



ENVIRONMENTALLY FRIENDLY, ONE-POT SYNTHESSES OF 2-(1H-BENZO[d]IMIDAZOLE-2-YL)-N-ARYLBENZAMIDES

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Eco-friendly, one-pot three-component syntheses of 2-(1H-benzo[d]imidazole-2-yl)-N-arylbenzamides have been developed by combining Phthaloyl dichloride with anilines and o-phenylenediamine in glycerol without any external catalyst. These reactions involve easy workup, provide excellent yields and use glycerol as solvent at 100 °C for 60-90 min which are the merits of this preparation.

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Introduction

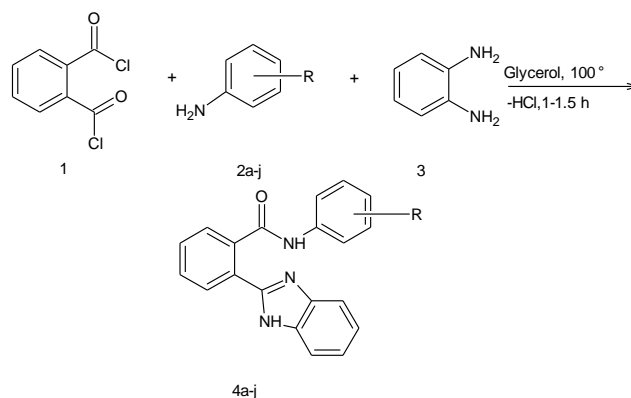
Development of efficient and environmentally friendly methods is an important challenge in modern organic syntheses.¹ In many synthetic organic processes, solvents represent a severe pollution problem. Thus, the replacement of hazardous solvents with relatively green solvents or the altogether elimination of use of hazardous solvents in chemical processes has been one of the key achievements of green chemistry.² 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.³ In the past decade, water,⁴ glycerol,⁵ polyethylene glycol⁶ and ionic liquids⁷ have been used as green solvents in organic reactions. As a result, serious efforts are being made to develop glycerol as a solvent for most of the organic syntheses and processes wherever possible.

Hawkins⁸ and Perry⁹ reported the preparation of N-arylphthalimide acids by the reaction of phthalic anhydride with arylamines at room temperature in chloroform. Young et al reported¹⁰ the preparation of N-(2-aminophenyl)phthalimide by the reaction of phthalic anhydride with o-phenylenediamine in DMF. Perry et al¹¹ prepared these compounds in chloroform. Keeping the above results in mind, we now wish to report our synthetic studies on reactions of phthaloyl dichloride **1** with anilines and with o-phenylenediamine **3**.

Results and discussion

As illustrated in Scheme 1, a mixture of phthaloyl dichloride **1**, aniline **2a** and o-phenylenediamine **3** was heated at 100 °C in glycerol for 60 min resulting in the formation of 2-(1H-benzo[d]imidazole-2-yl)-N-phenylbenzamide **4a** (Table 1, entry 1). Then, this one-pot reaction of **1** (1 mmol), **2a** (1 mmol) and **3** (1 mmol) was optimized by doing a series of experiments in the presence

of different solvents at different temperatures (Table 1). However, it is greatly notable that the one-pot reaction in glycerol at 100 °C for 60 min gave reasonably high yield (80 %) of the product **4a** compared to other solvents such as PEG-600, ethylene glycol, DMF, DMSO and polyphosphoric acid (PPA) (Table 1, entry 11).



Scheme 1. One-pot synthesis of compounds **4a-4j** (R=H(a), p-Cl(b), p-Me(c), o-Me(d), p-Br(e), p-I(f), p-MeO(g), p-OH(h), p-NO₂(i), m-NO₂(j))

Table 1. Effect of solvent and Temperature on one-pot reaction of phthaloyl dichloride, aniline and o-phenylenediamine

Entry	Solvent	Temp., °C	Time, min	Yield of 4a , %
1	Glycerol	100	60	80
2	Glycerol	RT	240	-
3	PEG-600	RT	300	-
4	PEG-600	100	150	60
5	Ethylene glycol	RT	300	-
6	Ethylene glycol	100	150	55
7	DMF	RT	300	40
8	DMF	100	150	45
9	DMSO	RT	300	30
10	DMSO	100	180	35
11	PPA	100	90	20

Using the above-stated optimized conditions, the synthesis of **4a-4j** was carried out by heating the mixture of **1**, **2a-2j** and **3** in glycerol at 100 °C for 60-90 min. Products were obtained in good yield and no side products were detected.

