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Catalytic synthesis of bis-2,3-dihydroquinazolin-4(1*H*)-ones and 2,3-dihydroquinazolin-4 (1*H*)-ones derivatives with the aid of silica-supported Preyssler nanoparticles (SPNP)

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One-pot three-component condensation of isatoic anhydride with primary amines or ammonium carbonate and aromatic aldehydes in refluxing ethanol in the presence of catalytic amounts of silica-supported Preyssler nanoparticles (SPNP) afforded the corresponding 2,3-dihydroquinazolin-4(1*H*)-ones in high yields. Bis-dihydroquinazolinones were synthesized for the first time by a novel pseudo five-component condensation of isatoic anhydride, a primary amine, and a dialdehyde in water. The catalyst is reusable and can be applied several times without any decrease in product yield.

Keywords: Silica-supported Preyssler nanoparticles (SPNP), Heteropolyacid, 2,3-dihydroquinazolin-4(1*H*)-ones, Bisdihydroquinazolinones, Nanocatalyst, Isatoic anhydride

INTRODUCTION

One-pot transformations, particularly multi-component reactions (MCRs) are of current interest to organic chemists [1]. Since the first MCR reported in 1850 by Strecker [2], this methodology has emerged as an especially attractive synthetic strategy for rapid and efficient
library generation due to the fact that the products are formed in a single step and diversity can be achieved simply by varying the reaction components. MCRs leading to interesting heterocyclic scaffolds are particularly useful for the creation of diverse chemical libraries of drug-like molecules for biological screening [3]. 2,3-Dihydroquinazolinone derivatives are an important class of fused heterocycles that display a wide range of biological, pharmacological, and medicinal properties involving antitumor, antibiotic, antipyretic, analgesic, antihypertonic, diuretic, antihistamine, antidepressant, and vasodilating activities [4]. In addition, 2,3-dihydroquinazolinones have been shown to act as potent tubulin inhibitors with impressive antiproliferative activity against several human cancer cell lines [5]. Furthermore, these compounds can act analogously to the antimitotic agent colchicine [6].

Additionally, these compounds can easily be oxidised to their quinazolin-4(3*H*)-one analogues [7], which are important biologically active heterocyclic compounds [8]. The usual procedure for the preparation of 2,3-dihydroquinazolin-4(1*H*)-ones involves condensation of the appropriate derivatives of anthranilamide with an aldehyde or ketone using p-toluenesulfonic acid as a catalyst under vigorous conditions [9]. Similar reactions have been reported to proceed under basic conditions [10]. This procedure affords dihydroquinazolinones in good yields, but requires long reaction times. The three step synthesis starting from isatoic anhydride or anthranilic acid has been reported [11] and other methods such as reductive cyclisation of o-nitrobenzamides with aldehydes and ketones [12], reaction of isatoic anhydride with Schiff bases [13], and reduction of quinazolin-4(3H)-ones [14] are also reported for the synthesis of these compounds. Due to the unique properties of nanoparticles along with their novel properties and potential applications in different fields [14], the synthesis and characterization of catalysts with lower dimensions has become an active topic of research over the last decade. As the particle size decreases, the relative number of surface atoms increases, and thus activity increases. Moreover, due to quantum size effects, nanometer-sized particles may exhibit unique properties for a wide range of applications [15]. Along this line, polyoxometalates (POMs) are attracting much attention as building blocks for functional

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composite materials because of their interesting nanosized structures [16]. They are ideal models for the construction of hybrid systems, so they are regarded as potential candidates to be transformed into nanometer-sized materials. In recent years, considerable effort has been devoted to the design and controlled fabrication of nanostructured POMs for using in green reactions. This interest has resulted in the development of numerous protocols for the synthesis of nanostructured materials over a range of sizes. Therefore, the field of nano POMs and their applications continues to attract significant attention, so the number of publications and patents continue to grow, and new researchers are entering the field. Thus, plenty of room exists for expanding the exploration of the opportunities for these materials and further exploring, so developing new POMs is still a challenge for POM chemistry. However, in spite of extensive investigations on the synthesis and characterization of Keggin-type nanocatalysts [17], the synthesis of sodium 30-tungstopentaphosphate nanocatalysts has been largely overlooked. A Preyssler acid is a highly acidic catalyst with excellent catalytic activity in a variety of acid catalyzed reactions [18,19]. The catalyst consists of an anion with a formula of $[NaP_5W_{30}O_{110}]^{14-}$ which has unusual five-fold symmetry achieved by fusion of five $\{PW_6O_{22}\}$ groups. The central sodium ion is not lying on the equator of the anion but in a plane roughly defined by oxygen atoms of the phosphate groups. The presence of the sodium cation reduces the overall anion symmetry from D5h to C5v [20]. Silica-supported Preyssler nano structures were obtained through a micro emulsion method. Although this procedure has been reported previously, this method has never been reported for the synthesis of Preyssler nano structures with different morphologies.

EXPERIMENTAL

Instrument and chemical materials

All materials were of commercial quality and were used as received. The products purity was determined by GC-MS analysis. Mass spectra were recorded on a Shimadzu QP 1100 BX mass spectrometer. Elemental analysis was performed using an Electrothermal 9100 apparatus. IR spectra were recorded in KBr pellets on a Shimadzu IR-470 spectrophotometer. 1H and 13C NMR spectra were determined on a Bruker 300 DRX Avance instrument at 300 MHz.

General procedure

Catalyst Preparation. Supported heteropolyacid catalyst was synthesized according to the literature [21] using a support in powder form (SiO_2) with an aqueous solution of the heteropolyacids. After stirring the mixture, the solvent was evaporated, dried at 120°C and calcined at 250°C in a furnace prior to use. Silica-supported Preyssler nano structures were obtained by the microemulsion method [22].

Synthesis of 2,3-dihydroquinazolin-4(1H)-ones. Silica-supported Preyssler nanoparticles heteropolyacid catalyst (SPNP) (0.03 mmol), isatoic anhydride (1 mmol), primary amine or ammonium acetate (1.1 mmol), and aromatic aldehyde (1 mmol) were added to 5 mL of water or ethanol and the mixture was stirred in a round-bottomed flask under reflux for the appropriate time (see Tables 1, 2). After completion of the reaction, which was confirmed by TLC (eluent: n-hexane/ethyl acetate: 2/1), the water was decanted, hot ethanol (5 mL) was added to the residue which was then filtered. The resulting solution was condensed under reduced pressure. Finally the crude product was filtered, and recrystallized from ethanol.

