ONE-POT SYNTHESES OF 2-(1*H*-BENZO[*d*]OXAZOLE-2-YL)-*N*-ARYLBENZAMIDES BY SELF-CATALYSIS

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A novel, efficient, and high-yielding one-pot three-component method was developed for the synthesis of 2-(1*H*-benzo[*d*]oxazole-2-yl)-N-arylbenzamides by combining phthaldichloride with anilines & o-aminophenol in water without any external catalyst. The environmentally friendly procedure, easy operation and mild reaction conditions enable the tolerance of a wide scope of functionalities as well as high reaction efficiency.

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INTRODUCTION

In today's world, the development of efficient, economical and environmentally friendly synthesis 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 among others.[3] In the past decade, water,[4] glycerol,[5] polyethylene glycol,[6] ionic liquids have been used as green solvents in organic reactions. Among all the green solvents, water is the safest, cheapest and non-toxic solvent.[8] As a result, serious efforts are being made to develop water as a solvent for most of the organic syntheses and processes wherever possible.

Benzoxazoles are important building blocks in medicinal chemistry and can be found in a number of drug candidates under investigation for the treatment of various diseases.[8] The classical approach for the synthesis of benzoxazoles involves coupling of carboxylic acids with *o*-aminophenols by dehydration catalysed by acids.[8] However, the utility and applicability of this protocol is often compromised since it is usually run in volatile organic solvents and requires stoichiometric or excess corrosive and toxic oxidants such as DDC (dicyclohexyl carbodiimide), HgO , NiO_2 , $AgNO_3$, KO_2 or H_2O_2/LiOH.[8]

Keeping the above results in mind, we now wish to report a synthesis of 2-(1*H*-benzo[*d*]oxazole-2-yl)-N-arylbenzamides by combining phthaldichloride with anilines and *o*-aminophenol in water without any external catalyst at 100 °C for 60-90 min.

EXPERIMENTAL

^{1}H and ^{13}C-NMR spectra were recorded in DMSO-d_6 at 400 MHz and 100 MHz respectively. Chemical shifts (δ) are reported parts per million (ppm) and are referenced to tetramethylsilane (TMS) as internal standard. NMR multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad signal. The yields are based on isolated compounds after purification. 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. Mass spectra were recorded on Agilent-LCMS instrument under CI conditions and given by Q+1 values only. Starting materials phthaldichloride and substituted anilines were obtained from commercial sources and were used as such.

General procedure for preparation of 2-(1*H*-benzo[*d*]oxazole-2-yl)-N-arylbenzamides by one-pot synthesis

A mixture of phthaldichloride (**1**) (10 mM), substituted anilines (**2a-2h**) (10 mM), *o*-phenylenediamine (**3**) (10 mM), and water (30 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 (20 mL) and dried. The product was recrystallized from ethanol solvent to obtain 2-(1*H*-benzo[*d*]oxazole-2-yl)-N-arylbenzamide (**4a-4h**).

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

M.P. 217-218 °C. IR (KBr) : 3050-3430 (br, m, -NH-), 1713 cm^{-1} (s, s, -CO-). ^{1}H NMR δ = 6.8-7.9 (m, 13H, Ar-H), 9.8 (s, 1H, -CO-NH, D_2O exchangeable); ^{13}C NMR δ = 116, 118, 119, 123, 123, 127, 128, 128, 130, 130, 131, 131, 134, 134, 153, 167; HRMS calcd. for $C_{20}H_{14}N_2O_2$ $[M+H]^+$ 314.8469. Found 314.8426.

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

M.P. 202-204 °C. IR (KBr): 3042-3457 (br, m, -NH-), 1711 cm^{-1} (s, s, -CO-). ^{1}H NMR δ = 6.8-7.9 (m, 12H, Ar-H),

9.9 (s, 1H, -CO-NH, D_2O exchangeable); ^{13}C NMR δ =116, 118, 119, 123, 123, 127, 128, 129, 130, 130, 131, 131, 134, 135, 153, 167. HRMS calcd. for $C_{20}H_{13}ClN_2O_2$ $[M+H]^+$ 349.4876. Found: 349.4849.