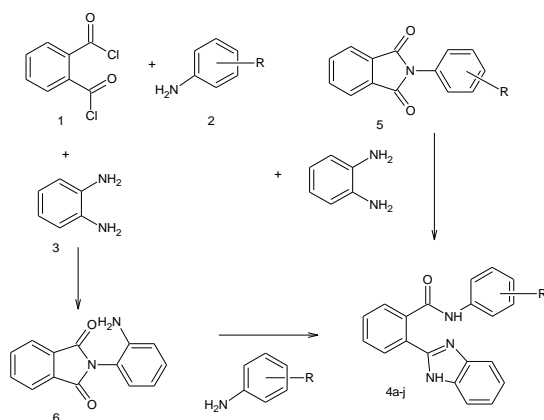
Their structures have been established on the basis of spectral properties such as IR, NMR and mass spectra. (Scheme 1) (Table 2).

Table 2. Characterization data, reaction time and yields of **4a-4j** obtained from **1**, **2a-2j** and **3**.

Entry	Starting material	Product obtained	Time, min	Yield, %*
1	2a	4a	60	80
2	2b	4b	65	80
3	2c	4c	70	75
4	2d	4d	80	75
5	2e	4e	85	80
6	2f	4f	90	80
7	2g	4g	80	75
8	2h	4h	65	80
9	2i	4i	75	80
10	2j	4j	75	85

*Yields of crude products

Two possible reaction routes can be proposed to account for the formation of **4** in the one-pot synthesis from **1**, **2** and **3**. One among them is when phthaldichloride **1** reacts with aniline **2** to form the imide intermediate **5** by liberating hydrogen chloride. Then **5** was attacked by phenylenediamine **3** to form **4**. In the second probable reaction route, reaction of phthaldichloride **1** with *o*-phenylenediamine **3** yields the intermediate **6** by liberation hydrogen chloride. Then, **6** was attacked by **2** to form **4**. Intermediate **6** was prepared separately by the reaction between **1** and **3**, then then treatment of **6** with **2** in water gave **4**.



Scheme 2. Possible reaction routes to form compounds **4** from compounds **1**, **2** and **3**.

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. ¹H NMR spectra were recorded in DMSO–d₆ using TMS as internal standard using 400 MHz spectrometer. Mass spectra were recorded on Agilent–LCMS

instrument under CI conditions and given by Q+1 values only. Starting materials **1** and **2** were obtained from commercial sources and used as such.

General procedure for preparation of **4a-j** from **1**, **2a-j** and **3** by one-pot synthesis

A mixture of **1** (10 mM), **2a-2j** (10 mM), **3** (10 mM), and glycerol (20 ml) was heated at 100 °C for 60-90 min. At the end of this period, a colourless solid separated out from reaction mixture which was collected by filtration. The isolated solid was washed with water (10 ml) and dried. The product was recrystallized from a suitable solvent to obtain **4a-4j**.

2-(1H-Benzo[d]imidazole-2-yl)-N-phenylbenzamide (**4a**)

Melting point: >250 °C; IR (KBr): 3038-3353 cm⁻¹ (broad, medium, -NH- and -OH groups put together), 1703 cm⁻¹ (sharp, strong, -CO- of acid group), 1690 cm⁻¹ (sharp, strong, -CO- of acid group), 1632 cm⁻¹ (sharp, strong, -CO- of amide group); ¹H NMR δ_H(400 MHz; DMSO-d₆; Me₄Si) 7.1-8.1 (m, 13H, Ar-H), 10.3(s, 1H, -CO-NH, D₂O exchangeable), 12.7(s, 1H, -NH, D₂O exchangeable); HRMS calcd for C₂₀H₁₅N₃O [M+H]⁺: 314.32326, Found: 314.32329.