Selected spectroscopic data:

3-Ethyl-2,3-dihydro-2-(4-hydroxyphenyl) quinazolin-4(1*H*)-one (4c):

IR (KBr, cm^{-1}): 3440, 1680. δ_H (300 MHz, $CDCl_3$, δ/ppm): 1.00 (t, J = 7.1 Hz, 3 H, CH_3), 2.85 (dq, J = 13.6, 7.0 Hz, 1 H, CH), 3.73 (dq, J = 13.6, 7.2 Hz, 1 H, CH), 5.73 (d, J = 1.9 Hz, 1 H, CH), 6.67 (m, 4 H, ArH), 7.14 (m, 3 H, ArH), 7.24 (d, J = 1.9 Hz, 1 H, NH), 7.64 (dd, J = 7.6, 1.4 Hz, 1 H, ArH), 9.45 (s, 1 H, OH). δ_C (300 MHz, $CDCl_3$, δ/ppm): 14.5, 71.7, 115.8, 116.4, 116.7, 118.6, 128.9, 129.5, 133.0, 134.4, 148.2, 159.2, 163.3. Anal. Calcd for $C_{16}H_{16}N_2O_2$: C 72.31, H 4.62, N 9.91%; Found C 72.22, H 4.71, N 9.82%; HRMS (EI) Calcd. for $C_{16}H_{16}N_2O_2$ $[M]^+$, 343.1003, Found 343.1008;

2-(4-nitrophenyl)-3-propyl-2,3-dihydroquinazolin-4(1*H*)-one (4i):

IR (KBr, cm^{-1}): 3420, 1680. δ_H (300 MHz, $CDCl_3$) 0.94 (t, J = 7.3 Hz, 3 H, CH_3), 1.65 (m, 2 H, CH_2), 2.79 (ddd, J = 14.1, 8.6, 5.8 Hz, 1 H, CH), 4.09 (ddd, J = 13.9, 8.7, 6.6 Hz, 1 H, CH), 5.86 (s, 1 H, CH), 7.35 (m, 8 H, ArH). δ_C (300 MHz, $CDCl_3$) 12.7, 22.4, 48.1, 71.6, 116.1, 117.5, 120.9, 125.4, 128.6, 129.5, 134.9, 145.5, 148.4, 149.3, 164.2. Anal. Calcd for $C_{17}H_{17}N_3O_3$: C, 65.63; H, 5.52; N, 13.56. Found: C, 65.52; H, 5.45; N, 13.49. HRMS

(EI) Calcd. for $C_{17}H_{17}N_3O_3$ $[M]^+$, 311.1002, Found 311.1005;

2-(4-chlorophenyl)-3-(4-isopropylphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (4k):

IR (KBr, cm^{-1}): 3427, 3280, 2964, 1645, 1513, 1393, 1325, 1242, 990, 8825, 755; δ_H (300 MHz, DMSO-d_6) 7.96 (1H, d, J=8.4Hz), 7.75 (1H,d, J=6.9Hz), 7.64 (1H,d, J=2.4Hz), 7.57 (1H, d, J=8.4 Hz), 7.26 (7H, m), 6.73 (2H,m), 6.27 (1H, d, J=2.4Hz), 2.87 (1H,m), 1.18 (6H, d, J=6.9 Hz); δ_C (300 MHz, DMSO-d_6) 162.1, 146.2, 139.7, 138.5, 133.8, 132.8, 130.3, 128.9, 128.4, 127.2, 126.6, 121.5, 117.7, 115.4, 114.6, 71.7, 32.9, 23.9; HRMS (EI) Calcd. for $C_{23}H_{21}ClN_2O$ $[M]^+$, 376.1000, Found 376.1006; Anal. Calcd for $C_{23}H_{21}ClN_2O$ C 73.30, H 5.62, N 7.43%; Found C 73.11, H 5.42, N 7.31%;

3-(4-isopropylphenyl)-2-(4-methoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (4l):

IR (KBr, cm^{-1}): 3425, 3297, 2955, 1630, 1507, 1393, 1334, 1247, 1175, 1026, 835, 705; δ_H (300 MHz, DMSO-d_6) 7.76 (1H, d, J=7.5 Hz), 7.55 (1H, s), 7.28 (7H, m), 6.85 (2H, d, J=8.4 Hz), 6.75 (2H, t, J=8.4 Hz), 6.17 (1H, s), 3.74 (3H, s), 2.87 (1H, m), 1.19 (6H, d, J=6.9 Hz); δ_C (300 MHz, DMSO-d6) 162.2, 159.3, 146.5, 145.7, 138.5, 133.6, 132.9, 127.9, 127.6, 126.4, 125.9, 117.5, 115.4, 114.8, 113.6, 72.4, 54.9, 32.9, 23.8; HRMS (EI) Calcd. for $C_{24}H_{24}N_2O_2$ $[M]^+$, 372.2003, Found 372.1007; Anal. Calcd for $C_{24}H_{24}N_2O_2$: C 77.39, H 6.49, N 7.51%; Found C 77.45, H 6.53, N 7.41%;

2-(benzo[d][1,3]dioxol-5-yl)-3-(4-isopropyl-phenyl)-2,3-dihydroquinazolin-4(1*H*)-one (4m):

IR (KBr, cm^{-1}): 3438, 2965, 1646, 1507, 1402, 1237, 1029, 757; δ_H (300 MHz, DMSO-d_6) 7.75 (1H, d, J=7.5 Hz), 7.59 (1H, s), 7.23 (5H, m), 6.96 (1H, s), 6.79 (4H, m), 6.19 (1H, s), 5.97 (2H, s), 2.89 (1H, m), 1.17 (6H, d, J=6.6 Hz); δ_C (300 MHz, DMSO-d_6) 162.4, 147.5, 147.2, 146.4, 146.0, 138.7, 134.7, 133.7, 127.9, 126.5, 125.8, 119.7, 117.5, 115.6, 114.8, 107.9, 106.7, 101.3, 72.4, 32.9, 23.9; HRMS (EI) Calcd. for $C_{24}H_{22}N_2O_3$ $[M]^+$, 386.2001, Found 386.1006; Anal. Calcd for $C_{24}H_{22}N_2O_3$: C 74.58, H 5.75, N 7.26%; Found C 74.42, H 5.81, N 7.37%;

2,3-bis(4-methoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (4q):

IR (KBr, cm^{-1}): 3425, 2938, 2835, 1637, 1512, 1393, 1442, 1245, 1176, 1027, 997, 830, 764; δ_H (300 MHz, DMSO-d_6) 7.72 (1H, d, J=7.8 Hz), 7.42 (1H, s), 7.28 (3H, m), 7.17 (2H, d, J=8.7 Hz), 6.85 (4H, m) 6.77 (2H, t, J=7.8 Hz), 6.17 (1H, s), 3.75 (3H, s), 3.70 (3H, s); δ_C (300 MHz, DMSO-d_6) 162.4, 159.3, 157.5, 146.7, 133.6, 132.9, 127.9, 127.8, 127.4, 117.4, 115.2, 114.6, 113.9, 113.6, 72.9, 55.1, 55.5; HRMS (EI) Calcd. for $C_{22}H_{20}N_2O_3$ $[M]^+$, 360.1004, Found 360.1008; Anal. Calcd for $C_{22}H_{20}N_2O_3$: C 73.32, H 5.58, N 7.76%; Found C 73.22, H 5.43, N 7.65%;

2,3-Dihydro-2-(3-nitrophenyl)-3-(thiazol-2-yl)quinazolin-4(1*H*)-one (4Z17):

