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Article

$H_3PW_{12}O_{40}$ catalyzed synthesis of benzoxazine and quinazoline in aqueous media

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ABSTRACT

A heteropolyacid efficiently catalyzed the cyclocondensation reaction of 2-aminobenzamide and salicylamide with aldehydes and ketones to afford good yields of benzoxazine and quinazoline ring systems in an aqueous medium. The method gives clean reactions, has simple workup procedure, and uses environment friendly conditions.

1. Introduction

Heteropolyacids (HPAs) are strong Brönsted acids that can catalyze a wide variety of reactions in both homogeneous and heterogeneous phases to offer more efficient and cleaner processes [1–7]. They are effective catalysts in various reactions because their catalytic mechanisms can be diverse at the molecular level [1,2]. Among them, Keggin-type [8] HPAs have long been known to be good catalysts for oxidation reactions [9,10]. Oxazinones constitute an important class of heterocycles, which have attracted much interest due to their wide range of biological activities [11–20]. Oxazinones have also been utilized as useful synthetic precursors for the preparation of organic compounds [21–23]. 2-Substituted 1,3-benzoxazinones can be synthesized from salicylamide and aldehydes using concentrated sulfuric acid [24,25], an amine catalyst in refluxing benzene or toluene [26], *p*-toluenesulfonic acid monohydrate (TsOH) in refluxing toluene [27,28], or a dehydration reaction with polyphosphonate ethyl ester (PPE) in refluxing chloroform [29]. The preparation of 2-aryl-2-trifluoromethyl-2,3-dihydro-4H-1,3-benzoxazine-4-ones using isocyanates and 3-alkoxyphenols in the presence of triethylamine [30] was also reported. Recently, a chiral Brönsted acid was applied for the preparation of 1,3-benzoxazine-4-ones [31]. However, many of these procedures have limitations such as tedious work-up [24–28], toxic solvents [26,28], low yields [24,25,30], long reaction times [30] or/and harsh reaction conditions [24,25]. Therefore, the development of a new catalytic route is an active area of research.

As a new catalytic route, we designed a simple procedure that can be used to synthesize a series of 2,3-dihydro-4H-1,3-benzoxazine-4-ones derivatives. Quinazolines and their derivatives are versatile *N*-containing heterocyclic compounds, which have a broad spectrum of biological and pharmacological activities. Substitution at the 2- and 3-positions of the quinazoline nucleus plays a pivotal role in different activities such as anticancer [32], anti-inflammatory [33], antidiuretic [34], and anticonvulsant [35] activities. 2,3-Dihydroquinazolin-4(1H)-ones

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in particular have good biological activities and are also key intermediates for the synthesis of quinazolin-4(3H)-ones [36,37]. Several methods have been reported for the synthesis of quinazolinone and aryl-substituted quinazolinone compounds [38–66]. The one-pot three-component condensation of isatoic anhydride, aldehydes, and amines is the most convenient method for the preparation of these compounds. Many catalysts have been reported for this reaction [67–76], and although many of these methods are effective, some of them suffer in terms of long reaction times [67], harsh reaction conditions and low yields [69], special effort to prepare the catalyst [77], or/and failure in the reaction with aromatic ketones. As part of our ongoing program to develop new catalysts to promote organic transformations [78–80], we report here the use of $H_3PW_{12}O_{40}$ as an efficient and reusable catalyst for the synthesis of benzoxazine and quinazoline ring systems under very mild conditions.

2. Experimental

All chemicals were obtained commercially from Aldrich or Merck Chemical Co. and used as received. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 AVANCE (400 and 100 MHz for ^{1}H and ^{13}C, respectively) using DMSO-d_6 as solvent. Chemical shifts are reported on the δ scale relative to internal Me_4Si. Melting points (mp) were determined on a Thermo Scientific IA9200 and are uncorrected. Mass spectra were obtained on an Agilent instrument, and infrared (IR) spectra were determined on a Bruker instrument.

2.1. General procedure for the synthesis of 1,3-benzoxazine-4-one derivatives

A mixture of salicylamide (1 mmol), aldehyde (1 mmol), and $H_3PW_{12}O_{40}$ (5 mol%) in water/ethanol (5:1) was heated at 80 °C. The reaction was followed by TLC analysis. After completion of the reaction, the mixture was cooled, the solvent was removed under reduced pressure, and a small amount of water (5 mL) was added to dissolve the catalyst, which was filtered off. Then, the residue was recrystallized with ethanol to get the pure product. The analytical data for selected products were as follows.

2-(3-Bromophenyl)-2H-benzo[e][1,3]oxazin-4(3H)-one (**3c**). mp: 187–189 °C; IR (KBr, cm^{-1}): ν 3175, 3066, 2894, 1682, 1611, 1467, 1279, 1143, 1072; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 9.02 (s, 1H, NH), 7.80 (dd, J = 1.6, 7.8 Hz, 1H, Ar-CH), 7.76 (t, J = 2.0, 1H, Ar-CH), 7.65 (dq, J = 0.8, 8.0 Hz, 1H, Ar-CH), 7.59 (d, J = 7.6 Hz, 1H, Ar-CH), 7.53 (td, J = 1.6, 7.8 Hz, 1H, Ar-CH), 7.43 (t, J = 8.0 Hz, 1H, Ar-CH), 7.14 (td, J = 1.2, 7.6 Hz, 1H, CH), 7.07 (dd, J = 0.8, 8.2 Hz, 1H, Ar-CH), 6.42 (d, J = 1.6 Hz, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 83.97, 117.28, 118.75, 122.10, 122.93, 126.85, 127.92, 130.57, 131.27, 132.93, 135.09, 139.95, 157.09, 162.82. Analysis Calcd. for $C_{14}H_{10}BrNO_2$: C, 55.29; H, 3.31; N, 4.61. Found: C, 55.19; H, 3.39; N, 4.71.

