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ONE-POT HETEROCONDENSATION FOR BENZOXAZINONE DERIVATIVES USING SODIUM PERBORATE AS CATALYST

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Abstract – An efficient synthesis of series of benzoxazinones, employing sodium perborate tetrahydrate (SPB) as a condensing agent is described. SPB in water and formic acid system is proved as a selective catalyst of hydration for cyanides. The rate enhancement and high yield is attributed to the coupling of suitable catalyst with this solvent system. This methodology eliminates the number of steps during the reaction.

INTRODUCTION

Efavirenz (Sustiva), a benzoxazinone derivative, is a non-nucleoside reverse transcriptase inhibitor that was approved by the FDA in 1998 and is presently in clinical use for the treatment of AIDS. The fight against HIV by developing more efficacious drugs than Efavirenz has been the prime driving force for benzoxazinone derivatization which has attained considerable attention.[1-6] The derivatives of benzoxazinone have also reported to possess progesterone receptor modulatory,[7] peroxisome proliferatory activated receptory[8,9] and antimycobacterial activities.[10,11]

Recent years have witnessed a phenomenal growth in the reactions occurring in aqueous medium,[12] safe handling and usage of less expensive catalysts.[13] SPB[14] (sodium perborate), being cheap and large industrial chemical (over 500,000 tons per annum), is used as a source of “active oxygen” in detergents, means is alternative to various forms of chlorine for fibre bleaching. Further, few applications are found in organic synthesis[15-19] and here its potential utility examined as a selective hydrolyzing agent for organic transformations. Moreover, it is a reagent of choice for these types of synthesis, by serving as a viable alternative to peroxides and peroxy acids as safer reagent results in relatively innocuous side products.[20,21]

Keeping in view of all these above reports it was thought worthwhile to perform one-pot heterocondensation of *o*-hydroxy aromatic aldehydes, hydroxylamine hydrochloride and various aromatic or heteroaromatic aldehydes to afford 2-substituted-2,3-dihydrobenzo[*e*][1,3]oxazin-4-ones. The

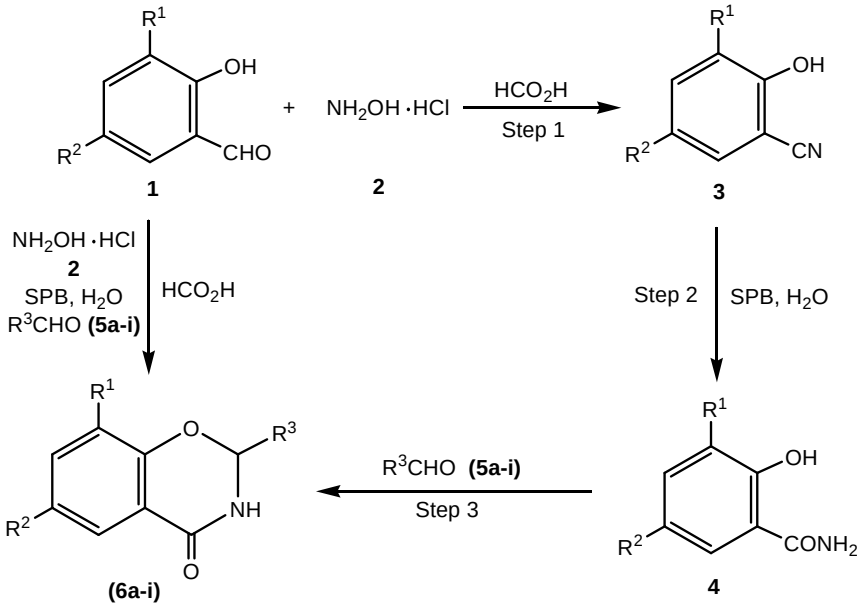
application of water-formic acid-SPB system in conjunction with one-pot heterocondensation provides unique chemical processes with special attributes in context of green chemistry. Thus, this protocol should be welcome in these environmentally conscious days.

