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CATALYST-FREE & WATER MEDIATED: STEP-WISE, TANDEM & ONE-POT SYNTHESES OF 2-(1*H*-BENZO[D]OXAZOLE-2-YL)-*N*-ARYLBENZAMIDES

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ABSTRACT
Catalyst-free & water mediated, step-wise, tandem & one-pot three-component synthesis of 2-(1*H*-benzo[d]oxazole-2-yl)-*N*-arylbenzamides have been developed by combining phthalic anhydride with anilines & *o*-aminophenol. These reactions involve easy workup, provide excellent yields and use water as solvent which are the merits of this preparation.

KEYWORDS: water, phthalic anhydride, anilines, *o*-aminophenol.

INTRODUCTION
In today's world, the development of efficient, economical & environmentally friendly synthesis 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 among others [III]. In the past decade, water [IV], glycerol [V], polyethylene glycol [VI], ionic liquids [VII] have been used as green solvents in organic reactions. Among all the green solvents, water is the safest, cheapest & non-toxic solvent [VIII]. 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 [IX]. The classical approach for the synthesis of benzoxazoles involves coupling of carboxylic acids with *o*-aminophenols by dehydration catalysed by acids [X].However, the utility and applicability of this protocol is often compromised since it is usually run in volatile organic

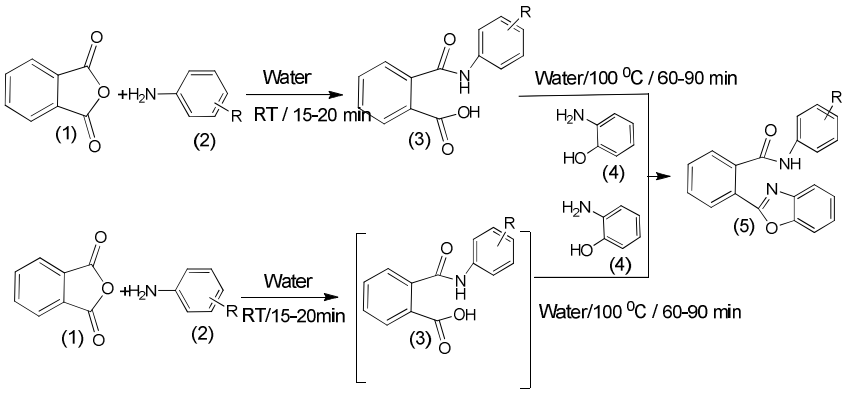
solvents and requires stoichiometric or excess corrosive and toxic oxidants such as DDC (dicyclohexyl carbodiimide) [XI], HgO [XII], NiO_2 [XIII], $AgNO_3$ [XIV], KO_2 [XV] or H_2O_2/LiOH [XVI].

Keeping the above results in mind and in continuation of our earlier work [XVII], we now wish to report our synthetic studies on reactions of phthalic anhydride **l** with anilines and *o*-aminophenol/*o*-aminothiophenol **4.** This is probably first report to prepare 2-(1*H*-benzo[d]oxazole/thiazole -2-yl)-*N*-arylbenzamides in water.

RESULTS AND DISCUSSION

As illustrated in **SCHEME 1**, phthalic anhydride **1** was reacted with aniline **2a** to form 2-(arylcarbamoyl)benzoic acid **3a** in water at RT for 15 min. **3a** was then reacted with *o*-aminophenol **4a** in refluxing water for 60 min resulting in the formation of 2-(1H-benzo[d]oxazole-2-yl)-N-phenylbenzamide **5a** (**TABLE 1, entry 1)**. The structure of the product was assigned on the basis of its spectral properties -IR, NMR & Mass (For details, please see the Experimental Section). **5a** could also be prepared by the tandem method involving the sequences **1+2a 3a 4 5a (SCHEME 1)**. In this tandem method, **1** was treated with **2a** in water at RT for 15 min until the disappearance of **1** was found on TLC. To the same reaction mixture, **4** was added and the reaction mixture refluxed for 60 min until the disappearance of **3a** took place as shown by TLC examination of reaction mixture with an authentic sample of **3a**. The mixture was then processed to obtain **5a** identical with the same product obtained earlier in the step-wise route **(SCHEME 1)**.