2-(4-Fluorophenyl)-2H-benzo[e][1,3]oxazin-4(3H)-one (**3d**). mp: 176–178 °C; IR (KBr, cm^{-1}): ν 3189, 3045, 2868, 1687, 1627, 1451, 1263, 1109; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 8.99 (s, 1H, NH), 7.80 (dd, J = 1.6, 8.0 Hz, 1H, Ar-CH), 7.66–7.61 (m, 2H, Ar-CH), 7.53 (td, J = 1.6, 7.6 Hz, 1H, Ar-CH), 7.29 (t, J = 9.2 Hz, 2H, Ar-CH), 7.14 (td, J = 0.8, 7.6 Hz, 1H, Ar-CH), 7.05 (dd, J = 0.8, 8.0 Hz, 1H, Ar-CH), 6.40 (d, J = 1.6 Hz, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 84.40, 115.76, 115.98, 117.21, 118.76, 122.83, 127.92, 130.16, 130.25, 135.01, 157.29, 163.08, 164.42. Analysis Calcd. for $C_{14}H_{10}FNO_2$: C, 69.13; H, 4.14; N, 5.76. Found: C, 69.21; H, 4.03; N, 5.64.

4-(4-Oxo-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-yl)benzonitrile (**3f**). mp: 219–221 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 9.12 (d, J = 1.6 Hz, 1H, NH), 7.94 (d, J = 8.4 Hz, 2H, Ar-CH), 7.79 (dd, J = 1.6, 7.8 Hz, 1H, Ar-CH), 7.76 (d, J = 8.0 Hz, 2H, Ar-CH), 7.53 (td, J = 2.0, 7.8 Hz, 1H, Ar-CH), 7.14 (td, J = 0.8, 7.6 Hz, 1H, Ar-CH), 7.08 (dd, J = 0.8, 8.4 Hz, 1H, Ar-CH), 6.53 (d, J = 1.6 Hz, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 83.88, 112.75, 117.32, 118.76, 118.88, 123.04, 127.93, 128.72, 133.05, 135.16, 142.49, 156.95, 162.68.

2-(2-Chloro-5-nitrophenyl)-2H-benzo[e][1,3]oxazin-4(3H)-one (**3g**). mp: 197–198 °C; IR (KBr, cm^{-1}): ν 3334, 3079, 2919, 1690, 1612, 1525, 1469, 1387, 1255, 1149, 1057; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 9.14 (s, 1H, NH), 8.48 (d, J = 2.4 Hz, 1H, Ar-CH), 8.34 (dd, J = 2.8, 8.8 Hz, 1H, Ar-CH), 7.89 (d, J = 8.8 Hz, 1H, Ar-CH), 7.85 (dd, J = 1.2, 7.8 Hz, 1H, Ar-CH), 7.56 (td, J = 1.6, 7.2 Hz, 1H, Ar-CH), 7.20 (t, J = 7.6 Hz, 1H, Ar-CH), 7.10 (d, J = 8.4 Hz, 1H, Ar-CH), 6.72 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 81.66, 117.19, 118.56, 123.41, 124.19, 126.58, 128.06, 132.14, 135.30, 135.51, 139.95, 146.80, 156.92, 162.87. Analysis Calcd. for $C_{14}H_9ClN_2O_4$: C, 55.19; H, 2.98; N, 9.19. Found: C, 55.27; H, 2.80; N, 9.08.

2-(Naphthalen-1-yl)-2H-benzo[e][1,3]oxazin-4(3H)-one (**3h**). mp: 213–215 °C; IR (KBr, cm^{-1}): ν 3184, 3080, 2930, 1682, 1609, 1582, 1405, 1218, 1149, 1081; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 9.14 (s, 1H, NH), 8.45–8.43 (m, 1H, Ar-CH), 8.05-8.01 (m, 2H, Ar-CH), 7.89 (dd, J = 1.6, 7.6 Hz, 1H, Ar-CH), 7.78 (d, J = 6.4 Hz, 1H, Ar-CH), 7.63–7.55 (m, 3H, Ar-CH), 7.52 (td, J = 2.0, 7.8 Hz, 1H, Ar-CH), 7.17 (td, J = 1.2, 7.6 Hz, 1H, Ar-CH), 7.03 (d, J = 1.2 Hz, 1H, Ar-CH), 7.00 (d, J = 0.8 Hz, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 84.40, 117.17, 119.03, 122.81, 124.97, 125.54, 126.55, 126.95, 127.02, 128.04, 129.10, 130.81, 130.84, 132.09, 134.04, 134.91, 157.58, 163.28. Analysis Calcd. for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.41; H, 4.62; N, 5.17.

Spiro[benzo[e][1,3]oxazine-2,1'-cyclohexan]-4(3H)-one (**3i**). mp: 180–182 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 8.63 (s, 1H, NH), 7.73 (dd, J = 1.6, 7.6 Hz, 1H, Ar-CH), 7.49 (td, J = 1.6, 8.0 Hz, 1H, Ar-CH), 7.07 (td, J = 0.8, 6.8 Hz, 1H, Ar-CH), 6.99 (dd, J = 0.8, 8.0 Hz, 1H, Ar-CH), 1.99–1.96 (m, 2H, CH_2), 1.63–1.23 (m, 8H, 4CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 21.88, 24.62, 35.85, 88.02, 117.38, 118.35, 122.14, 127.47, 134.81, 141.18, 161.45.