RESULTS AND DISCUSSION

Since literature[22-26] revealed that 2-substituted-2,3-dihydrobenzo[*e*][1,3]oxazin-4-one synthesis were carried out in three different steps. Firstly, *o*-hydroxybenzonitrile (**3**) was prepared consisting two functional groups (–CN and –OH). Among these two, only the cyano group is transformed to yield corresponding amides ($–CONH_2$) in the presence of various oxidising agents to yield *o*-hydroxybenzamide intermediate (**4**) in step 2. Then in final step intermediate (**4**) undergoes cyclization reaction with aldehydes (**5a-g**) to give 2-substituted-2,3-dihydrobenzo[*e*][1,3]oxazin-4-ones (**6a-i**) as product. To carry out such synthesis in three steps is not only tedious with reduced yields but that requires hazardous chemicals[27] like HCl,[28] secondary amines (pyrrolidine, morpholine) as base[29] which contaminates final products. As isolation of the intermediates and the re-employing it as a reactant or substrate for target moiety synthesis led to yield losses as compared to one-pot heterocondensation synthesis. By optimizing the reaction conditions to obtain the desired product successfully, considering the sufficient purity in lesser time, an attempt has been made to develop new simple procedure for the preparation of heterocyclic compounds of biological interest. We report herein, for the first time a three component condensation of *o*-hydroxyaromatic aldehydes (**1**), hydroxylamine hydrochloride (**2**) and various aromatic or heteroaromatic aldehydes (**5a-i**), catalysed by SPB to give final moiety (2,3-dihydrobenzo[*e*][1,3]oxazin-4-ones) as shown in Scheme 1. Various experimental trials were carried out to standardise the reaction conditions. The key element in our approach is the novel utilization of *o*-hydroxyaromatic aldehydes (**1**) as a bifunctional building block whose application to the construction of various benzofused oxygen heterocycles of chemical and biological interest is investigated.

o-Hydroxy aldehyde (**1**) was taken with hydroxylamine hydrochloride in formic acid, where *in situ* formed oxime get transformed to cyanide via the elimination of water to give *o*-hydroxybenzonitrile (**3**) without touching the OH group. The completion of this transformation was checked by TLC which then followed by the addition of SPB dissolved in water and aldehyde (aromatic/heteroaromatic) and the reaction proceeds efficiently. Here, SPB specifically hydrolises the cyano group of (**3**) to amide, here again the hydroxyl group remained as such and leads to *o*-hydroxybenzamide (**4**) intermediate in the reaction mixture itself. The addition of aqueous solution of SPB makes this synthetic procedure mild and catalytic. As shown in Table 1, both aromatic and heteroaromatic aldehydes were tolerated equally to cyclize and gave final products (**6a-i**) in good to excellent yields. The best suitable solvent for the onward steps is the system of formic acid and water (1:1, v/v). To our surprise, the addition of water to formic acid in the first step,

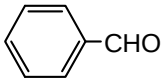
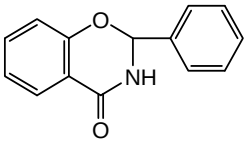
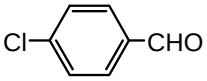
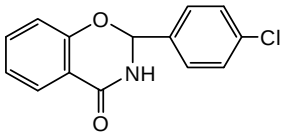
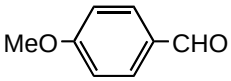
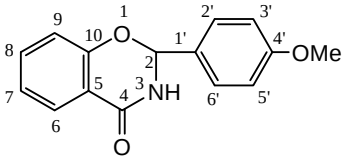
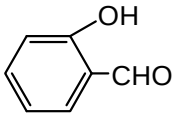
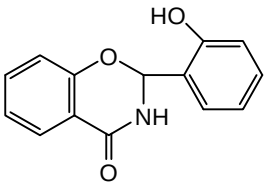
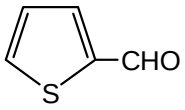
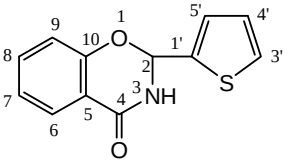
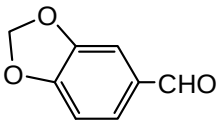
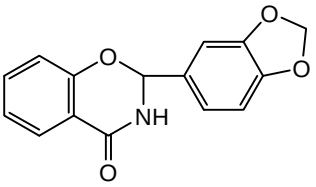
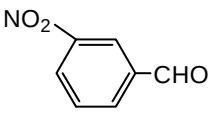
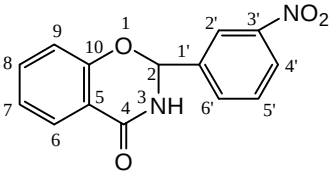
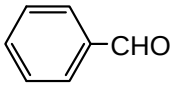
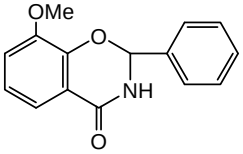
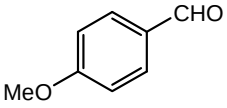
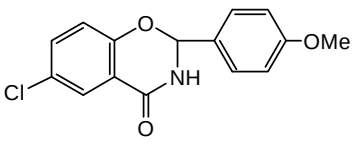
leads to no product formation as the elimination of water becomes harder. Other solvents and different solvent found systems like methanol, acetonitrile, ethyl acetate, chloroform, ethanol: water, chloroform: water, were also tried, but found to possess poor solubility of both hydroxylamine hydrochloride and SPB leads to very low yield (21-30%). In the course of optimization for the second step of these reaction conditions, the reason for the low yields (21-30%) is the regeneration of the corresponding amides (in step 3) through hydrolysis. Although polar solvents deactivate the activity of catalysts to some extent, we discovered that the reaction in the water and formic acid system is very effective in the presence of 5 equivalents of catalyst.