IR (KBr, cm^{-1}): 3365, 3078, 2962, 1639, 1527, 1505, 1445, 1392. δ_H (300 MHz, DMSO-d_6) 7.96 (m, 10H, Ar-H), 7.50 (d, J = 3.24 Hz, 1H, CH), 8.33 (d, J = 3.24, 1H, NH). δ_C (300 MHz, DMSO-d6) 67.8, 114.1, 116.2, 116.5, 119.2, 121.1, 123.5, 128.5, 130.4, 132.4, 135.7, 137.4, 142.3, 146.8, 148.7, 157.8, 160.9. Anal. Calcd for $C_{17}H_{14}N_4O_3S$: C 57.63, H 3.97, N 15.80%; Found C 57.52, H 3.90, N 15.72%; HRMS (EI) Calcd. for $C_{17}H_{14}N_4O_3S$ $[M]^+$, 360.1002, Found 360.1006;

2,3-Dihydro-2-(4-hydroxyphenyl)-3-(thiazol-2-yl)quinazolin-4(1*H*)-one (4Z18:)

IR (KBr, cm^{-1}): 3346, 1638, 1614, 1511, 1453. δ_H (300 MHz, DMSO-d_6) 7.56 (m, 10H, Ar-H), 7.25 (d, J = 3.18 Hz, 1H, CH), 8.04 (d, J = 3.2 Hz, 1H, NH), 9.45 (s, 1H, OH). δ_C (400 MHz, DMSO-d_6) 68.3, 114.6, 115.6, 115.4, 116.0, 118.5, 127.4, 128.2, 130.5, 135.7, 137.5, 147.4, 157.5, 158.1, 161.2. Anal. Calcd for $C_{17}H_{15}N_3O_2S$: C 62.75, H 4.65, N 12.92%; Found C 62.81, H 4.73, N 12.82%; HRMS (EI) Calcd. for $C_{17}H_{15}N_3O_2S$ $[M]^+$, 325.1002, Found 325.1005;

2-(4,5-dihydrothiazol-2-yl)-3-p-tolyl-2,3-dihydroquinazolin-4(1*H*)-one (4Z19):

IR (KBr, cm^{-1}): 3406, 3045, 1635, 1507, 1453, 1393. δ_H (300 MHz, DMSO-d_6) 2.15 (s, 3 H, CH_3), 7.65 (m, 10H, Ar-H), 7.35 (d, J = 3.27, 1H, CH), 8.15 (d, J = 3.27Hz, 1H, NH). δ_C (300 MHz, DMSO-d_6) 20.8, 68.3, 114.2, 115.8, 116.4, 118.5, 126.0, 128.6, 129.6, 135.8, 137.1, 137.6, 137.2, 147.4, 158.6, 161.3. Anal. Calcd for $C_{18}H_{17}N_3OS$: C 66.85, H 5.31, N 12.98%; Found C 66.80, H 5.22, N 12.80%; HRMS (EI) Calcd. for $C_{18}H_{17}N_3OS$ $[M]^+$, 325.1002, Found 325.1005;

2,3-Dihydro-2-(4-nitrophenyl)-3-(thiazol-2-yl)quinazolin-4(1*H*)-one (4Z20):

IR (KBr, cm^{-1}): 3325, 3103, 1637, 1615, 1510, 1445, 1393. δH (300 MHz, $CDCl_3$) 7.96 (m, 11H, Ar-H), 8.24 (s, 1H, NH). δ_C (300 MHz, $CDCl_3$) 68.4, 114.1, 116.1, 116.4, 119.1, 124.2, 127.4, 128.7, 135.4, 137.7, 146.6, 147.7, 147.7, 157.7, 160.8. Anal. Calcd for $C_{17}H_{14}N_4O_3S$: C 66.85, H 5.31, N 12.98%; Found C 66.80, H 5.22, N 12.80%; HRMS (EI) Calcd. for $C_{17}H_{14}N_4O_3S$ $[M]^+$, 354.1001, Found 354.1006;

2-(4-Chlorophenyl)-2,3-dihydro-3-(thiazol-2-yl) quinazolin-4(1*H*)-one (4Z21):

IR (KBr, cm^{-1}): 3360, 3333, 3078, 1624, 1613, 1508, 1433. δ_H (300 MHz, $CDCl_3$): 7.75 (m, 11H, Ar-H), 8.16 (d, J = 3.72 Hz, NH). δ_C (300 MHz, CDCl3): 67.9, 114.1, 116.0, 116.1, 118.2, 128.0, 128.6, 129.3, 133.3, 135.5, 137.7, 139.4, 146.6, 157.6, 161.1. Anal. Calcd for $C_{17}H_{14}ClN_3OS$: C, 59.38, H, 4.11, N, 12.22%; Found C 59.21, H, 4.01, N, 12.11%; HRMS (EI) Calcd. for $C_{17}H_{14}ClN_3OS$ [M]+, 343.1003, Found 343.1008;

2,3-Dihydro-2-[4(1,2,3,4-tetrahydro-4-oxo-3-p-tolylquinazolin-2-yl)phenyl]-3-p-tolylquinazolin-4(1*H*)-one (2a):

IR (KBr, cm^{-1}): 3293, 1644. δ_H (300 MHz, DMSO-d_6) 2.25 (s, 6 H, CH_3), 6.13 (d, J = 1.8 Hz, 2H, CH), 7.35-740 (m, 20 H, ArH), 7.55 (d, J = 1.8 Hz, 2 H, NH). δ_C (300 MHz, DMSO-d_6) 20.9, 72.5, 114.7, 115.4, 117.8, 126.4, 126.7, 127.9, 129.2, 133.8, 135.3, 138.2, 140.8, 146.5, 162.3. Anal. Calcd for $C_{36}H_{30}N_4O_2$: C, 78.50; H, 5.50; N, 10.10. Found: C, 78.41; H, 5.45; N, 9.78. HRMS (EI) Calcd. for $C_{36}H_{30}N4O_2$ $[M]^+$, 550.2004, Found 550.1007;

3-(4-Chlorophenyl)-2-{4-[3-(4-chlorophenyl)-1,2,3,4-tetrahydro-4-oxoquinazolin-2-yl]phenyl}-2,3-dihydroquinazolin-4(1*H*)-one (2c):

IR (KBr, cm^{-1}): 3322, 1616. δ_H (300 MHz, DMSO-d_6) 6.18 (s, 2 H, CH), 7.16-7.45 (m, 22 H, 20×ArH, 2×NH). δ_C (300 MHz, DMSO-d_6) 70.9, 113.3, 113.4, 116.3, 125.5, 126.5, 126.7, 128.9, 132.7, 137.9, 139.3, 145.2, 160.8. Anal. Calcd for $C_{34}H_{24}Cl_2N_4O_2$: C, 69.0; H, 4.0; N, 9.40. Found C, 68.85; H, 3.89; N, 9.22. HRMS (EI) Calcd. for $C_{34}H_{24}Cl_2N_4O_2$ $[M]^+$, 590.2001, Found 590.1006;

2,3-Dihydro-2-{4-[1,2,3,4-tetrahydro-4-oxo-3-(thiazol-2-yl)quinazolin-2-yl]phenyl}-3-(thiazol-2-yl)quinazolin-4(1*H*)-one (2d):