N,*N*'-methylenebis(2-hydroxybenzamide) (**3j**). mp: 299–300 °C; IR (KBr, cm^{-1}): ν 3396, 3896, 1639, 1594, 1491, 1330, 1225, 1112; ^{1}H NMR (400MHz, DMSO-d_6): δ_H (ppm) 12.22 (broad, 2H, 2OH), 9.47 (s, 2H, 2NH), 7.91 (dd, J = 1.6, 8.0 Hz, 2H, Ar-CH), 7.39 (t, J = 8.0 Hz, 2H, Ar-CH), 6.92–6.87 (m, 4H, Ar-CH), 4.90 (t, J = 5.2 Hz, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C

(ppm) 44.86, 116.05, 117.78, 119.22, 129.18, 134.34, 159.87, 169.02. Analysis Calcd. for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79. Found: C, 62.80; H, 4.82; N, 9.69.

*2.2. General procedure for the synthesis of 2-substituted-2,3-dihydroquinazolin-4(1H)-one derivatives **(6a–6u)***

A mixture of 2-aminobenzamide (1 mmol), aldehyde (1 mmol), and $H_3PW_{12}O_{40}$ (1 mol%) in H_2O/CTAB (6 mL) was heated at 80 °C for an appropriate time. After completion of the reaction (monitored by TLC), the mixture was cooled and filtered. The crude residue was washed with warm water (5 mL) and recrystallized with ethanol to give the pure product. The analytical data for selected products were as follows.

2-(4-Nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one (**6b**). mp: 198–200 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ_H (ppm) 8.52 (d, *J* = 2.0 Hz, 1H, NH), 8.25 (d, *J* = 8.8 Hz, 2H, Ar-CH), 7.74 (d, *J* = 8.8 Hz, 2H, Ar-CH), 7.60 (dd, *J* = 1.2, 7.6 Hz, 1H, Ar-CH), 7.33 (broad, 1H, NH), 7.26 (td, *J* = 1.6, 8.0 Hz, 1H, Ar-CH), 6.76 (d, *J* = 7.6 Hz, 1H, Ar-CH), 6.69 (td, *J* = 0.8, 7.6 Hz, 1H, Ar-CH), 5.91 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ_C (ppm) 65.72, 115.00, 115.35, 117.92, 124.04, 127.86, 128.48, 134.02, 147.68, 147.88, 149.78, 163.73.

4-(4-Oxo-1,2,3,4-tetrahydroquinazolin-2-yl)benzonitrile (**6d**). mp: 249–251 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ_H (ppm) 8.48 (d, *J* = 2.4 Hz, 1H, NH), 7.87 (d, *J* = 8.4 Hz, 2H, Ar-CH), 7.65 (d, *J* = 8.0 Hz, 2H, Ar-CH), 7.60 (dd, *J* = 1.6, 8.0 Hz, 1H, Ar-CH), 7.29 (broad, 1H, NH), 7.26 (td, *J* = 1.6, 7.6 Hz, 1H, Ar-CH), 6.75 (dd, *J* = 0.4, 8.0 Hz, 1H, Ar-CH), 6.68 (td, *J* = 0.8, 7.2 Hz, 1H, Ar-CH), 5.85 (d, *J* = 2.8 Hz, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ_C (ppm) 65.94, 111.50, 114.96, 115.34, 117.87, 119.11, 127.84, 128.13, 132.87, 134.00, 147.77, 147.81, 163.76.

2-*p*-Tolyl-2,3-dihydroquinazolin-4(1H)-one (**6i**). mp: 226–227 °C; ^{1}H NMR (400MHz, DMSO-d$_6$): δ_H (ppm) 8.24 (s, 1H, NH), 7.60 (dd, *J* = 1.2, 7.8 Hz, 1H, Ar-CH), 7.37 (d, *J* = 8.0 Hz, 2H, Ar-CH), 7.23 (td, *J* = 1.6, 7.8 Hz, 1H, Ar-CH), 7.19 (d, *J* = 7.6 Hz, 2H, Ar-CH), 7.06 (s, 1H, NH), 6.73 (dd, *J* = 0.8, 8.2 Hz, 1H, Ar-CH), 6.66 (td, *J* = 1.2, 7.4 Hz, 1H, Ar-CH), 5.70 (s, 1H, CH), 2.29 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ_C (ppm) 21.18, 66.80, 114.85, 115.44, 117.51, 127.25, 127.78, 129.26, 133.71, 138.17, 139.10, 148.36, 164.09.

2-(Naphthalen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (**6l**). mp: 175–177 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ_H (ppm) 8.38 (s, 1H, NH), 7.96–7.90 (m, 4H, Ar-CH), 7.70 (dd, *J* = 1.6, 8.8 Hz, 1H, Ar-CH), 7.64 (dd, *J* = 1.6, 7.8 Hz, 1H, Ar-CH), 7.56–7.51 (m, 2H, Ar-CH), 7.25 (td, *J* = 1.6, 7.8 Hz, 1H, Ar-CH), 7.19 (s, 1H, NH), 6.76 (d, *J* = 7.6 Hz, 1H, Ar-CH), 6.69 (td, *J* = 0.8, 7.6 Hz, 1H, Ar-CH), 5.94 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ_C (ppm) 67.28, 114.87, 115.40, 117.64, 125.30, 126.31, 126.84, 126.89, 127.83, 128.04, 128.43, 128.58, 132.92, 133.45, 133.81, 139.32, 148.34, 164.05.