Scheme 1

When the conversion of CN to $CONH_2$ group completed, the intermediate *o*-hydroxybenzamide starts condensing to give cyclized product with aldehydes (already present in the reaction mixture) immediately. At such mentioned reaction conditions, it was suspected that formic acid itself could react with intermediate (**4**) instead of aldehydes to give a different cyclized product, but the characterization of final products (**6a-i**) ruled out the possibility of product formed by involvement of formic acid. The IR spectra of (**6a-i**) contain characteristic absorption bands of stretching vibrations of C=O group at 1665-1680 cm^{-1}. The stretching vibrations of alkyl groups and alicyclic C–H bonds give rise to absorption in the region of 2960-2870 cm^{-1}, those of the C–H bonds in the aromatic ring appear at 3060-3030 cm^{-1}. In the IR spectra of compounds **6f** the bands of the fragment C–O–C are observed in the region 1080-1200 cm^{-1}. Also, the ^1H NMR spectrum showed the presence of singlet due to C_2-H at δ 7.0-7.15, characterized the formation of product in Scheme 1. Apart from IR and ^1H NMR, CHN analysis and mass spectra also supported the proposed product. Chemical shifts of ^{13}C NMR spectra is in accordance with the desired synthesized products and confirmation their formation.

Table 1. Reaction times and yields for the synthesis of 2-substituted-2,3-dihydrobenzo[*e*][1,3]oxazin-4-one (**6a-i**)

No	Com-pound	R_1	R_2	R_3	Product	Yield[a] (%)	Time (h)
1	**6a**	H	H			85	10-11
2	**6b**	H	H			88	10.5-11.5
3	**6c**	H	H			95	12.0-12.5
4	**6d**	H	H			75	12.0-13.0
5	**6e**	H	H			80	11.5-12.0
6	**6f**	H	H			84	12.5-13.5
7	**6g**	H	H			85	13.5-14.0
8	**6h**	OCH_3	H			84	12.5-13.0
9	**6i**	H	Cl			82	13.0-13.5

[a] isolated and unoptimized yields.

CONCLUSION

Sodium perborate tetrahydrate (SPB) was found to be an excellent homogenous catalyst employed to get the transformation of *o*-hydroxybenzonitrile into corresponding amides to provide wide variety of 2-substituted-2,3-dihydrobenzo[*e*][1,3]oxazin-4-ones in water and formic acid system. SPB is non-corrosive, water soluble and selective oxidising catalyst which not only extends the scope of organic synthesis but also a viable substitute for hazardous peroxides and peroxyacids. These results also illustrate that intermediate **4** is a useful substrate for the generation of an array of oxygen fused heterocycles with three points of diversity and for synthesis of mentioned target moiety.