IR (KBr, cm^{-1}): 3321, 1616. δ_H (300 MHz, DMSO-d_6) 6.94-7.89 (m, 20 H). δ_C (300 MHz, DMSO-d_6) 68.2, 114.6, 116.5, 118.8, 125.8, 126.3, 128.6, 128.7, 135.5, 137.9, 139.2, 145.6, 160.8. Anal. Calcd for $C_{28}H_{20}N_6O_2S_2$: C, 62.70, H, 3.80; N, 15.64. Found: C, 62.57; H, 3.69; N, 15.58. HRMS (EI) Calcd. for $C_{28}H_{20}N_6O_2S_2$ $[M]^+$, 536.1004, Found 536.1007;

3-Ethyl-2-[4-(3-ethyl-1,2,3,4-tetrahydro-4-oxoquiazolin-2-yl]phenyl)-2,3 dihydroquinazolin-4(1*H*)-one (2f):

IR (KBr, cm^{-1}): 3305, 2977, 1625. δ_H (300 MHz, DMSO-d_6) 1.04 (t, J = 7.0 Hz, 6 H, CH3), 2.77 (dt, J = 13.6, 7.0 Hz, 2 H, CH), 3.83 (dt, J = 13.6, 7.0 Hz, 2 H, CH), 5.85 (s, 2 H, CH), 7.05-7.30 (m, 14 H, 12×ArH, 2×NH). δ_C (300 MHz, DMSO-d_6) 13.9, 69.9, 114.7, 115.5, 117.9, 126.8, 127.9, 133.7, 142.0, 146.6, 162.5. Anal. Calcd for $C_{22}H_{26}N_4O_2$: C, 73.24; H, 6.10; N, 13.12. Found: C, 73.10; H, 5.98; N, 13.03. HRMS (EI) Calcd. for $C_{22}H_{26}N_4O_2$ $[M]^+$, 426.2004, Found 426.2009;

3-Benzyl-2-[4-(3-benzyl-1,2,3,4-tetrahydro-4-oxoquinazolin-2-yl)phenyl]-2,3-dihydroquinazolin-4(1*H*)-one (2g):

IR (KBr, cm^{-1}): 3290, 1644. δ_H (300 MHz, DMSO-d_6) 3.77 (d, J = 15.4 Hz, 2 H, CH), 5.25 (d, J = 15.4 Hz, 2 H, CH), 5.74 (d, J = 2.3 Hz, 2 H, CH), 7.0-7.56 (m, 22 H, ArH), 7.37 (2 H, d, J = 2.3 Hz, NH). δ_C (300 MHz, DMSO-d_6) 45.99, 68.2, 113.5, 113.4, 116.3, 125.1, 125.9, 126.2, 126.4, 127.6, 132.5, 136.3, 139.8, 145.0, 161.6. Anal. Calcd for $C_{36}H_{30}N4O_2$: C, 78.53; H, 5.56; N, 10.14. Found: C, 78.42; H, 5.45; N, 9.92. HRMS (EI) Calcd. for $C_{36}H_{30}N_4O_2$ $[M]^+$, 550.2005, Found 550.2008;

2,3-Dihydro-2-(1,2,3,4-tetrahydro-4-oxoquinazolin-2-yl)quinazoline-4(1*H*)-one (3h):

IR (KBr, cm^{-1}): 3354, 3300, 1638. δ_H (300 MHz, DMSO-d_6) 4.83 (m, 2 H, CH), 6.89-7.70 (m, 10 H, 8×ArH, 2×NH), 8.44 (2 H, d, J = 5.3 Hz, NH). δ_C (300 MHz, DMSO-d_6) 67.7, 117.1, 117.5, 118.6, 126.4, 127.3, 132.4, 132.5, 144.9, 167.4. Anal. Calcd for $C_{16}H_{14}N_4O_2$: C, 65.33; H, 4.82; N, 19.06. Found: C, 65.23; H, 4.71; N, 18.89. HRMS (EI) Calcd. for $C_{16}H_{14}N_4O_2$ $[M]^+$, 294.1004, Found 294.1007;

2,3-Dihydro-2-[4-(1,2,3,4-tetrahydro-4-oxo-quinazolin-2-yl)phenyl]quinazolin-4(1*H*)-one (2i):

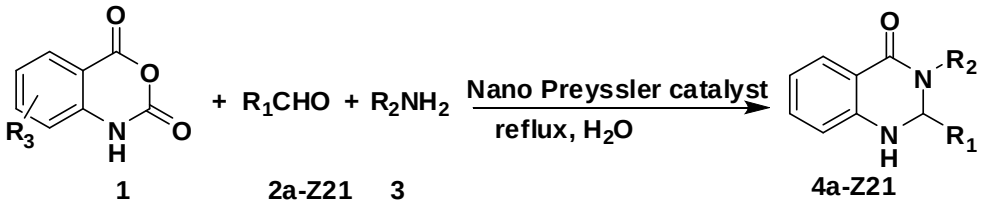
IR (KBr, cm^{-1}): 3266, 3185, 1643. δ_H (300 MHz, DMSO-d_6) 5.75 (d, J = 2.0 Hz, 2 H, CH), 6.67–8.11 (m, 16 H, 12×ArH, 4×NH). δ_C (300 MHz, DMSO-d_6): 66.7, 114.9, 115.7, 117.6, 127.2, 127.8, 133.9, 142.5, 148.1, 164.6. Anal. Calcd for $C_{22}H_{18}N_4O_2$: C, 71.34; H, 4.95; N, 15.16. Found: C, 71.26; H, 4.89; N, 14.98. HRMS (EI) Calcd. for $C_{22}H_{18}N_4O_2$ $[M]^+$, 370.1001, Found 370.1006;

RESULTS AND DISCUSSION

We synthesized mono- and disubstituted 2,3-dihydroquinazolin-4(1H)-ones. Water as a solvent resulted in shorter reaction times than ethanol (Table 1). For the synthesis of disubstituted derivatives, isatoic anhydride, a primary amine, and an aromatic aldehyde in the presence of silica-supported Preyssler nanoparticles heteropolyacid (SPNP) were reacted in ethanol or water under reflux conditions to afford the expected products (Scheme 1).