2-(Pentan-3-yl)-2,3-dihydroquinazolin-4(1H)-one (**6m**). mp: 157–158 °C; IR (KBr, cm^{-1}): *ν* 3356, 3183, 3059, 2964, 1925, 1643, 1506, 1485, 1390, 1263, 1150; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ_H (ppm) 7.80 (s, 1H, NH), 7.55 (dd, *J* = 1.6, 7.6 Hz, 1H, Ar-CH), 7.20 (td, *J* = 1.6, 7.8 Hz, 1H, Ar-CH), 6.74 (dd, *J* = 0.4, 8.0 Hz, 1H, Ar-CH), 6.62 (td, *J* = 0.8, 7.2 Hz, 1H, Ar-CH), 6.45 (s, 1H, NH), 4.73 (t, *J* = 1.6 Hz, 1H, CH), 1.58–1.50 (m, 2H, CH_2), 1.41–1.31 (m, 2H, CH_2), 1.30–1.24 (m, 1H, CH), 0.90–0.85 (m, 6H, 2CH_3); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ_C (ppm) 12.24, 12.40, 21.22, 46.04, 66.48, 114.64, 115.22, 116.97, 127.73, 133.45, 149.15, 164.55. Analysis Calcd. for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.44; H, 8.29; N, 12.71.

2,2-Dimethyl-2,3-dihydroquinazolin-4(1H)-one (**6n**). mp: 182–184 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ_H (ppm) 7.94 (s, 1H, NH), 7.57 (dd, *J* = 1.2, 7.6 Hz, 1H, Ar-CH), 7.21 (td, *J* = 1.6, 8.0 Hz, 1H, Ar-CH), 6.66 (s, 1H, NH), 6.64–6.59 (m, 2H, Ar-CH), 1.37 (s, 6H, 2CH_3); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ_C (ppm) 29.43, 67.28, 114.27, 114.69, 116.88, 127.62, 133.67, 147.53, 163.52.

2-(4-Chlorophenyl)-2-methyl-2,3-dihydroquinazolin-4(1H)-one (**6r**). mp: 209–210 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ_H (ppm) 8.81 (s, 1H, NH), 7.67 (s, 1H, NH), 7.50–7.46 (m, 3H, Ar-CH), 7.36 (d, *J* = 8.8 Hz, 2H, Ar-CH), 7.21 (td, *J* = 1.6, 8.4 Hz, 1H, Ar-CH), 6.76 (d, *J* = 8.0 Hz, 1H, Ar-CH), 6.59 (td, *J* = 0.8, 7.6 Hz, 1H, Ar-CH), 1.62 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ_C (ppm) 30.88, 70.33, 114.77, 115.42, 117.51, 127.60, 127.72, 128.43, 132.24, 133.87, 147.19, 147.39, 164.17.

5-Chloro-1'H-spiro[indoline-3,2'-quinazoline]-2,4'(3'H)-dione (**6u**). mp: 174–175 °C; IR (KBr, cm^{-1}): *ν* 3266, 2968, 1731, 1650, 1616, 1480, 1269, 1188, 1149; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ_H (ppm) 10.48 (broad, 1H, NH), 8.40 (d, *J* = 1.2 Hz, 1H, NH), 7.60 (dd, *J* = 1.6, 8.0 Hz, 1H, Ar-CH), 7.50 (d, *J* = 2.4 Hz, 1H, Ar-CH), 7.39 (dd, *J* = 2.4, 8.4 Hz, 1H, Ar-CH), 7.34 (d, *J* = 1.2 Hz, 1H, NH), 7.26–7.21 (m, 1H, Ar-CH), 6.87 (d, *J* = 8.4 Hz, 1H, Ar-CH), 6.69 (td, *J* = 0.8, 8.0 Hz, 1H, Ar-CH), 6.62–6.59 (m, 1H, Ar-CH); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ_C (ppm) 71.49, 112.12, 114.35, 114.69, 117.85, 125.86, 126.59, 127.34, 131.08, 131.76, 133.88, 141.53, 146.99, 164.16, 176.25. Analysis Calcd. for $C_{15}H_{10}ClN_3O_2$: C, 60.11; H, 3.36; N, 14.02. Found: C, 60.23; H, 3.27; N, 13.91.

*2.3. General procedure for the synthesis of 2-substituted-quinazolin-4(3H)-one derivatives (**7a–7j**)*

A mixture of 2-aminobenzamide (1 mmol), aldehyde (1 mmol), and $H_3PW_{12}O_{40}$ (3 mol%) in water/ethanol (2:1, 6 mL) was heated at 100 °C, and the reaction was followed by TLC analysis. After the reaction was completed, the mixture was cooled, the solvent was removed under reduced pressure, a small amount of water (5 mL) was added to the mixture, and the product precipitated from the reaction mixture was separated by simple filtration. The residue was recrystallized with ethanol to give the pure product. The analytical data for selected products were as follows.

2-Phenylquinazolin-4(3H)-one (**7a**). mp: 235–237 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ_H (ppm) 12.43 (broad, 1H, NH), 8.19–8.14 (m, 3H, Ar-CH), 7.84 (td, *J* = 5.6, 7.6 Hz, 1H, Ar-CH), 7.75 (d, *J* = 7.6 Hz, 1H, Ar-CH), 7.61 (m, 4H, Ar-CH); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ_C (ppm) 121.41, 126.32, 127.04, 127.84, 127.91, 128.22, 129.08, 131.86, 133.24, 135.06, 162.95.

2-(3-Bromophenyl)quinazolin-4(3H)-one (**7c**). mp: 292–294 °C; IR (KBr, cm^{-1}): *ν* 3026, 2886, 1681, 1606, 1560, 1473, 1308, 1270, 1151, 1070; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ_H (ppm) 10.55 (broad, 1H, NH), 8.38 (t, *J* = 2.0 Hz, 1H, Ar-CH),

8.19 (dt, *J* = 0.8, 7.8 Hz, 1H, Ar-CH), 8.15 (dd, *J* = 1.2, 8.0 Hz, 1H, Ar-CH), 7.84 (td, *J* = 1.6, 7.6 Hz, 1H, Ar-CH), 7.80–7.75 (m, 2H, Ar-CH), 7.54–7.49 (m, 2H, Ar-CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 117.78, 121.59, 122.34, 126.33, 127.24, 127.28, 127.97, 130.86, 131.20, 134.43, 135.05, 148.94, 151.64, 162.85. Analysis Calcd. for $C_{14}H_9BrN_2O$: C, 55.84; H, 3.01; N, 9.30. Found: C, 55.65; H, 2.91; N, 9.15.