The reaction of **3a** (1mmol) with **4** (1mmol) was optimized by doing a series of experiments in the presence of different solvents and ionic liquids at different temperature **(TABLE 1)**. However, it is greatly notable that the reaction of **3a** with **4** at 100°C for 60 min in water, unlike in other solvents such as glycerol, PEG-600, ethylene glycol, DMF, DMSO, ionic liquids [bmim][Br], [bmim][OH] and PPA gave reasonably high yield (85%) of the product **5a** (**TABLE 1, entry 1).**

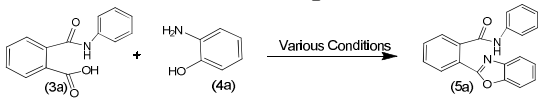


Scheme 1: Synthesis of 5a-5l by step-wise &Tandem reaction in water

Using the above-stated optimised conditions, in both, the step-wise & tandem reactions, **5a-5l** have been prepared by the condensation of phthalic anhydride **1** with anilines **2a-2l** in water to form 2-(arylcarbamoyl)benzoic acids **3a-3l** as intermediates at RT for 15-20 min.Thereafter, **3a-3l** were condensed with **4** at reflux for 60-90 min in water with good yield and no side products were detected. Their structures have been established on the basis of spectral such as IR, NMR & Mass spectra. **(SCHEME 1) (TABLE 3** [XVIII-XXI] **4 & 6).**

TABLE 1

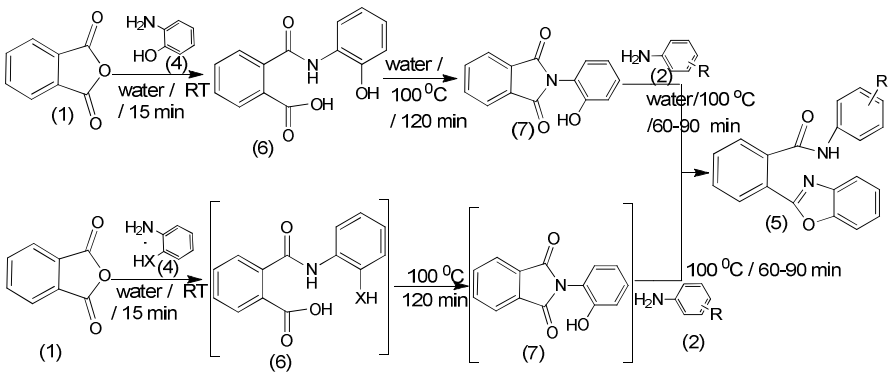
Effect of **Solvent & Temperature** on reaction of **3a** with **4a** yielding **5a.**



Entry	Solvent	Temp. /^{o} c	Time (min)	Yield of 5a(% molar)
1	**H_2O**	**100**	**90**	**85**
2	Glycerol	100	120	85
3	H_2O	RT	300	-
4	PEG-600	100	150	70
5	Ethyleneglycol	100	150	60
6	DMF	RT	300	30
7	DMF	100	240	35
8	DMSO	RT	300	40
9	DMSO	100	180	45
10	[bmim][Br]	100	90	75
11	[bmim][OH]	100	90	45
12	PPA	100	90	60

