1**. Nevertheless, it was observed that the multi component reaction of [**1 (1 mmol), 2 (1 mmol), 3a & (1 mmol)]** utilising water as reaction medium for 2-2.5 hr at 95-100 ^oC resulted in promising yields (85%) (**Table 1)**.

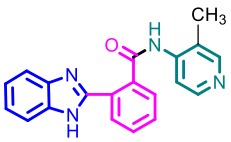
Scheme-1





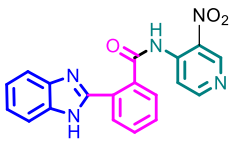
4a

85%



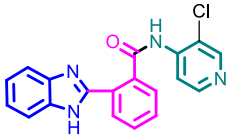
4b

82%



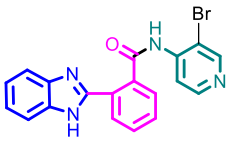
4c

83%



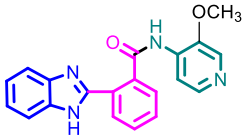
4d

82%



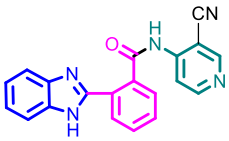
4e

83%



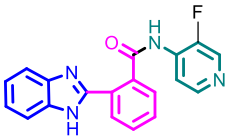
4f

84%



4g

85%

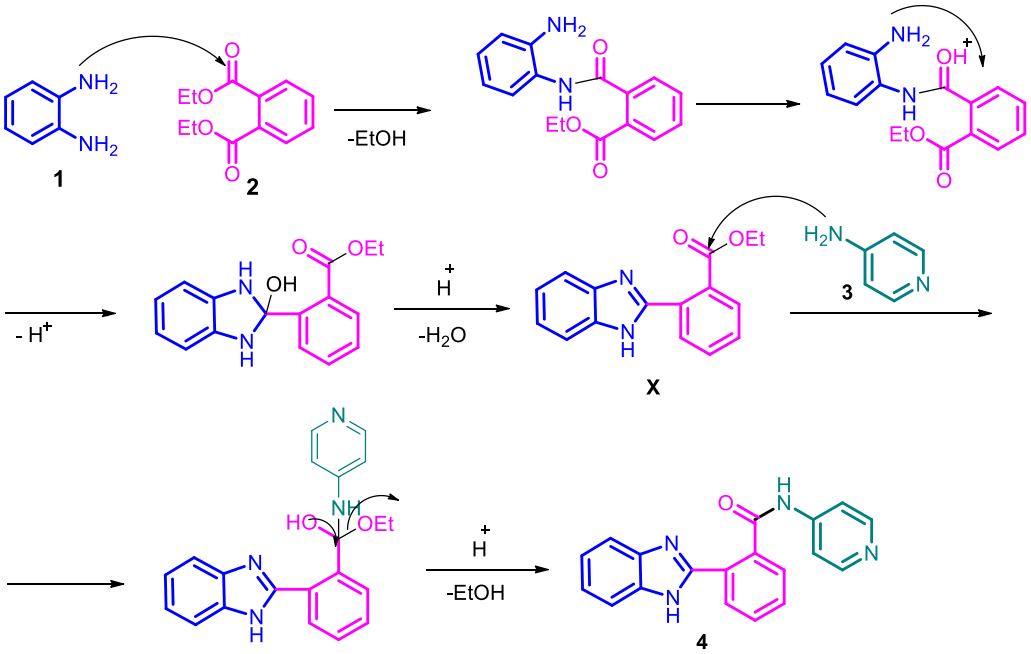


4h

85%

Using the above-stated optimised conditions, the synthesis of **4a-4h** was carried out by heating the mixture of **1, 2** and **3a-3h** in water at 95-100 ^oC for 2-2.5 hr. Products were obtained in good yield and no side products were detected. Their structures have been established on the basis of spectral properties such as NMR and mass spectra. The scope of the one-pot three component reaction development process was established using the best optimized reaction conditions by altering electron deficient & electron rich of different pyridin-4-amines and no impact was observed.

In the probable mechanism shown in Scheme-2, reaction of Benzene-1,2-diamine **1** reacted with Diethyl phthalate **2** to form **X** as an intermediate. The latter X is then attacked by **3** to form 4.