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

M.P. 221-223 ºC. IR (KBr): 3065-3458 (br, m, -NH-), 1716 cm^{-1} (s, s, -CO-). ^1H NMR δ = 2.0 (s, 3H, -CH3), 6.8-7.9 (m, 12H, Ar-H), 9.8 (s, 1H, -CO-NH, D2O exchangeable); ^{13}C NMR δ = 23, 115, 118, 119, 123, 123, 127, 128, 128, 130, 130, 131, 131, 134, 134, 152, 167; HRMS calcd. for $C_{21}H_{16}N_2O_2$ $[M+H]^+$ 329.5833. Found 329.5837.

2-(1*H*-Benzo[*d*]oxazole-2-yl)-*N*-(4-bromophenyl)benzamide (4d)

M.P. 209-211 ºC. IR (KBr): 3048-3458 (br, m, -NH-), 1706 cm-1 (s, s, -CO-). ^1H NMR δ = 2.2 (s, 3H, -CH3), 6.8-7.9 (m, 12H, Ar-H), 9.8 (s, 1H, -CO-NH, D2O exchangeable); ^{13}C NMR δ = 116, 118, 119, 123, 123, 127, 128, 129, 130, 130, 131, 131, 134, 135, 153, 168. HRMS calcd. for $C_{20}H_{13}BrN_2O_2$ $[M+H]^+$ 393.3772. Found 393.3736.

2-(1*H*-Benzo[*d*]oxazole-2-yl)-*N*-(4-iodophenyl)benzamide (4e)

M.P. 211-213 ºC. IR (KBr): 3033-3425 (br, m, -NH-), 1713 cm^{-1} (s, s, -CO-). ^1H NMR δ = 6.8-7.9 (m, 12H, Ar-H), 9.8 (s, 1H, -CO-NH, D_2O exchangeable); ^{13}C NMR δ = 115, 119, 119, 122, 123, 127, 128, 128, 130, 130, 131, 132, 134, 134, 153, 167. HRMS calcd. for $C_{20}H_{13}IN_2O_2$ $[M+H]^+$ 441.1752. Found 441.1725.

2-(1*H*-Benzo[*d*]oxazole-2-yl)-*N*-(4-methoxyphenyl)benzamide (4f)

M.P. 139-141 ºC. IR (KBr): 3051-3462 (br, m, -NH-), 1712 cm^{-1} (s, s, -CO-). ^1H NMR δ = 3.6 (s, 3H, -OCH3), 6.8-8.0 (m, 12H, Ar-H), 9.8 (s, 1H, -CO-NH, D_2O exchangeable); ^{13}C NMR δ = 55, 116, 118, 119, 123, 123, 126, 128, 129, 131, 132, 132, 133, 134, 135, 153, 168. HRMS calcd. for $C_{21}H_{16}N_2O_3$ $[M+H]^+$ 345.2773. Found 345.2726.

2-(1*H*-Benzo[*d*]oxazole-2-yl)-*N*-(4-hydroxyphenyl)benzamide (4g)

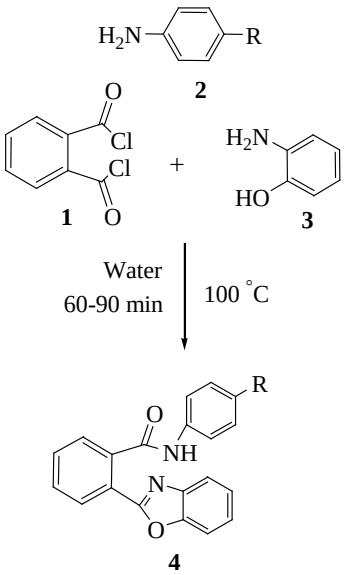
M.P. >220 ºC. IR (KBr): 3058-3472 (br, m, -NH-), 1709 cm^{-1} (s, s, -CO-). ^1H NMR δ = 6.8-8.0 (m, 12H, Ar-H), 8.2 (s, 1H, -OH), 9.8 (s, 1H, -CO-NH, D_2O exchangeable); ^{13}C NMR δ = 114, 115, 117, 121, 123, 126, 127, 128, 131, 132, 132, 133, 134, 134, 150, 164. HRMS calcd. for $C_{20}H_{14}N_2O_3$ $[M+H]^+$ 331.1664. Found 331.1627.