2-(4-Methoxyphenyl)quinazolin-4(3H)-one (**7e**). mp: 243–245 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 12.43 (broad, 1H, NH), 8.19 (d, *J* = 9.2 Hz, 2H, Ar-CH), 8.13 (dd, *J* = 0.8, 7.8 Hz, 1H, Ar-CH), 7.81 (td, *J* = 1.6, 7.6 Hz, 1H, Ar-CH), 7.70 (d, *J* = 7.6 Hz, 1H, Ar-CH), 7.48 (td, *J* = 1.2, 7.4 Hz, 1H, Ar-CH), 7.09 (d, *J* = 9.2 Hz, 2H, Ar-CH), 3.85 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 55.93, 114.46, 121.12, 125.24, 126.29, 126.60, 127.73, 129.92, 135.02, 149.37, 152.34, 162.33, 162.78.

2-(4-Hydroxyphenyl)quinazolin-4(3H)-one (**7f**). mp: 259–261 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 11.43 (broad, 2H, NH and OH), 8.12–8.07 (m, 3H, Ar-CH), 7.78 (td, *J* = 1.6, 7.6 Hz, 1H, Ar-CH), 7.67 (d, *J* = 8.0 Hz, 1H, Ar-CH), 7.75(td, *J* = 1.2, 8.0 Hz, 1H, Ar-CH), 6.90 (d, *J* = 8.8 Hz, 2H, Ar-CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 115.85, 121.01, 123.66, 126.27, 127.47, 129.99, 134.81, 149.51, 152.99, 161.29, 163.18.

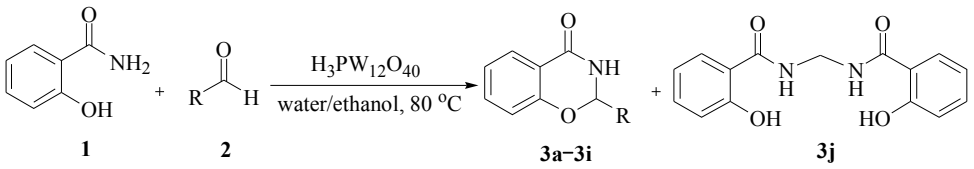
2-(Pyridin-2-yl)quinazolin-4(3H)-one (**7i**). mp: 163–164 °C; IR (KBr, cm^{-1}): *ν* 3253, 2883, 1675, 1601, 1562, 1470, 1420, 1329, 1136, 1085; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 11.85 (broad, 1H, NH), 8.77 (dq, *J* = 0.8, 4.8 Hz, 1H, Ar-CH), 8.46 (dt, *J* = 1.2, 7.6 Hz, 1H, Ar-CH), 8.19 (dq, *J* = 0.4, 7.6 Hz, 1H, Ar-CH), 8.08 (td, *J* = 2.0, 8.0 Hz, 1H, Ar-CH), 7.88 (td, *J* = 1.6, 7.6 Hz, 1H, Ar-CH), 7.81 (dt, *J* = 0.8, 7.6 Hz, 1H, Ar-CH), 7.67 (ddd, *J* = 1.2, 4.8, 7.6 Hz, 1H, Ar-CH), 7.58 (td, *J* = 1.6, 7.6 Hz, 1H, Ar-CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 122.48, 122.64, 126.57, 127.06, 127.76, 128.18, 135.20, 138.48, 148.89, 149.17, 149.47, 150.44, 161.25. Analysis Calcd. for $C_{13}H_9N_3O$: C, 69.95; H, 4.06; N, 18.82. Found: C, 69.81; H, 4.17; N, 18.69.

2-(1-Phenylethyl)quinazolin-4(3H)-one (**7j**). mp: 210–212 °C; IR (KBr, cm^{-1}): *ν* 3166, 3044, 2960, 2911, 1685, 1607, 1490, 1393, 1293, 1196, 1150, 1031; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 12.28 (broad, 1H, NH), 8.06 (dd, *J* = 1.2, 7.6 Hz, 1H, Ar-CH), 7.78 (td, *J* = 1.6, 7.6 Hz, 1H, Ar-CH), 7.66 (d, *J* = 7.6 Hz, 1H, Ar-CH), 7.46 (td, *J* = 0.8, 7.6 Hz, 1H, Ar-CH), 7.39 (d, *J* = 7.2 Hz, 2H, Ar-CH), 7.31 (t, *J* = 7.2 Hz, 2H, Ar-CH), 7.22 (t, *J* =7.2 Hz, 1H, Ar-CH), 4.10 (q, *J* = 7.2 Hz, 1H, CH), 1.61 (d, *J* = 7.2 Hz, 3H, CH3); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 19.82, 44.33, 114.25, 121.38, 126.16, 126.58, 127.31, 127.52, 127.90, 128.93, 134.73, 142.94, 149.21, 154.94. Analysis Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.89; H, 5.50; N, 11.02.

3. Results and discussion

Our approach to the synthesis of 1,3-benzoxazine-4-one derivatives (Scheme 1) started from the condensation of salicylamide and aldehydes using $H_3PW_{12}O_{40}$ as the catalyst under green conditions.

Initially the condensation reaction between salicylamide and *p*-nitrobenzaldehyde was employed as the model reaction to screen for the optimum conditions (Table 1). Among the heteropolyacids tested, $H_3PW_{12}O_{40}$ showed the best catalytic performance (Table 1, entries 2–4). When the model reaction was conducted without a catalyst, a very low yield of the 1,3-benzoxazine-4-one was obtained (Table 1, entry 1).