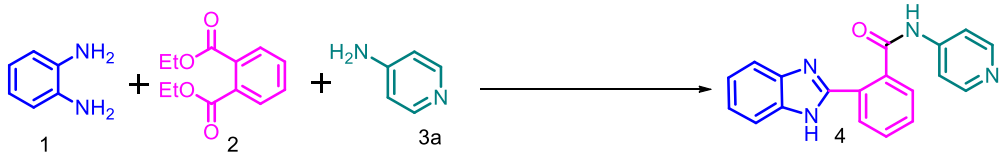


EXPERIMENTAL SECTION

Melting points are uncorrected and were determined in open capillary tubes in sulphuric acid bath. TLC was run on silica gel – G and visualization was done using iodine or UV light. IR spectra were recorded using Perkin – Elmer 1000 instrument in KBr pellets. ^{1}H NMR spectra were recorded in DMSO – d_6 using TMS as internal standard using 400 MHz spectrometer. Mass spectra were recorded on Agilent-LCMS instrument. Starting materials were obtained from commercial sources and used as such.

TABLE 1

Effect of **Solvent & different acid catalysts** on reaction of **1, 2, 3a** yielding **4a.**



Entry	Solvent	Temp. /º c	20 mol% catalyst	Time (hr)	Yield of 5a(% molar)
1	PEG-600	95-100	HCl	4	70
2	Ethylene glycol	95-100	HCl	4	70
3	DMF	95-100	HCl	3.5	50
4	DMSO	95-100	HCl	3.5	45
5	Water	95-100	HCl	3.5	75
6	PEG-600	95-100	H_3PO_4	3.0	75
7	Ethylene glycol	95-100	H_3PO_4	3.0	70
8	DMF	95-100	H_3PO_4	2.5	50
9	DMSO	95-100	H_3PO_4	2.5	48
10	**Water**	**95-100**	**H_3PO_4**	**2.0**	**85**
11	PEG-600	95-100	H_2SO_4	3.5	78
12	Ethylene glycol	95-100	H_2SO_4	3.5	72
13	DMF	95-100	H_2SO_4	3.0	53
14	DMSO	95-100	H_2SO_4	3.0	55
15	Water	95-100	H_2SO_4	2.5	82

General procedure for preparation of 4 from 1, 2 & 3 by one-pot synthesis:

A mixture of **1** (10 mM), **2** (10 mM), **3** (10 mM), and Water (50 ml) was heated at 95-100 ºC for 2-2.5 hr. At the end of this period, a colourless solid separated out from the reaction mixture which was collected by filtration. The isolated solid was washed with water (30 ml) and dried. The crude product was recrystallized from a suitable solvent to obtain **4**.

2-(1H-benzo[d]imidazol-2-yl)-N-(pyridin-4-yl)benzamide (4a)

Melting Range: 238-240 ºC; ^{1}H-NMR (400 MHz; DMSO-d_6; TMS): δ 7.0-8.0 (m, 12H, Ar-H), 10.4 (s, 1H, -NH), 12.8 (s, 1H, -NH); ^{13}C NMR (100 MHz; DMSo-d6): 115.3, 120.2, 121.8, 123.2, 127.3, 128.5, 128.9, 129.0, 129.0, 130.5, 130.7, 133.2, 135.6, 137.6, 138.7, 150.9, 151.0, 167.6; $M^{+\cdot}1$ = 315.

2-(1H-benzo[d]imidazol-2-yl)-N-(3-methylpyridin-4-yl)benzamide (4b)

Melting Range: >240 ºC; ^{1}H-NMR (400 MHz; DMSO-d_6; TMS): δ 2.2 (s, 3H, -CH_3), 7.1-8.0 (m, 11H, Ar-H), 10.4 (s, 1H, -NH), 12.6 (s, 1H, -NH); ^{13}C NMR (100 MHz; DMSo-d6): 20.3, 115.0, 120.0, 121.6, 123.2, 127.3, 128.5, 128.7, 129.3, 129.5, 130.3, 130.7, 132.8, 136.8, 137.7, 138.9, 150.1, 151.0, 168.7; $M^{+\cdot}1$ = 329.

2-(1H-benzo[d]imidazol-2-yl)-N-(3-nitropyridin-4-yl)benzamide (4c)

Melting Range: 210-212 ºC; ^{1}H-NMR (400 MHz; DMSO-d_6; TMS): δ 7.1-8.0 (m, 11H, Ar-H), 10.5 (s, 1H, -NH), 12.8 (s, 1H, -NH); ^{13}C NMR (100 MHz; DMSo-d6): 114.3, 121.0, 121.8, 123.5, 126.4, 127.8, 128.8, 129.5, 129.9, 131.2, 132.7, 132.9, 136.8, 137.8, 138.6, 150.2, 151.2, 168.6; $M^{+\cdot}1$ = 360.