2-(1*H*-Benzo[*d*]oxazole-2-yl)-*N*-(4-nitrophenyl)benzamide (4h)

M.P. 178-181 ºC; IR (KBr): 3052-3461 (br, m, -NH-), 1705 cm^{-1} (s, s, -CO-). ^1H NMR δ = 6.8-8.0 (m, 12H, Ar-H), 9.8 (s, 1H, -CO-NH, D_2O exchangeable); ^{13}C NMR δ = 115, 119, 119, 122, 123, 125, 127, 128, 130, 130, 131, 132, 134, 134, 153, 164. HRMS calcd. for $C_{20}H_{13}N_3O_4$ $[M+H]^+$ 360.4682. Found 360.4655.

RESULTS AND DISCUSSION

At the outset of this study, we heated a mixture of **1,** aniline (**2a**) and **3** at 100 ºC in water for 60 min resulting in the formation of (**4a**) (Table 1, entry 1) as illustrated in scheme 1.



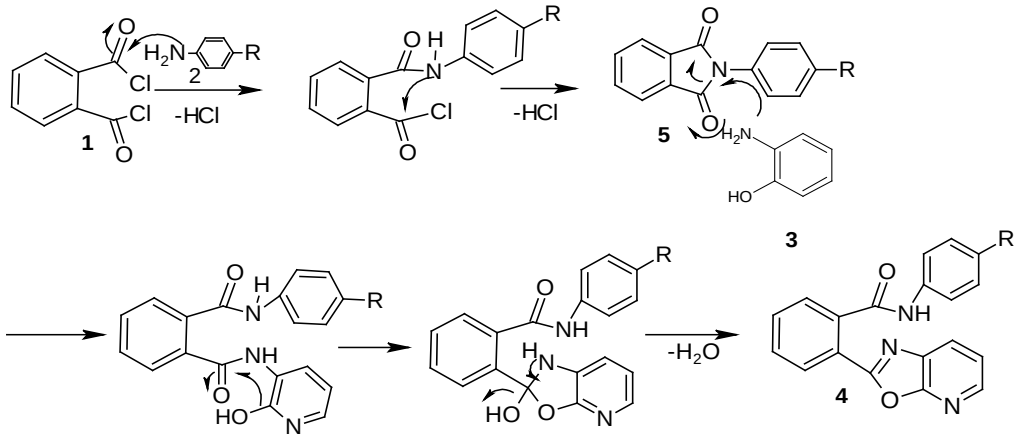
R = (a) H, (b) Cl, (c) Me, (d) Br, (e) I, (f) OMe, (g) OH, (h) NO_2

Scheme 1. Synthesis of **4a-h** in water.