2-(1H-Benzo[d]imidazole-2-yl)-N-(4-chlorophenyl)benzamide (**4b**)

Melting point: >250 °C; IR (KBr): 3036-3355 cm⁻¹ (broad, medium, -NH- and -OH groups put together), 1705 cm⁻¹ (sharp, strong, -CO- of acid group), 1692 cm⁻¹ (sharp, strong, -CO- of acid group), 1634 cm⁻¹ (sharp, strong, -CO- of amide group); ¹H NMR δ_H(400 MHz; DMSO-d₆; Me₄Si) 7.0-8.0 (m, 12H, Ar-H), 10.3(s, 1H, -CO-NH, D₂O exchangeable), 12.5 (s, 1H, -NH, D₂O exchangeable); HRMS calcd for C₂₀H₁₄ClN₃O [M+H]⁺: 348.32326, Found: 348.32329.

2-(1H-Benzo[d]imidazole-2-yl)-N-(4-methylphenyl)benzamide (**4c**)

Melting point: >250 °C; IR (KBr): 3035-3355 cm⁻¹ (broad, medium, -NH- and -OH groups put together), 1708 cm⁻¹ (sharp, strong, -CO- of acid group), 1692 cm⁻¹ (sharp, strong, -CO- of acid group), 1635 cm⁻¹ (sharp, strong, -CO- of amide group); ¹H NMR δ_H(400 MHz; DMSO-d₆; Me₄Si) 2.4 (s, 3H, CH₃), 7.0-8.0 (m, 12H, Ar-H), 10.3(s, 1H, -CO-NH, D₂O exchangeable), 12.6 (s, 1H, -NH, D₂O exchangeable); HRMS calcd for C₂₁H₁₇N₃O [M+H]⁺: 328.32326, Found: 328.32329.

2-(1H-Benzo[d]imidazole-2-yl)-N-(2-methylphenyl)benzamide (**4d**)

Melting point: > 250 °C; IR (KBr): 3032-3350 cm⁻¹ (broad, medium, -NH- and -OH groups put together), 1700 cm⁻¹ (sharp, strong, -CO- of acid group), 1692 cm⁻¹ (sharp, strong, -CO- of acid group), 1633 cm⁻¹ (sharp, strong, -CO- of amide group); ¹H NMR δ_H(400 MHz; DMSO-d₆; Me₄Si) 2.3 (s, 3H, CH₃), 7.0-8.0 (m, 12H, Ar-H), 10.4 (s, 1H, -CO-NH,

D₂O exchangeable), 12.6(s, 1H, -NH, D₂O exchangeable); HRMS calcd for C₂₁H₁₇N₃O [M+H]⁺: 328.32326, Found: 328.32329.

2-(1H-Benzo[d]imidazole-2-yl)-N-(4-bromophenyl)benzamide (4e)

Melting point: > 250 °C; IR (KBr): 3040-3357 cm⁻¹ (broad, medium, -NH- and -OH groups put together), 1713 cm⁻¹ (sharp, strong, -CO- of acid group), 1695 cm⁻¹ (sharp, strong, -CO- of acid group), 1635 cm⁻¹ (sharp, strong, -CO- of amide group); ¹H NMR δ_H(400 MHz; DMSO-d₆; Me₄Si) δ 7.0-8.0 (m, 12H, Ar-H), 10.4(s, 1H, -CO-NH, D₂O exchangeable), 12.6 (s, 1H, -NH, D₂O exchangeable); HRMS calcd for C₂₀H₁₄BrN₃O [M+H]⁺: 392.32326, Found: 392.32329.

2-(1H-Benzo[d]imidazole-2-yl)-N-(4-iodophenyl)benzamide (4f)

Melting point: 240-242 °C; IR (KBr): 3031-3351 cm⁻¹ (broad, medium, -NH- and -OH groups put together), 1701 cm⁻¹ (sharp, strong, -CO- of acid group), 1691 cm⁻¹ (sharp, strong, -CO- of acid group), 1639 cm⁻¹ (sharp, strong, -CO- of amide group); ¹H NMR δ_H(400 MHz; DMSO-d₆; Me₄Si) δ 7.0-8.0 (m, 12H, Ar-H), 10.2(s, 1H, -CO-NH, D₂O exchangeable), 12.8 (s, 1H, -NH, D₂O exchangeable); HRMS calcd for C₂₀H₁₄IN₃O [M+H]⁺: 440.32326, Found: 440.32329.