Scheme 1. Synthesis of 1,3-benzoxazine-4-one derivatives.

Table 1
Condensation of salicylamide and 4-nitronenzaldehydes under different reaction conditions.

Entry	Catalyst (mol%)	Solvent	Temperature (°C)	Time (h)	Isolated yield (%)
1	None	H_2O	60	12	8
2	$H_3PMo_{12}O_{40}$ (6)	H_2O	60	12	52
3	$H_4SiW_{12}O_{40}$ (6)	H_2O	60	12	41
4	$H_3PW_{12}O_{40}$ (5)	H_2O	60	12	73
5	$H_3PW_{12}O_{40}$ (5)	H_2O	r.t	18	25
6	$H_3PW_{12}O_{40}$ (5)	EtOH	reflux	12	70
7	$H_3PW_{12}O_{40}$ (5)	CH_3CN	reflux	14	65
7	$H_3PW_{12}O_{40}$ (5)	THF	reflux	14	22
9	$H_3PW_{12}O_{40}$ (5)	CH_2Cl_2	reflux	18	10
10	$H_3PW_{12}O_{40}$ (5)	H_2O/EtOH (1:1)	80	12	75
11	$H_3PW_{12}O_{40}$ (5)	H_2O/EtOH (3:1)	80	12	85
12	$H_3PW_{12}O_{40}$ (5)	H_2O/EtOH (5:1)	80	12	94
13	$H_3PW_{12}O_{40}$ (5)	H_2O/EtOH (5:1)	reflux	12	92
14	$H_3PW_{12}O_{40}$ (3)	H_2O/EtOH (5:1)	80	12	64
15	$H_3PW_{12}O_{40}$ (1)	H_2O/EtOH (5:1)	80	12	38
16	$H_3PW_{12}O_{40}$ (7)	H_2O/EtOH (5:1)	80	12	88
17 [a]	$H_3PW_{12}O_{40}$ (5)	H_2O/EtOH (5:1)	80	12	94, 91, 85

Reaction conditions: salicylamide 1 mmol, 4-nitrobenzaldehyde 1 mmol, catalyst 1–7 mol%.
[a] The catalyst was reused for three runs.

Table 2
Synthesis of 1,3-benzoxazine-4-one derivatives using salicylamide (1 mmol) and aldehydes (1 mmol) catalyzed by $H_3PW_{12}O_{40}$ (5 mol%) in H_2O/ EtOH (5:1) at 80 °C.

Entry	R	Product	Time (h)	Yield [a] (%)	mp (°C) (Ref. [24])
1	C_6H_5–	**3a**	14	81	154–156 (168–169)
2	4-$O_2NC_6H_4$–	**3b**	12	94	216–218 (222–223)
3	3-BrC_6H_4–	**3c**	12	92	187–189
4	4-FC_6H_4–	**3d**	12	91	176–178
5	4-ClC_6H_4–	**3e**	12	89	196–198 (205–206)
6	4-CNC_6H_4–	**3f**	12	90	219–221 (226–227)
7	2-Cl-5-$O_2NC_6H_3$–	**3g**	18	81	197–198
8	1-Naphtyl–	**3h**	14	86	213–215
9	–$(CH_2)_5$–(Cyclohexanyl–) [b]	**3i**	14	75	180–182 (188–190)
10	H	**3j** [c]	12	71	299–300

[a] Isolated total yield.
[b] 2 mmol ketone was used.
[c] Bisamid was the product formed.

Next, the effect of solvents was examined at different temperatures (Table 1, entries 4–13). The condensation reaction in a mixture of ethanol/water (1:5 v/v) at 80 °C gave the best results in terms of time and yield, and this solvent system was also environmentally acceptable (Table 1, entry 12). The effect of $H_3PW_{12}O_{40}$ loading was also studied (Table 1, entries 12–16). $H_3PW_{12}O_{40}$ of 5 mol% was the optimum amount of catalyst for the reaction to give maximum yield (Table1, entry 12).

The possibility of recycling the catalyst was examined with the model reaction. When the reaction was completed, the reaction mixture was cooled and filtered to remove the product. The filtrate was either evaporated under reduced pressure to give the catalyst or it was directly used for the next run. No appreciable loss of catalyst activity was observed after three successive runs (Table 1, entry 17).

To explore the scope and limitation of this method, the $H_3PW_{12}O_{40}$ catalyzed reaction was extended to salicylamide and various aromatic aldehydes (Table 2). As expected, the reactions proceeded smoothly, and the desired products were obtained in good to excellent yields.

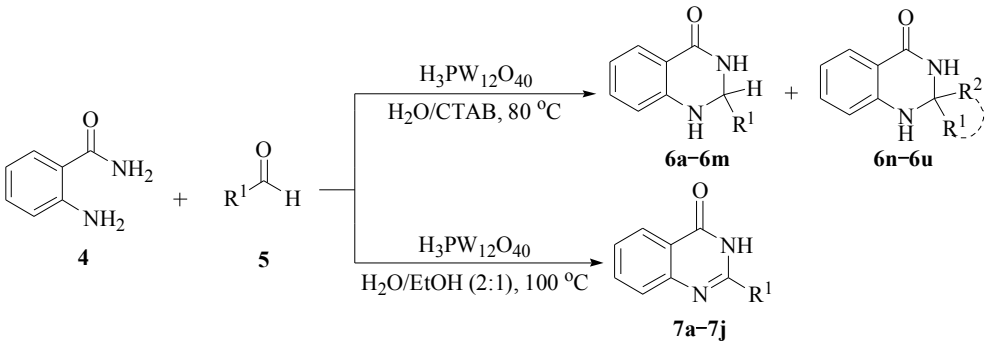
A series of aromatic aldehydes with either electron-withdrawing or electron-donating groups were investigated (Table 2, entries 1–8). Cyclohexanone reacted with salicylamide giving 75% yield of the expected product **3i** (Table 2, entry 9), while formaldehyde in the reaction with salicylamide under the optimal reaction conditions gave bisamide **3j** in 71% yield (Table 2, entry 10). The reaction of formaldehyde with salicylamide using an acid catalyst was previously reported to give an unidentified polymer [24].