EXPERIMENTAL

The temperature of the reaction mixture was measured with a non-contact mini-Gun type IR thermometer (model 8868). IR spectra were recorded on a Perkin-Elmer FTIR-1710 spectrometer using KBr pellets. ^{1}H NMR spectra were obtained on Bruker Avance spectrospin 300 (300 MHz) using TMS as internal standard and chemical shift are in δ. Elemental analysis was performed on a Heraeus CHN-Rapid analyzer. The melting points (uncorrected) were determined on a Thomas Hoover melting point apparatus. ^{13}C NMR pectra were recorded on 75.6 MHz on a Bruker Topspin spectrometer (300 MHz). Mass spectra were recorded on a ToF MS. All reactants were purchased from Sigma-Aldrich and Lanchester and used as such without further purification.

General procedure for the synthesis of 2-substituted-2,3-dihydrobenzo[e][1,3]oxazin-4-ones (6a-i)

A solution of *o*-hydroxyaromaticaldehyde (0.01 mol) and $NH_2OH{\cdot}HCl$ (0.013 mol) taken in 99% HCO_2H (5-10 mL) is refluxed for 1-2 h and then added SPB (8.3g, 5 eq.) dissolved in water (5-10 mL) and the reaction mixture was stirred at 80 °C. The progress of reaction was monitored through TLC (Merck TLC: mean particle size 10-12 μm; particle size distribution 5-20 μm; layer thickness 250 μm; plate height 30 mm). After 8-10 h, aldehyde (0.01 mol) was added. Upon completion, allow the reaction mixture to cool and then filter it. The reaction mixture is diluted with water (50-60 mL) neutralized under ice cooling with 5% aqueous NaOH and extracted with Et_2O (2 x 30 mL). The ethereal extracted is dried with Na_2SO_4 and concentrated using a rotary evaporator to give final product **(6a-i)** which is further purified by column chromatography [column of silica gel, elution with *n*-hexane: AcOEt 9:1 (v/v)].

2-Phenyl-2,3-dihydrobenzo[*e*][1,3]oxazin-4-one (6a). Mp 166-168 °C (lit.,[29] 168 °C). IR ν_{max} (KBr, cm^{-1}): 3160, 3060, 1675. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.07 (s, 1H), 7.31-8.22 (m, 9H, Ar-H), 10.69 (s, 1H, NH). HRMS: M^+ 225.0 Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.66; H, 4.88; N, 6.22. Found: C, 74.65; H, 4.86; N, 6.23.

2-(4-Chlorophenyl)-2,3-dihydrobenzo[*e*][1,3]oxazin-4-one (6b). Mp 204-206 °C (lit.,[27] 205-206 °C). IR ν_{max} (KBr, cm^{-1}); 3165, 3060, 1680. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.12 (s, 1H), 7.24 (d, 2H, Ar-H), 7.42 (d,

2H, Ar-H), 7.55-8.21 (m, 4H, Ar-H), 10.72 (s, 1H, NH). HRMS: M^+ 259.8. Anal. Calcd for $C_{14}H_{10}NO_2Cl$: C, 64.73; H, 3.85; N, 5.39. Found: C, 64.75; H, 3.85; N, 5.36.

2-(4-Methoxyphenyl)-2,3-dihydrobenzo[*e*][1,3]oxazin-4-one (6c). Mp 165-166 °C (lit.,[27] 166-167 °C). IR ν_{max} (KBr, cm^{-1}); 3175, 3065, 1675. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.84 (S, 3H, OCH_3), 7.01 (s, 1H), 7.21 (d, 2H, Ar-H), 7.39 (d, 2H, Ar-H), 7.47-8.12 (m, 4H, Ar-H), 10.70 (s, 1H, NH). HRMS: M^+ 255.3. Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.09; N, 5.49. Found: C, 70.56; H, 5.07; N, 5.51. ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: C_2-98.97, C_4-161.49, C_5-119.22, C_6-129.56, C_7-120.27, C_8-132.83, C_9-114.38, C_{10}-158.56, $C_{1'}$-134.62, $C_{2'}$-126.98, $C_{3'}$-112.46, $C_{4'}$-159.07, $C_{5'}$-112.46, $C_{6'}$-126.98, C(-OCH_3)-55.59.