Alternative synthesis of 5a-5l

As illustrated in Scheme-2, **1** was reacted with 4a-4b in water at RT for 15 min to form 2-((2-hydroxyphenyl)carbamoyl)benzoic acid **6a**. The product was characterized by comparison of its physical & spectral data with that of same product reported [XVIII, XXII] earlier. **6a** was then converted into 2-(2-hydroxyphenyl)isoindoline-1, 3-dione **7a** by refluxing in water for 120 min **(SCHEME 2).** The product was characterized by comparison of its physical & spectral data with that of same product reported [XXIII, XXIV] earlier**. 7a** was then reacted with **2a** in refluxing water for 60 min resulting in the formation of **5a. 5a** could also be prepared by tandem method involving the sequence **(1+4 7 [2a] 5a) (SCHEME 2).** In the tandem method, **1** was treated with **4** in water to from **6a** at RT for 15 min. The completion of reaction was checked by TLC until the disappearance of **1** took place. Then, reaction mixture was refluxed in water for 120 min to from **7a**. To the resulting mixture, **2a** was added and the whole thing refluxed for 60 min giving **5a** and on processing the mixture no side products were detected. Structure of the final product was established by its comparison with authentic sample prepared earlier in step-wise route shown in Scheme-1. **(SCHEME 2)**

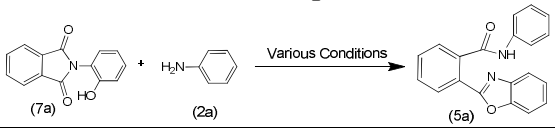


Scheme 2: Alternative Synthesis of 5a-5l by step-wise & Tandem reaction in water.

The reaction of **7a** with **2a** was examined by carrying out a series of experiments in the presence of different solvents and ionic liquids at different temperatures **(TABLE 2)**. It is found from these experiments that the reaction of **7a** with **2a** in refluxing water for 60 min, unlike in other solvents such as glycerol, PEG-600, ethylene glycol, DMF, DMSO, ionic liquids [bmim][Br], [bmim][OH] and PPA gave reasonably high yields (85%) of the product **5a** and in good purity. (**TABLE 2, entry 1).**

TABLE 2

Effect of **Solvent & Temperature** on reaction of **7** with **2a** yielding **5a.**



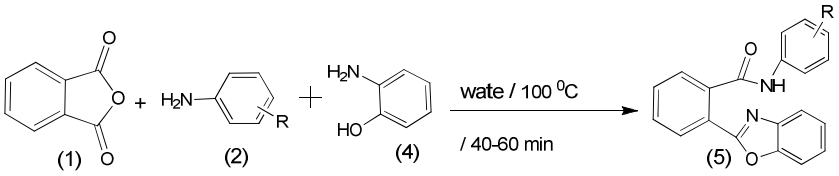
Entry	Solvent	Temp. /^{o} c	Time (min)	Yield of 5a (%)
1	**H2O**	**100**	**120**	**85**
2	Glycerol	100	180	75
3	H_2O	RT	300	-
4	PEG-600	100	150	65
5	Ethylene glycol	100	180	40
6	DMF	RT	300	20
7	DMF	100	180	25
8	[bmim][Br]	100	120	70
9	[bmim][OH]	100	120	75

10	DMSO	RT	300	25
11	DMSO	100	180	35

Using the above-stated optimised conditions, in both the step-wise & tandem reactions, **5a-5l** have been prepared by the treatment of **7** with several others anilines **2a-2l** in refluxing water for 60-90 min with good yield and no side products were detected. Their structures have been established on the basis of IR, NMR & Mass. **(SCHEME 1)** (Table 5 & 6, included in ESI).

One-pot synthesis of 5a-5l

Encouraged by above results, the preparation **5a-5l** was carried out in one-pot by heating a mixture of **1, 2a-2l** and **4(SCHEME 3)** in water at 100 ^{o}C for 40-60 min. Products were obtained in good yield and no side products were detected. Structures of the products have been established by comparison with authentic samples which were prepared in step wise fashion in Scheme-1. **(SCHEME-3) (Table 6, included in ESI).**



Scheme 3: Synthesis of 5a-5l by one-pot synthesis in water.

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 **1, 2 & 4** were obtained from commercial sources and used as such.

General procedures for preparation of 3

A mixture of **1** (10 mM) and **2** (10 mM) was stirred at RT for 15-20 min in water. 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 (10 ml) and dried. The product was recrystallized from a suitable solvent to obtain **3**.