This study was the first example of the synthesis of a series of oxazinone derivatives using salicylamide and various aldehydes catalyzed by $H_3PW_{12}O_{40}$ in a green medium.

Using the optimized conditions for the synthesis of benzoxazine, the heteropolyacid catalyzed reactions of 2-aminobenzamide with various aldehydes were investigated. High yields of the dihydroquinazolinones (**6a–6m**) and quinazolinones (**7a–7j**) were obtained (Scheme 2).

The reaction of 2-aminobenzamide with 4-chlorobenzaldehyde in the presence of $H_3PW_{12}O_{40}$ was investigated under different reaction conditions. Different temperatures (r.t., 60, 80, and 100 °C) and catalyst loadings (0.5, 1, and 2 mol%) in various solvents (H_2O, CH_3CN, THF, H_2O/EtOH, and H_2O/CTAB) were used. The optimized conditions for the reaction to give the highest yield of dihydroquinazoline **6e** were an equimolar amount of compound **4** and *p*-chlorobenzaldehyde mixed with 1 mol% $H_3PW_{12}O_{40}$ catalyst in H_2O/CTAB (6 mL, 0.02 g/mL) at 80 °C. For the preparation of quinazolinone **7b**, the optimized conditions were an equimolar ratio of compound **4** and *p*-chlorobenzaldehyde **5** (R = *p*-Cl-C_6H_4) mixed with $H_3PW_{12}O_{40}$ (3 mol%) in H_2O/EtOH (2:1) at 100 °C. The efficiency of this methodology was evaluated by the condensation of structurally diverse aldehydes and ketones with 2-aminobenzamide under the optimal reaction conditions described above (Table 3).

Aromatic aldehydes containing various electron-donating and electron-withdrawing groups were converted to the corresponding 2-substituted-2,3-dihydroquinazolin-4(1H)-ones



Scheme 2. Synthesis of substituted-2,3-dihydroquinazolin-4(1H)-ones (**6a–6u**) and 2-substituted-quinazolin-4(3H)-ones (**7a–7j**).

Table 3
$H_3PW_{12}O_{40}$ mediated synthesis of substituted 2,3-dihydroquinazolin-4(1H)-ones [a] and 2-substituted-quinazolin-4(3H)-ones [b].

Entry	R_1	Product	Time (h)	Isolated yield (%)	mp (°C) (Refs.)
1	C_6H_5–	**6a**	1	83	218–220 (217–219 [83])
2	4-$O_2NC_6H_4$–	**6b**	0.5	95	198–200 (199–201 [83])
3	4-$O_2NC_6H_4$–	**6b**	0.5	95, 90, 79 [c]	198–200 (199–201 [83])
4	3-$O_2NC_6H_4$–	**6c**	0.5	92	193–195 (195–196 [83])
5	4-CNC_6H_4–	**6d**	0.5	92	249–251 (249–251 [84])
6	4-ClC_6H_4–	**6e**	0.5	88	207–209 (206–207 [83])
7	4-FC_6H_4–	**6f**	0.5	90	197–199 (199–200 [68])
8	3-BrC_6H_4–	**6g**	0.5	87	228–229 (229–231 [85])
9	4-HOC_6H_4–	**6h**	0.6	85	276–278 (279–280 [68])
10	4-MeC_6H_4–	**6i**	0.75	86	226–227 (224–226 [83])
11	4-$MeOC_6H_4$–	**6j**	0.75	82	181–182 (184–186 [83])
12	2-Pyridyl–	**6k**	1	80	185–187 (187–188 [68])
13	2-Naphtyl–	**6l**	1	82	175–177 (172–174 [85])
14	$(CH_3CH_2)_2CH$– [d]	**6m**	1.2	81	157–158
15	Acetone [e]	**6n**	0.5	83	182–184 (183–184 [84])
16	2-Butanone [f]	**6o**	1.1	81	181–183 (182–183 [84])
17	Acetophenone [f]	**6p**	21	79	223–225 (224–225 [86])
18	4′-Nitroacetophenone [f]	**6q**	16	81	149–150 (151–152 [86])
19	4′-Chloroacetophenone [f]	**6r**	18	80	209–210 (210–212 [86])
20	–$(CH_2)_5$-(Cyclohexanyl) [f]	**6s**	1.2	72	218–220 (221–223 [86])
21	Isatine	**6t**	14	59	258–260 dec (261–263 dec [87])
22	5-Chloroisatine	**6u**	14	65	174–175
23	C_6H_5–	**7a**	4	78	235–237 (237–238 [68])
24	4-ClC_6H_4–	**7b**	3.5	83	>300 (>300 [68])
25	4-ClC_6H_4–	**7b**	3.5	83, 80, 76 [c]	>300 (>300 [68])
26	3-BrC_6H_4–	**7c**	3.5	81	292–294
27	4-MeC_6H_4–	**7d**	4.5	75	238–240 (240–241 [68])
28	4-$MeOC_6H_4$–	**7e**	4.5	72	243–245 (245–246 [68])
29	4-HOC_6H_4–	**7f**	5	73	259–261 (262–264 [47])
30	1-Naphtyl–	**7g**	3.5	79	271–273 (278–281 [66])
31	2-furyl–	**7h**	3.5	75	220–222 (221–222 [68])
32	2-Pyridyl–	**7i**	4	76	163–164
33	–$CH(CH_3)C_6H_5$	**7j**	4	68	210–212

[a] Reaction conditions: 2-aminobenzamide 1 mmol, aldehydes 1 mmol, $H_3PW_{12}O_{40}$ 1 mol%, H_2O/CTAB 6 mL, 0.02 g/mL, 80 °C.
[b] Reaction conditions: 2-aminobenzamide 1 mmol, aldehydes 1 mmol, $H_3PW_{12}O_{40}$ 3 mol%, H_2O/EtOH = 2:1, reflux.
[c] Catalyst was recycled for three runs.
[d] 2 mmol carbonyl compounds used.
[e] 5 mmol acetone used.