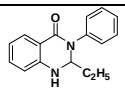
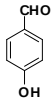
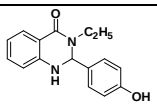
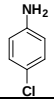
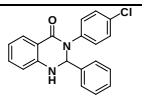
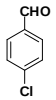
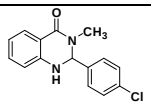
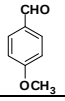
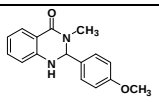
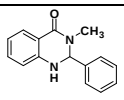
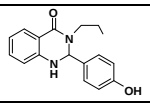
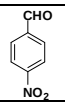
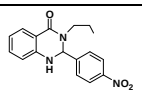
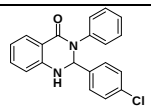
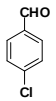
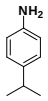
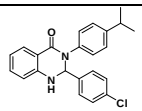
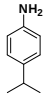
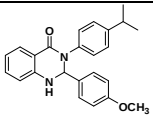
Several aliphatic and aromatic amines were used for this reaction. Aliphatic amines afforded the

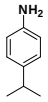
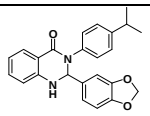
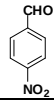
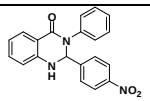
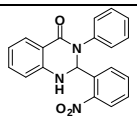
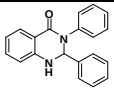
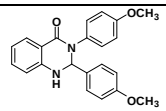
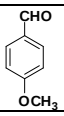
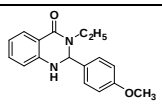
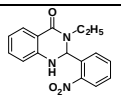
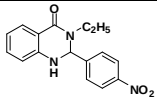
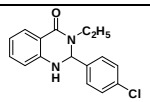
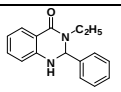
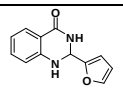
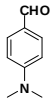
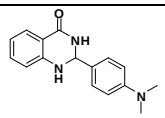
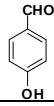
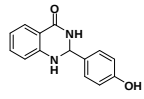
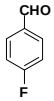
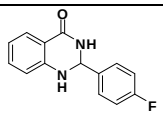
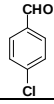
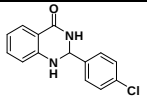
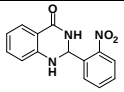
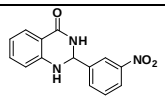
products in a shorter time compared to the aromatic analogues. Aromatic aldehydes carrying either electron-releasing or electron-withdrawing substituents afforded high yields of products. Aliphatic aldehydes could not be used in this procedure because they undergo aldol condensation under the reaction conditions. After optimizing the conditions, the generality toward various amines and benzaldehydes was explored. The results obtained are listed in Table 1.

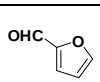
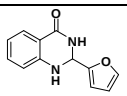
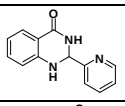
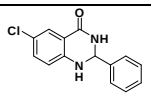
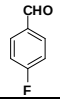
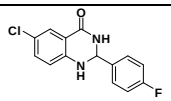
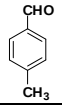
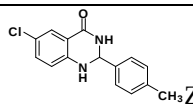
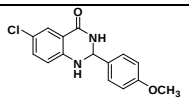
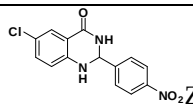
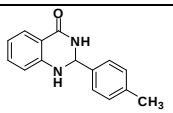
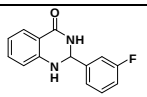
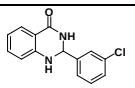
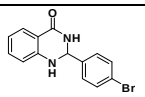
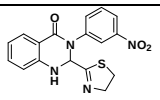
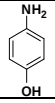
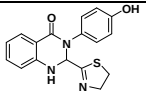
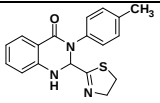
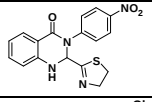
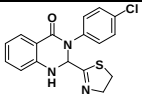


Scheme 1. Synthesized mono- and disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones using silica-supported Preyssler nanoparticles heteropolyacid (SPNP) under reflux conditions

Table 1. Silica-supported Preyssler nanoparticles (SPNP) catalyzed synthesis of 2,3-disubstituted 2,3-dihydroquinazolin-4(1*H*)-one derivatives by the reaction of isatoic anhydride with primary amines and aldehydes in water and ethanol under reflux conditions in proper times

Entry	Aldehyde(2)	Amine(3)	Product(4)	Time (h)		[a]Yield(%)		Mp (^{O}C)
				EtOH	H_2O	EtOH	H_2O	
1	HCHO	NH_3	 a	2	1	88	92	142-145
2		$C_2H_5NH_2$	 b	425	2.5	83	87	134–137 (lit.23)
3		$C_2H_5NH_2$	 c	3	1	85	81	180–182
4			 d	5	1.5	81	86	214–217 (lit.24)
5		CH_3NH_2	 e	2.5	1	87	80.5	188–190 (lit.23)
6		CH_3NH_2	 f	3	1.5	72	83	145–146 (lit.23)
7		CH_3NH_2	 g	1.5	3.5	74	87.5	164–165 (lit.23)
8		$CH_3CH_2CH_2NH_2$	 h	1	4.5	72	82.5	135-137
9		$CH_3CH_2CH_2NH_2$	 i	1	2.5	82.5	89.5	120–121
10			 j	4	2	71	78.5	214–217 (lit.34)
11			 k	2	4	89	95	190-192
12			 l	1.5	2.5	93	97	171-172

13			 m	2	4	82.5	91	210-212
14			 n	1	4	70	81.5	195–197 (lit.24)
15			 o	1.5	4	69	80	186–188 (lit.24)
16			 p	1	3.5	68	82.5	205–208 (lit.24)
17			 q	2.5	5	82	95.5	227-228
18		$C_2H_5NH_2$	 r	1	4.5	89	71.5	125–128 (lit.25)
19		$C_2H_5NH_2$	 s	3	5	82	95	175–178 (lit.25)
20		$C_2H_5NH_2$	 t	3	4.5	82	96	157–160 (lit.25)
21		$C_2H_5NH_2$	 u	1	4	82.5	89.5	134–137 (lit.25)
22		$C_2H_5NH_2$	 w	1	3.5	80	89.5	136–137 (lit.25)
23		NH_3	 x	2	4.5	78	79	167.2-168.5
24		NH_3	 y	3	5.5	79	81	228-229 (lit.26)
25		NH_3	 z	4	6	82	85	279.1-280.9 (lit.27)
26		NH_3	 Z1	3.5	5	81	83	199-200 (lit.5)
27		NH_3	 Z2	3	4.5	80	81.5	205-206 (lit.28)
28		NH_3	 Z3	2	3	86.5	92	193-194 (lit.27)
29		NH_3	 Z4	3	5	84	92	216.2-217.1 (Lit.29)
30		NH_3	Z5	3	4.5	85	91	212-214 (Lit.29)

31		NH_3	 Z6	5.5	4.5	76	79	166–167 (lit.30)
32		NH_3	 Z7	5	4	78	80	187–188 (lit.31)
33		NH_3	 Z8	5.5	3	81	83.5	249-250 (lit.32)
34		NH_3	 Z9	6	3.5	80.5	82	249-250
35		NH_3	 Z10	4.5	3	82.5	85	251, dec.
36		NH_3	 Z11	4	2.5	86	92	220-221
37		NH_3	 Z12	6	3.5	81.5	83	220 -221
38		NH_3	 Z13	5	2.5	85	89	233–234 (lit.28)
39		NH_3	 Z14	5.5	4	82	85	266-267
40		NH_3	 Z15	5	3	81	88	188-190 (lit.33).
41		NH_3	 Z16	6	3	80	84	206–207
42			 Z17	5	6	81	86	164–166
43			 Z18	5	2.5	74	85	260 dec
44			 Z19	5	3	79	86	196–197
45			 Z20	5	3	75	83.5	184–186
46			 Z21	5	3.5	74.5	80	174–175

[a]Isolated yields.