2-(1H-Benzo[d]imidazole-2-yl)-N-(4-methoxyphenyl)benzamide (4g)

Melting point: >250 °C; IR (KBr): 3030-3350 cm⁻¹ (broad, medium, -NH- and -OH groups put together), 1700 cm⁻¹ (sharp, strong, -CO- of acid group), 1691 cm⁻¹ (sharp, strong, -CO- of acid group), 1631 cm⁻¹ (sharp, strong, -CO- of amide group); ¹H NMR δ_H(400 MHz; DMSO-d₆; Me₄Si) δ 2.7 (s, 3H, CH₃), 7.0-8.0 (m, 12H, Ar-H), 10.5(s, 1H, -CO-NH, D₂O exchangeable), 12.7 (s, 1H, -NH, D₂O exchangeable); HRMS calcd for C₂₁H₁₇N₃O₂ [M+H]⁺: 344.32326, Found: 344.32329.

2-(1H-Benzo[d]imidazole-2-yl)-N-(4-hydroxyphenyl)benzamide (4h)

Melting point: >250 °C; IR (KBr): 3030-3343 cm⁻¹ (broad, medium, -NH- and -OH groups put together), 1701 cm⁻¹ (sharp, strong, -CO- of acid group), 1689 cm⁻¹ (sharp, strong, -CO- of acid group), 1635 cm⁻¹ (sharp, strong, -CO- of amide group); ¹H NMR δ_H(400 MHz; DMSO-d₆; Me₄Si) δ 7.0-8.0 (m, 12H, Ar-H), 8.5(s, 1H, -OH, D₂O exchangeable), 10.2(s, 1H, -CO-NH, D₂O exchangeable), 12.4(s, 1H, -NH, D₂O exchangeable); HRMS calcd for C₂₀H₁₅N₃O₂ [M+H]⁺: 330.32326, Found: 330.32329.

2-(1H-Benzo[d]imidazole-2-yl)-N-(4-nitrophenyl)benzamide (4i)

Melting point: >250 °C; IR (KBr): 3031-3351 cm⁻¹ (broad, medium, -NH- and -OH groups put together), 1700 cm⁻¹ (sharp, strong, -CO- of acid group), 1694 cm⁻¹ (sharp, strong, -CO- of acid group), 1632 cm⁻¹ (sharp, strong, -CO- of

amide group); ¹H NMR δ_H(400 MHz; DMSO-d₆; Me₄Si) δ 7.0-8.0 (m, 12H, Ar-H), 10.4(s, 1H, -CO-NH, D₂O exchangeable), 12.7(s, 1H, -NH, D₂O exchangeable); HRMS calcd for C₂₀H₁₄N₄O₃ [M+H]⁺: 359.32326, Found: 359.32329.

2-(1H-Benzo[d]imidazole-2-yl)-N-(3-nitrophenyl)benzamide (4j)

Melting point: >250 °C; IR (KBr): 3039-3359 cm⁻¹ (broad, medium, -NH- and -OH groups put together), 1709 cm⁻¹ (sharp, strong, -CO- of acid group), 1699 cm⁻¹ (sharp, strong, -CO- of acid group), 1638 cm⁻¹ (sharp, strong, -CO- of amide group); ¹H NMR δ_H(400 MHz; DMSO-d₆; Me₄Si) δ 7.0-8.0 (m, 12H, Ar-H), 10.2(s, 1H, -CO-NH, D₂O exchangeable), 12.8(s, 1H, -NH, D₂O exchangeable); HRMS calcd for C₂₀H₁₄N₄O₃ [M+H]⁺: 359.32326, Found: 359.32329.

Conclusion

In summary, a green synthetic method have been developed for the synthesis of **4a-4j** with good yield in glycerol through a one-pot, three-component synthesis.

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