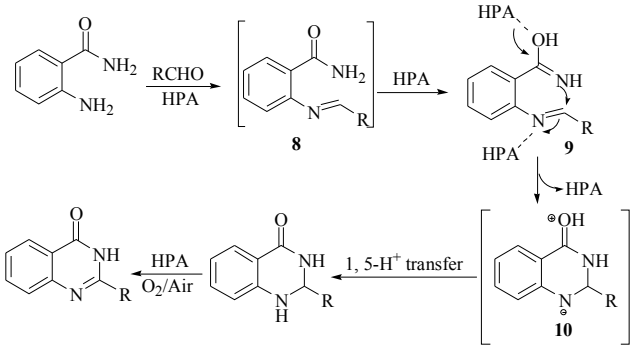
(Table 3, entries 1–11) and 2-substituted-quinazolin-4(3H)-ones (Table 3, entries 23–29) in good yields.

Heteroaromatic aldehydes such as 2-pyridinecarbaldehyde (Table 3, entries 12 and 32), furfural (Table 3, entry 31) and aliphatic aldehydes (Table 3, entries 14 and 33), and ketones such as acetone, 2-butanone, acetophenone, 4′-nitroacetophenone, 4′-chloroacetophenone, cyclohexanone, isatine, and 5-chloroisatine (Table 3, entries 15–22) afforded the desired products in good to high yields. Naphthaldehyde derivatives also reacted well with 2-aminobenzamide to form products in reasonable yields (Table 3, entries 13 and 30).

This methodology was also examined for the condensations of 2-aminobenzamide and aliphatic, aromatic, and cyclic ketones to afford the 2,2-disubstituted quinazolinones (Table 3, entries 15–19), and spiro-quinazolinones (Table 3, entries 20–22). The results in Table 3 revealed that aromatic aldehydes containing electron-withdrawing groups were more favorable for the formation of product, which was in agreement with the mechanism suggested here. Aliphatic aldehydes and ketones reacted more slowly and required higher equivalents to give a reasonable yield of the corresponding products. This could be due to the lower reactivity of ketones [77,81] or the enhancement of the enolizability of the carbonyl compounds in the presence of $H_3PW_{12}O_{40}$, which would make the reaction more difficult [82].

The reusability of the catalyst is an important aspect of green chemistry. After the completion of the model reaction (monitored by TLC), water was added to the reaction mixture, and it was filtered off to separate the catalyst from the product. The catalyst remaining in the aqueous filtrate was recovered by evaporating the filtrate to dryness, or the aqueous filtrate was reused directly for the next run. After three successive runs, the catalyst did not show any significant change in activity (Table 3, entries 3 and 25).

A proposed mechanism for the condensation reaction of 2-aminobenzamide with aldehydes and ketones in the presence of $H_3PW_{12}O_{40}$ is shown in Scheme 3. It is the regular acid-catalyzed reactions mechanism, with $H_3PW_{12}O_{40}$ as the acid that protonates the carbonyl compound to facilitate the nucleophilic attack of the amine group to form the imine **8**. Coordination of the catalyst to the O atom of the enol-amine group and/or the N atom of the imine group in **9** enhances the cy-



Scheme 3. Proposed mechanism for the synthesis of quinazolinone derivatives.

clization to give **10**. Species **10** can undergo a 1,5-proton shift to give the corresponding dihydroquinazolinones. Finally, the dihydroquinazolinones are oxidized to the corresponding quinazolinones in the presence of the catalyst and air.

4. Conclusions

1,3-benzoxazine-4-one derivatives were synthesized by the reaction of salicylamide and aldehydes using $H_3PW_{12}O_{40}$ as the catalyst under green conditions. An efficient protocol was given for the synthesis of dihydroquinazolinones and quinazolinones using $H_3PW_{12}O_{40}$ as a recyclable catalyst in aqueous medium, which has the advantages of high yields, short reaction times, easy work-up, green procedure avoiding toxic organic solvents, and the use of a readily available, inexpensive and relatively non-toxic catalyst. The present method is a good alternative to existing methods for the synthesis of oxazinone and quinazolinone derivatives.

Acknowledgments

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Graphical Abstract

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$H_3PW_{12}O_{40}$ catalyzed synthesis of benzoxazine and quinazoline in aqueous media

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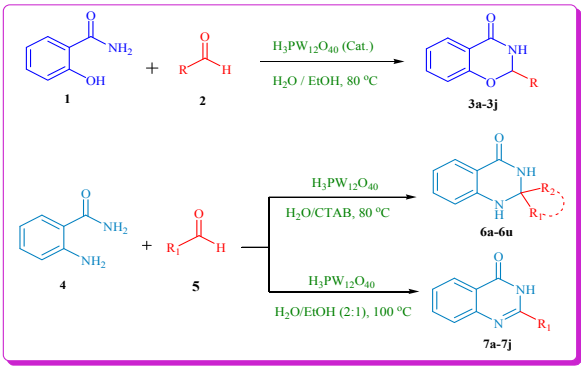
$H_3PW_{12}O_{40}$ was used as an efficient catalyst for the preparation of benzoxazine and quinazoline ring systems in aqueous media. Advantages include high yields, short reaction times, easy work-up, and green procedure.



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