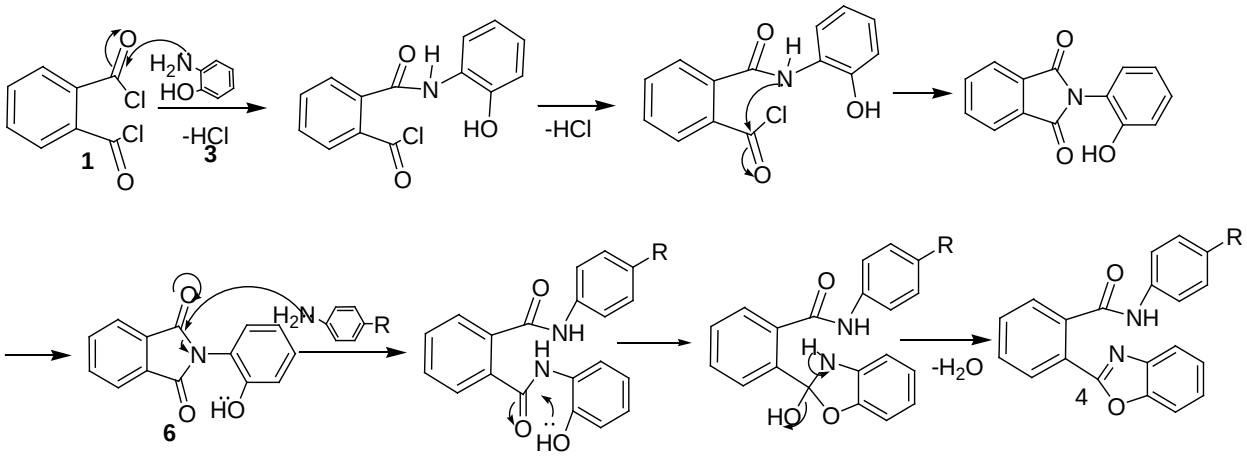
The structure of the product was assigned on the basis of its spectral properties IR, NMR and MS. Then, this one-pot reaction of **1** (1 equiv.), **2a** (1 equiv.) and **3** (1 equiv.) was optimized by doing a series of experiments. Initially, the reaction was carried out in various solvents such as water, glycerol, PEG-600, ethylene glycol, DMF, DMSO and PPA and out of this, water at 100 ºC afforded the desired product with the best yield **(**Table 1, entry 1**).** In the next step, we tested the effect of temperature at 25-30, 50-55 and 100 ˚C in water as solvent. At 100 ˚C, in water as solvent the desired product was given in 86 % yield.

With our optimized reaction conditions in hand (Table 1, entry 1), scope and limitations of the proposed method were investigated as shown in Table 2. First, we examined the substrate scope of anilines. The synthesis of **4a-4h** was carried out by heating the mixtures of **1, 2a-2h** and **3** in water at 100 ºC 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 MS. **(**Scheme 1**)** (Table 2).

Two probable mechanisms (Schemes 2and 3) have been proposed to account for the formation of **4** in the one-pot synthesis from **1, 2** and **3.** In the first mechanism**,** phthaldichloride **1** reacts with aniline **2** to form the imide intermediate **5** by liberating HCl. Then **5** was attacked by



Scheme 2. First of the two proposed mechanisms of the synthesis.



Scheme 3. Second of the two proposed mechanisms of the synthesis.

o-aminophenol **3** to form **4** in about two steps in the presence of HCl as catalyst.

Table 1. Effect of solvent and temperature on one-pot reaction of **1**, **2** and **3** to yield **4a**.

Entry	Solvent	Temp./° C	Time, min	Yield (% molar)
1	Water	100	60	86
2	Glycerol	100	120	80
3	PEG-600	100	120	78
4	Ethyleneglycol	100	100	75
5	DMF	100	90	60
6	DMSO	100	90	65
7	PPA	100	90	50
8	Water	25-30	600	80
9	Water	50-55	360	82

In the second probable mechanism**,** shown in scheme 3, a reaction of phthaldichloride **1** with *o*-aminophenol **3** yields the intermediate **6** by liberation of HCl.

Then, **6** was attacked by **2** to form **4** in two steps in the presence of HCl as catalyst. It seems likely that both the mechanisms are operating in this reaction. The difference between the two mechanisms in that the first mechanism involves a prior condensation of **1** with **2** followed by condensation with **3** whereas the second mechanism involves an initial condensation of **1** with **3** followed by condensation with **2**.

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

Entry	Starting Material	Product obtained	Time, min	Yield≠
1	**2a**	**4a**	60	86
2	**2b**	**4b**	70	84
3	**2c**	**4c**	90	85
4	**2d**	**4d**	75	83
5	**2e**	**4e**	80	80
6	**2f**	**4f**	90	80
7	**2g**	**4g**	80	81
8	**2h**	**4h**	90	84

≠ Refers to yields of crude products only.

CONCLUSION

In summary, one-pot reaction has been developed for the synthesis of 2-(1*H*-benzo[*d*]oxazole-2-yl)-N-arylbenzamides with good yields. This method has an environmentally friendly procedure, easy operation and mild reaction conditions. It shows tolerance of a wide variety of functionalities as well as high reaction efficiency.

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