Following the obtained results, other derivatives of 2,3-dihydroquinazolin-4(1*H*)-one were synthesised by using different types of amines and aldehydes under aqueous or solvent-free conditions (Scheme 1). Aliphatic and aromatic amines as heteroaromatic model compounds also successfully afforded the desired products (Table 1).

Silica nanostructures were obtained through a sol-gel method. In this study, the gelation time is defined as the time between pouring the solution into the container and the time at which the solution ceases to discernibly flow under the influence of gravity. The conditions used are shown in Table 2 (Experimental section).

Table 2. Conditions of silica nanostructures production via sol-gel

4	C_2H_5OH/TEOS molar ratio	A
2	pH	B
12	Water/TEOS molar ratio	C
20 min	Stiring time	F
220 ^OC	Drying temperature	G
6 h	Drying time	H
4	C_2H_5OH/TEOS molar ratio	A

The obtained nanostructures were characterized by TEM, as shown in Figure 1. This figure shows 40-nm spheres.

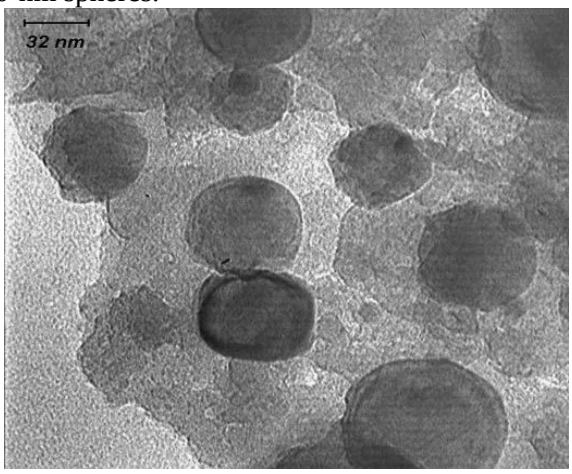


Fig. 1. TEM image of the synthesized nano-SiO_2.

The heteropolyacid $H_{14}[NaP_5W_{30}O_{110}]$ in the SiO_2 nanoparticle was confirmed by infrared spectroscopy, as shown in Figure 2. The asymmetric stretching frequency of the terminal oxygen is observed at 960 cm^{-1} and the P-O asymmetric stretching frequency is noted at 1080 and 1165 cm^{-1}. The prominent P-O bands at 960, 1080, and 1165 cm^{-1} are consistent with a C5V symmetry anion. These bands demonstrate that $H_{14}[NaP_5W_{30}O_{110}]$ is preserved in the HPA/SiO_2 nanoparticles. In addition, the protonated water of $H_{14}[NaP_5W_{30}O_{110}]$ also remained in the nanoparticles at 1730 cm^{-1}. It could be confirmed that the heteropolyacid $H_{14}[NaP_5W_{30}O_{110}]$ was successfully immobilized onto the SiO_2 nanoparticles since the heteropolyacid does not react with SiO_2 or with water, but it can remain in the silica nanoparticles without appreciable change of the structures.

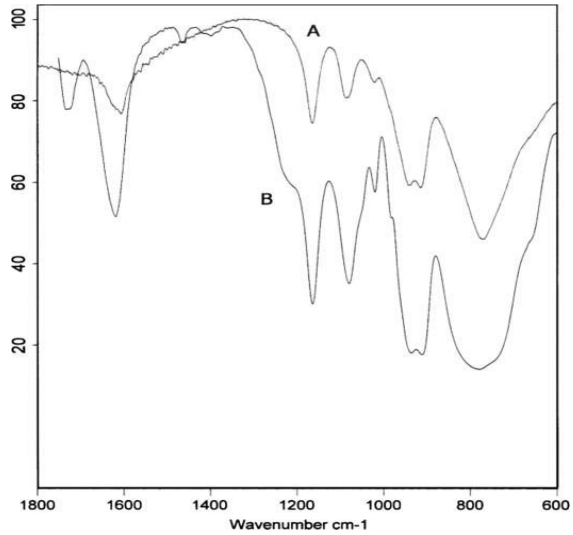
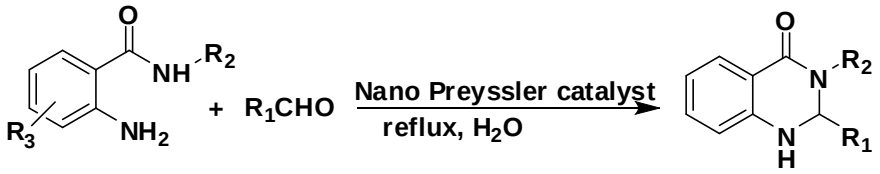
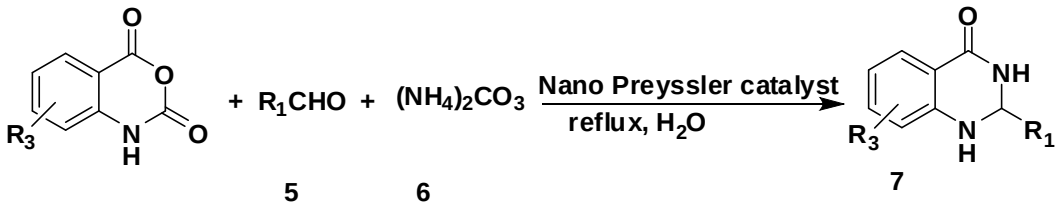


Fig. 2. Infrared spectroscopy of Preyssler heteropolyacid in bulk form (B) and nano form (A).

Considering the importance of such activities, a number of synthetic methods for their synthesis from isatoic anhydride (path 1) and anthranilamide (path 2) are reported (Schemes 1 and 2). Monosubstituted 2,3-dihydroquinazolin-4(1*H*)-ones were also successfully synthesized using ammonium carbonate as an ammonia source (Scheme 3).



Scheme 2. Synthesized disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones using silica-supported Preyssler nanoparticles heteropolyacid (SPNP) under reflux conditions



Scheme 3. Synthesis of monosubstituted 2,3-dihydroquinazolin-4(1*H*)-ones by using ammonium carbonate and silica-supported Preyssler nanoparticles heteropolyacid (SPNP) under reflux conditions in water as solvent

The direct three-component reactions worked well with a variety of arylamines bearing either electron-donating (Table 1, entries 11-17) or -withdrawing groups (Table 1, entries 4, 42-46) and phenethylamine (Table 1, entries 8 and 9). Also the reactions with arylamines and a range of benzaldehydes carrying either electron-donating or -withdrawing groups on the benzene ring afforded the desired products 4b-h in high yields. With other primary amines having an aromatic ring, the desired products 4j-l were produced in 78.5-97% yield (Table 1, entries 10-12). These reactions provided rapid access to various 2,3-dihydroquinazolin-4(1*H*)-one derivatives, (Table 1, 4a-k). We also checked the reusability of the catalyst by separation and reloading in a new run and found that the catalyst could be reused several times without any decrease in the product yield. An example is shown for the reaction of ethylamine with isatoic anhydride and 3-nitrobenzaldehyde, 4g (Table 1, entry 9).