General procedure for preparation of 5 from 3 & 4

A mixture of **3** (10 mM), **4** (10 mM) and water (20 ml) was refluxed at 100^{0}C for 60-90 min. 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 (10 ml) and dried. The crude product was recrystallized from a suitable solvent to obtain **5**.

General procedure for preparation of 5 by tandem reaction (1+2 → 3 → 5)

A mixture of **1** (10 mM) and **2** (10 mM) was stirred at RT in water for 15-20 min when colourless solid separated out from the reaction mixture. Then, to this solution **4** (10 mM) was added and the mixture refluxed at 100^{0}C for 60-90 min. Another colourless solid separated out from reaction mixture which was collected by filtration. The latter solid was washed with water (10 ml) and dried to obtained a crude products which was recrystallized from a suitable solvent to obtain **5**.

General procedure for preparation of 6 from 1 & 4:
A mixture of **1** (10 mM), **4** (10 mM) and water (20 ml) was stirred at RT for 15 min. At the end of this period, a colourless solid separated out from the reaction mixture which was collected by filtration. The latter solid was washed with water (10 ml) and dried. The crude product was recrystallized from a suitable solvent to obtain **6**.

Preparation of 7 from 6:
6 (10 mM) and water was refluxed at 100 ^{o}C for 90 min. At the end of this period, a colourless solid separated out from reaction mixture which was collected by filteration. The isolated solid was washed with water (10 ml) and dried. The crude product was recrystallized from a suitable solvent to obtain **7**.

General procedure for preparation of 5 from 7 & 2:
A mixture of **7** (10 mM), **2** (10 mM) and water was refluxed at 100 ^{o}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 hexane (10 ml) and dried. The product was recrystallized from a suitable solvent to obtain **5**.

General procedure for preparation of 5 by tandem reaction (1+4 → 7 → 2 5):
A mixture of **1** (10 mM), **4** (10 mM) and water (20 ml) was refluxed at 100 ^{o}C for 90 min. A colourless solid separated out from reaction mixture. Then, to this mixture at RT **2** (10 mM) was added and refluxed at 100 ^{o}C for 60-90 min. 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 suitable solvent to obtain **5**.

General procedure for preparation of 5 from 1, 2 & 4 by one-pot synthesis:
A mixture of **1** (10 mM), **2** (10 mM), **4** (10 mM), and water (20 ml) was refluxed at 100 ^{o}C for 40-60 min. 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 (10 ml) and dried. The crude product was recrystallized from a suitable solvent to obtain **5**.

2-(1*H*-benzo[d]oxazole-2-yl)-*N*-phenylbenzamide (5a)
M.P.= 218-220 ^{o}C; IR (KBr) : 3054-3455 cm-1 (broad, medium, -NH- group), 1703 cm-1 (sharp, strong, -CO- of amide group); 1H NMR δH (400 MHz; DMSO-d6; Me4Si): 6.89-7.97 (m, 13H, Ar-H), 9.84 (s, 1H, -CO-NH, D2O exchangeable); 13C NMR δC (100 MHz; DMSO-d6): 116.5, 118.8, 119.1, 123.3, 123.4, 127.3, 128.0, 128.8, 130.3, 130.3, 131.5, 131.9, 134.5, 134.6, 153.9, 167.1; HRMS calcd for C20H14N2O2 [M+H]+: 314.8469, Found: 314.8426.
Spectral and analytical data for other synthesized compounds are available in the online supplemental section.

CONCLUSION

In summary, practical and green synthetic methods have been developed for the synthesis of **5a-5l** in water through step wise fashion, tandem reaction and one-pot, three-component synthesis. Of all the methods discussed, one-pot, three-component synthesis **(SCHEME 3)** appears to be the better, less time and efficient method of products obtained, compared to the other two methods. Significant rate acceleration of the reaction in water observed and compared to commonly use of green solvents & ionic liquids. Through this reaction, variety of **5a-5l** synthesized in water with good yield.

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