2-(1H-benzo[d]imidazol-2-yl)-N-(3-chloropyridin-4-yl)benzamide (4d)

Melting Range: >240 ºC; ^{1}H-NMR (400 MHz; DMSO-d_6; TMS): δ 7.0-8.1 (m, 11H, Ar-H), 10.3 (s, 1H, -NH), 12.3 (s, 1H, -NH); ^{13}C NMR (100 MHz; DMSo-d6): 113.5, 119.2, 120.4, 122.6, 127.4, 127.9, 128.5, 129.4, 129.9, 130.1, 131.7, 132.5, 136.5, 137.9, 139.2, 149.1, 152.1, 166.7; $M^{+\cdot}$ = 348, $M^{+\cdot}2$ = 350.

2-(1H-benzo[d]imidazol-2-yl)-N-(3-chloropyridin-4-yl)benzamide (4d)
Melting Range: >240 ^{o}C; ^{1}H-NMR (400 MHz; DMSO-d_6; TMS): δ 7.0-8.1 (m, 11H, Ar-H), 10.3 (s, 1H, -NH), 12.3 (s, 1H, -NH); ^{13}C NMR (100 MHz; DMSo-d6): 113.5, 119.2, 120.4, 122.6, 127.4, 127.9, 128.5, 129.4, 129.9, 130.1, 131.7, 132.5, 136.5, 137.9, 139.2, 149.1, 152.1, 166.7; $M^{+\cdot}$ = 348, $M^{+\cdot}2$ = 350.

2-(1H-benzo[d]imidazol-2-yl)-N-(3-bromopyridin-4-yl)benzamide (4e)
Melting Range: >240 ^{o}C; ^{1}H-NMR (400 MHz; DMSO-d_6; TMS): δ 7.2-8.2 (m, 11H, Ar-H), 10.4 (s, 1H, -NH), 12.6 (s, 1H, -NH); ^{13}C NMR (100 MHz; DMSo-d6): 112.4, 117.3, 121.3, 121.9, 126.6, 127.8, 128.6, 129.9, 130.9, 131.1, 131.7, 132.8, 136.8, 137.9, 139.6, 149.2, 152.3, 166.8; $M^{+\cdot}$ = 392, $M^{+\cdot}2$ = 394.

2-(1H-benzo[d]imidazol-2-yl)-N-(3-methoxypyridin-4-yl)benzamide (4f)
Melting Range: 232-234 ^{o}C; ^{1}H-NMR (400 MHz; DMSO-d_6; TMS): δ 3.4 (s, 3H, Ar-H), 7.1-8.2 (m, 11H, Ar-H), 10.5 (s, 1H, -NH), 12.5 (s, 1H, -NH); ^{13}C NMR (100 MHz; DMSo-d6): 35.3, 111.2, 115.2, 122.4, 123.2, 126.3, 127.9, 128.9, 129.9, 131.1, 131.5, 131.9, 132.9, 136.9, 137.8, 139.8, 149.8, 152.5, 166.9; $M^{+\cdot}1$ = 346.

2-(1H-benzo[d]imidazol-2-yl)-N-(3-cyanopyridin-4-yl)benzamide (4g)
Melting Range: 238-240 ^{o}C; ^{1}H-NMR (400 MHz; DMSO-d_6; TMS): δ 7.0-8.0 (m, 11H, Ar-H), 10.7 (s, 1H, -NH), 12.7 (s, 1H, -NH); ^{13}C NMR (100 MHz; DMSo-d6): 113.4, 116.1, 123.5, 123.8, 126.5, 127.8, 128.7, 129.8, 130.5, 131.6, 132.6, 132.8, 135.7, 137.9, 139.9, 148.7, 151.6, 168.1; $M^{+\cdot}1$ = 341.

2-(1H-benzo[d]imidazol-2-yl)-N-(3-fluoropyridin-4-yl)benzamide (4h)
Melting Range: 225-228 ^{o}C; ^{1}H-NMR (400 MHz; DMSO-d_6; TMS): δ 7.1-8.1(m, 11H, Ar-H), 10.8 (s, 1H, -NH), 12.5 (s, 1H, -NH); ^{13}C NMR (100 MHz; DMSo-d6): 112.5, 116.3, 122.6, 123.9, 126.8, 127.6, 128.0, 129.2, 130.6, 131.0, 132.2, 132.4, 135.8, 137.7, 139.7, 148.6, 151.4, 168.3; $M^{+\cdot}1$ = 334.

CONCLUSION

In summary, green synthetic strategy have been developed for the synthesis of **4** in water through one-pot, three-component synthesis. These reactions provide excellent yields, involve easy workup and use water as solvent which are the merits of this preparation.

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