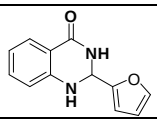
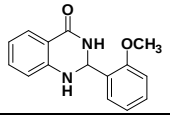
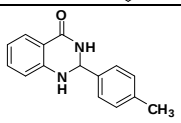
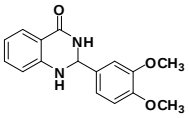
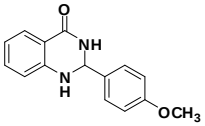
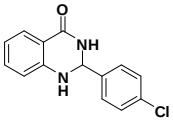
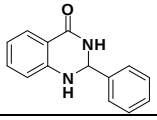
It is well known that some ammonium salts can be applied as the source of ammonia in the synthesis of nitrogen-containing heterocyclic compounds (Scheme 3).

Accordingly, 2-aryl substituted 2,3-dihydroquinazolin-4(1*H*)-ones 7 were efficiently synthesized when ammonium carbonate (6), isatoic anhydride (1) and an aromatic aldehyde 5, were treated with silica-supported Preyssler nanoparticles (SPNP) in ethanol under the same reaction conditions (Scheme 3, Table 3).

Some of the synthesized monosubstituted quinazolinones (Table 3, entries 2, 4, 5) have been recognized as potent anti-cancer compounds. For the preparation of our potential target compounds 2 and 3, isatoic anhydride was treated with primary amine and terphtaldehyde (4) or glyoxal (5) in the presence of silica-supported Preyssler nanoparticles (SPNP) (Scheme 4).

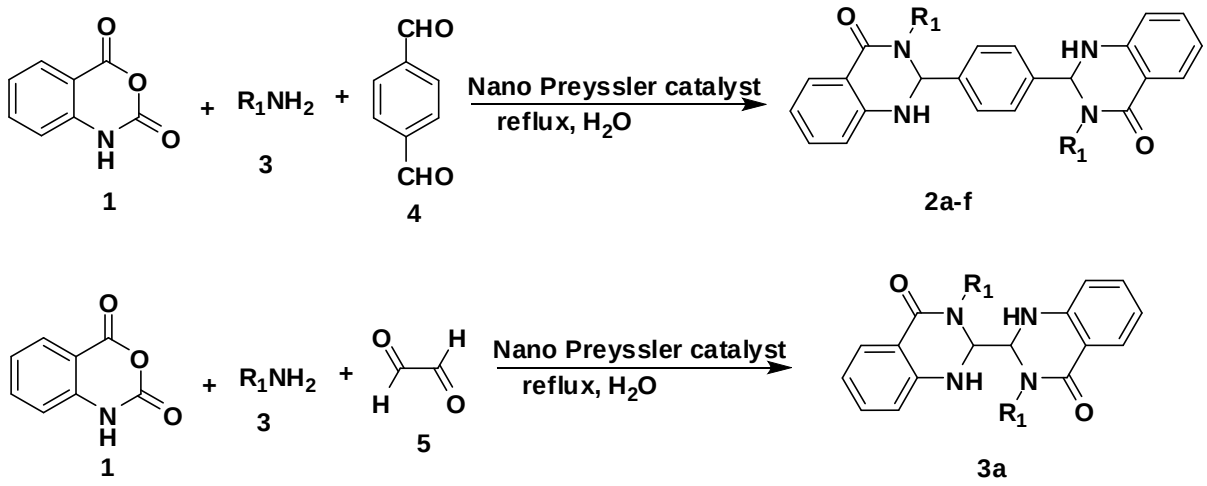
All bis-dihydroquinazolinones synthesized by this pseudo five-component reaction were reported for the first time and could be considered as potentially biologically active compounds with a quinazolinone core. In addition to the above-mentioned advantages are the simple work-up procedure, that makes this process environmentally friendly, and the easy purification, that requires only filtration of the products followed by recrystallization from ethanol (Table 4).

Table 3. Synthesis of 2-substituted 2,3-dihydroquinazolin-4(1*H*)-one derivatives in the presence of silica-supported Preyssler nanoparticles (SPNP) and water as solvent under reflux conditions

Entry	Product	Time (h)	[a]Yield (%)	Mp (°C)
1		4.5	80	164–165[34]
2		4	92	165–167[34]
3		3	93	233–234[35]
4		3.5	89	209–210[34]
5		3	87	180–181[36]
6		2.5	91	206–208[36]
7		2	94.5	219–222[36]

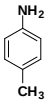
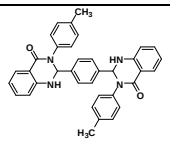
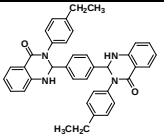
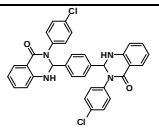
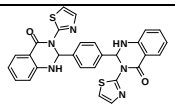
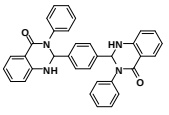
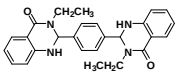
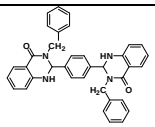
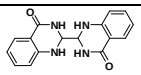
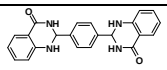
[a]Isolated yield.

Different organic solvents were examined for the reaction and we found that water was the solvent of choice (Table 4). Currently the use of non-toxic and environmentally friendly solvents is of much interest. Room temperature ionic liquids are novel solvents with outstanding environmental and technical features [37]. Ethanol proved to be



Scheme 4. Synthesis of Bis-2,3-dihydroquinazolin-4(1*H*)-ones derivatives using Silica-Supported Preyssler Nanoparticles (**SPNP**) and primary amine and terphtaldehyde under reflux conditions

Table 4. Synthesis of bis-2,3-dihydroquinazolin-4(1*H*)-ones in the presence of silica-supported Preyssler nanoparticles (SPNP) catalyst in water and/or ethanol solvents under reflux conditions

Entry	Aldehyde	Amine	Product	Time (h)		[a]Yield (%)	
				H_2O	EtOH	EtOH	H_2O
1			 a	3	4	67	70.5
2			 b	3	6	70	73.5
3			 c	4	9	60	64.5
4			 d	5.5	11.5	52	56.5
5			 e	2.5	5	63	67
6		$CH_3CH_2NH_2$	 f	3.5	5	65	71
7			 g	3.5	5.5	67	72.5
8		NH_3	 h	3.5	6	63	66.5
9		NH_3	 i	3.5	7.5	62.5	67.5

[a] Isolated yield (%)

almost as good as water, with ethanol giving a slightly better yield than tetra-*n*-butylammonium bromide. The use of water as a solvent for organic transformations offers several environmental benefits. In many reactions, significant rate enhancements are observed in water compared to

organic solvents. This acceleration has been attributed to many factors, including the hydrophobic effect, enhanced hydrogen bonding in the transition state, and the cohesive energy density of water [38]. When the reactions were conducted in water, the expected products were obtained in good yields and with better reaction times compared to organic solvents (Tables 3, 5). A part of the Preyssler heteropolyacid catalyst is solved in the water solvent. Preyssler heteropolyacid catalyst is also providing hydrogen bonding in the transition state more than ethanol in water solvent. The catalyst showed good efficiency for the synthesis of 2,3-dihydroquinazolin-4(*1H*)-one in water. Also, with nonpolar solvents such as carbon tetrachloride, dichloromethane and toluene, the desired adduct was not produced, likely due to insolubility of the isatoic anhydride.