2-(2-Hydroxyphenyl)-2,3-dihydrobenzo[*e*][1,3]oxazin-4-one (6d). Mp 172 °C. IR ν_{max} (KBr, cm^{-1}); 3350, 3160, 3065, 1670. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.13 (s, 1H), 7.24-8.12 (m, 8H, Ar-H), 10.76 (s, 1H, NH). HRMS: M^+ 241.0. Anal. Calcd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.56; N, 5.80. Found: C, 69.66; H, 4.59; N, 5.84.

2-Thiophen-2-yl-2,3-dihydrobenzo[*e*][1,3]oxazin-4-one (6e). Mp 174 °C. IR ν_{max} (KBr, cm^{-1}): 3160, 3060, 1675. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.76-6.81 (m, 1H, thienyl H), 7.00 (d, 2H, thienyl H), 7.11 (s, 1H), 7.49-8.22 (m, 4H, Ar-H), 10.77 (s, 1H, NH). HRMS: M^+ 231.3. Anal. Calcd for $C_{12}H_9NO_2S$: C, 62.33; H, 3.89; N, 6.06; S, 13.85. Found: C, 62.33; H, 3.88; N, 6.06; S, 13.86. ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: C_2-99.07, C_4-161.57, C_5-119.26, C_6-129.62, C_7-120.32, C_8-132.87, C_9-114.41, C_{10}-158.59, $C_{1'}$-146.32, $C_{3'}$-124.79, $C_{4'}$-125.88, $C_{5'}$-123.45.

2-Benzo[1,3]dioxol-5-yl-2,3-dihydrobenzo[*e*][1,3]oxazin-4-one (6f). Mp 198-199 °C (lit.,[29] 199-200 °C). IR ν_{max} (KBr, cm^{-1}): 3165, 3060, 1670. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.92 (s, 2H, OCH_2O), 6.72 (d, 2H, Ar-H), 7.11 (s, 1H), 7.14-7.89 (m, 5H, Ar-H), 10.77 (s, 1H, NH). HRMS: M^+ 268.90. Anal. Calcd for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.08; N, 5.20. Found: C, 66.92; H, 4.07; N, 5.19.

2-(3-Nitrophenyl)-2,3-dihydrobenzo[*e*][1,3]oxazin-4-ones (6g). Mp 217-218 °C (lit.,[27] 218-219 °C). IR ν_{max} (KBr, cm^{-1}): 3170, 3055, 1680. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.14 (s, 1H), 7.55-8.31 (m, 7H, Ar-H), 8.23 (s, 1H, Ar-H), 10.75 (s, 1H, NH). HRMS: M^+ 270.4. Anal. Calcd for $C_{14}H_{10}N_2O_4$: C, 62.22; H, 3.70; N, 10.37. Found: C, 62.21; H, 3.69; N, 10.37. ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: C_2-99.09, C_4-161.59, C_5-119.27, C_6-129.61, C_7-120.33, C_8-132.89, C_9-114.44, C_{10}-158.59, $C_{1'}$-143.49, $C_{2'}$-122.27, $C_{3'}$-149.28, $C_{4'}$-121.67, $C_{5'}$-129.67, $C_{6'}$-134.07.

9-Methoxy-2-phenyl-2,3-dihydrobenzo[*e*][1,3]oxazin-4-one (6h). Mp 188 °C. IR ν_{max} (KBr, cm^{-1}): 3175, 3060, 1665. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.07 (s, 1H), 7.31-8.22 (m, 8H, Ar-H), 10.69 (s, 1H, NH), 3.84 (s, 3H, OCH_3). HRMS: M^+ 255.0. Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.09; N, 5.49. Found: C, 70.59; H, 5.08; N, 5.47.

7-Chloro-2-(4-methoxyphenyl)-2,3-dihydrobenzo[*e*][1,3]oxazin-4-one (6i). Mp 176 °C. IR ν_{max} (KBr,

cm^{-1}); 3170, 3065, 1675. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.84 (s, 3H, OCH_3), 7.01 (s, 1H), 7.21 (d, 2H, Ar-H), 7.39 (d, 2H, Ar-H), 7.47-8.12 (m, 3H, Ar-H), 10.70 (s, 1H, NH). HRMS: M^+ 299. Anal. Calcd for $C_{15}H_{12}NO_3Cl$: C, 62.17; H, 4.14; N, 4.83. Found C, 62.14; H, 4.15; N, 4.85.

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