Table 5. Solvent effects in the reaction of $C_2H_5NH_2$, isatoic anhydride, and terephthalaldehyde (2,2'-(1,4-phenylene)bis(3-(4-ethylphenyl)-2,3-dihydroquinazolin-4(1*H*)-one)) (Table 4, 2b) in the presence of silica-supported Preyssler nanoparticles catalyst (SPNP) (Table 3, entry 2).

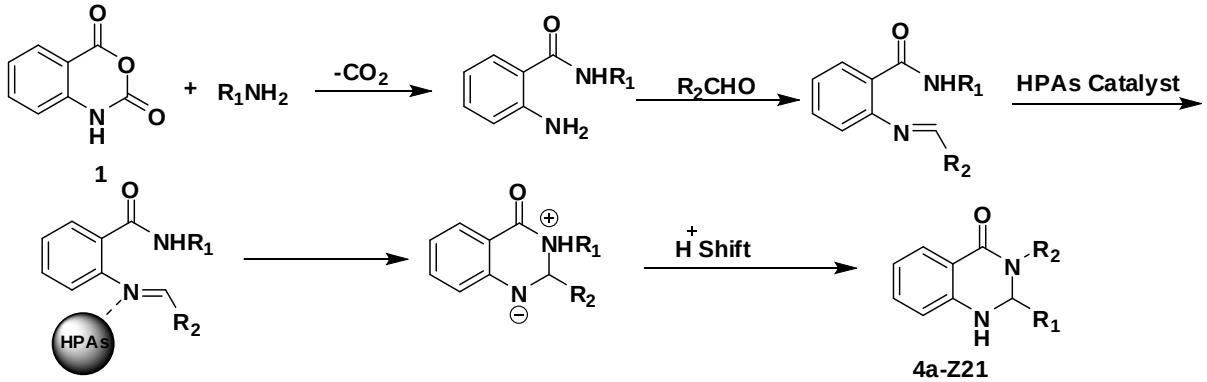
Entry	Solvent	[b]Yield (%)	Time (h)
1	H_2O	73.5	3
2	TBAB	61	8
3	C_2H_5OH	70	6
4	CH_3OH	37	12
5	CH_3CN	27	20
6	CH_2Cl_2	-	-
7	$C_6H_5CH_3$	-	-
8	CCl_4	-	-

[b]Isolated yield.

Generally, solid heteropolyacids form ionic crystals composed of heteropolyanions, counteractions (H^+, H_3O^+, $H_5O_2^+$, etc.) and hydration water. This water can be easily removed on heating, whereby the acid strength is increased due to the dehydration of protons. Not only water can enter and leave the heteropolyacid crystal. Misono and co-workers advanced two types of catalysis for heterogeneous acid catalysis by heteropolyacids - surface type and bulk type [39,40]. In surface type catalysis, the reactions occur on the surface of the supported heteropoly compounds and the catalytic activity usually depends on the surface acidity of the heteropolyacid. In this case, the reaction rate and the yield are parallel to the number and strength of the accessible surface acid sites. The bulk and surface type of mechanism is largely relevant to reactions of polar substrates on bulk and surface heteropoly compounds, These substrates are capable of absorbing into the catalyst bulk, and thus all protons both in the bulk and on the surface of the heteropolyacid, are suggested to participate in the catalytic reaction. Due to the flexible nature of the solid structure of some heteropolyacids, reactant molecules having polarity or basicity are readily absorbed into the solid lattice and react therein. In this case, heteropolyacid catalysts may be called ‘‘catalytically active solid solvents’’.

The Preyssler type heteropolyacid, $H_{14}[NaP_5W_{30}O_{110}]$, is remarkable owing to its exclusive physicochemical properties. They include strong Brønsted acidity, reversible transformations, solubility in polar solvents, high hydrolytic stability and high thermal stability, that are very important in catalytic processes.

A plausible mechanism for this reaction is shown in Scheme **5**. It is conceivable that the Preyssler heteropolyacid catalysts are coordinated to the oxygen atom of the carbonyl groups in different stages of the reaction, activating them for the nucleophilic attack of the amine and amide nitrogen atoms (Scheme 5).



Scheme 5. The mechanism of synthesized mono- and disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones using silica-supported Preyssler nanoparticles heteropolyacid (SPNP) under reflux conditions

CONCLUSION

In conclusion, a novel simple and environmentally friendly one-pot three-component method for the synthesis of 2,3-dihydroquinazolinones is reported. In this pseudo five-component procedure six C–N bonds are formed in a tandem one-pot process, which is comparable with other important reactions in multicomponent chemistry [41]. High yields, ease of work up procedure, use of cheap and commercially available starting materials, convenient manipulation, and mild reaction conditions are the advantages of this new method. We believe that the present methodology addresses the current trend toward green chemistry due to high yields, economy and reusability of the catalyst. By the reaction of a range of amines and dialdehydes, novel libraries of bisdihydroquinazolinones could be obtained, which would make this method a suitable candidate for combinatorial and parallel synthesis in drug discovery. Different organic solvents were examined for the reaction and we found that water was the solvent of choice. Importantly, the use of water as a solvent offers environmental benefits, as well as significant rate enhancements, likely due to several factors, including hydrophobic effect, large dielectric constant, extensive hydrogen bonding, high heat capacity, and optimum oxygen solubility. When the reactions were conducted in water, the expected products were obtained in good yields and with better reaction times compared to organic solvents or ionic liquids. This protocol will be useful for the synthesis of numerous fused heterocyclic compounds because of its non-toxicity and low-cost, short reaction time and high yield.

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СИНТЕЗА НА БИС-2,3-ДИХИДРОХИНАЗОЛИН-4(1Н)-ОНИ И ТЯХНИ ПРОИЗВОДНИ С ПОМОЩТА НА PREYSSLER‘ОВИ НАНОЧАСТИЦИ (SPNP) ВЪРХУ ПОДЛОЖКА ОТ СИЛИЦИЕВ ДИОКСИД

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(Резюме)

Проведени са едноетапни синтези чрез три-компонентна кондензация на изатоинов анхидрид с първични амини (или амониев карбонат) и ароматни алдехиди в среда от етанол при катализатор от Preyssler‘ови наночастици (SPNP) върху подложка от силициев диоксид. Постигнати са високи добиви от 2,3-дихидрохиназолин-4(1Н)-они. За пръв път са синтезирани бис-2,3-дихидрохиназолин-4(1Н)-они чрез нова псевдо-пет-компонентна кондензация на изатоинов анхидрид, първичен амин и диалдехид във вода. Катализаторът може да се употребява многократно без намаляване добива на продуктите.