Research Article

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

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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, and 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.

1. Introduction

One-pot transformations, particularly multicomponent reactions (MCRs), are of current interest by Salehi et al. [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 by Strecker [2]. MCRs leading to interesting heterocyclic scaffolds are particularly useful for the creation of diverse chemical libraries of drug-like molecules for biological screening by Domling [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 by Sadanandam et al. [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 by Chinigo et al.

[5]. Furthermore, these compounds can act analogously to the antimitotic agent colchicine [6]. Additionally, these compounds can easily be oxidized to their quinazolin-4(3*H*)-one analogues by Baker et al. [7], which are themselves important biologically active heterocyclic compounds, Moore et al. [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, by Ozaki et al. [9]. Similar reactions have been reported to proceed under basic conditions, by Kornet [10]. This procedure affords dihydroquinazolinones in good yields but requires long reaction times. The three-step synthesis starting from isatoic anhydride or an anthranilic acid has been reported by Shi et al. [11] and other methods such as reductive cyclisation of *o*-nitrobenzamides with aldehydes and ketones by Steiger et al. [12], reaction of isatoic anhydride with schiff bases, by Li et al. [13], and reduction of quinazolin-4(3*H*)-ones, by Gorla et al. [14], are also reported for the synthesis of these compounds. Over the last decade, due to the unique properties of nanoparticles

FIGURE 1: TEM image of the synthesized nano-SiO₂.

along with their novel properties and potential applications in different fields [14], the synthesis and characterization of catalysts with lower dimension has become an active topic of research. 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, by Martikainen and Stoof [15]. Along this line, polyoxometalates (POMs) are attracting much attention as building blocks for functional composite materials because of their interesting nanosized structures, by Ding et al. [16]. They are ideal models for the construction of hybrid systems, so they are regarded as the 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 continue 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 synthesis and characterization of Keggin-type nanocatalysts, by Sawant et al. [17], the synthesis of sodium 30-tungstophosphate nanocatalysts has been largely overlooked. A Preyssler acid is a highly acidic catalyst with excellent catalytic activity in a variety of acid catalyzed reactions, elsewhere [18, 19]. The catalyst consists of an anion with a formula of $[\text{NaP}_5\text{W}_{30}\text{O}_{110}]^{14-}$ which has an unusual five-fold symmetry achieved by fusion of five PW_6O_{22} groups. The central sodium ion lies not 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 D_{5h} to C_{5v} , by Müller et al. [20]. Silica-supported preyssler nanostructures were obtained through a microemulsion method. Although this procedure has been reported previously, this method has never been reported for the synthesis of Preyssler nanostructures with different morphologies.

FIGURE 2: Infrared spectroscopy of Preyssler heteropolyacid in bulk form (B) and nanoform (A).

2. Material and Methods

All materials were of commercial quality and were used as received. The product purities were 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 on KBr pellets on a Shimadzu IR-470 spectrophotometer. ^1H and ^{13}C NMR spectra were determined on a Bruker 300 DRX Avance instrument at 300 MHz, respectively.

2.1. Catalyst Preparation. Supported heteropoly acid catalyst was synthesized according to the literature, Alizadeh et al. [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 nanostructures were obtained through the microemulsion method by Heravi et al. [22].

2.2. General Procedure for the Synthesis of 2,3-Dihydroquinazolin-4(1H)-ones. Silica-Supported Preyssler nanoparticles heteropolyacid catalyst (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 at under reflux conditions for the appropriate time (see Tables 1 and 2). After completion of the reaction confirmed by TLC (eluent: *n*-hexane/ethyl acetate: 2/1), 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.

TABLE 1: Silica-supported preyssler nanoparticles catalyzed synthesis of 2,3-disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones 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 (°C)
				EtOH	H ₂ O	EtOH	H ₂ O	
1	HCHO	NH ₃	a	2	1	88	92	142–145
2		C ₂ H ₅ NH ₂	b	4.25	2.5	83	87	134–137 [23]
3		C ₂ H ₅ NH ₂	c	3	1	85	81	180–182
4			d	5	1.5	81	86	214–217 [24]
5		CH ₃ NH ₂	e	2.5	1	87	80.5	188–190 [23]
6		CH ₃ NH ₂	f	3	1.5	72	83	145–146 [23]
7		CH ₃ NH ₂	g	1.5	3.5	74	87.5	164–165 [23]
8		CH ₃ CH ₂ CH ₂ NH ₂	h	1	4.5	72	82.5	135–137
9		CH ₃ CH ₂ CH ₂ NH ₂	i	1	2.5	82.5	89.5	120–121
10			j	4	2	71	78.5	214–217 [34]

TABLE 1: Continued.

Entry	Aldehyde (2)	Amine (3)	Product (4)	Time (h)		^a Yield (%)		Mp (°C)
				EtOH	H ₂ O	EtOH	H ₂ O	
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 [24]
15			o	1.5	4	69	80	186–188 [24]
16			p	1	3.5	68	82.5	205–208 [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 [1]
19		$C_2H_5NH_2$	s	3	5	82	95	175–178 [1]
20		$C_2H_5NH_2$	t	3	4.5	82	96	157–160 [1]

TABLE 1: Continued.

Entry	Aldehyde (2)	Amine (3)	Product (4)	Time (h)		^a Yield (%)		Mp (°C)
				EtOH	H ₂ O	EtOH	H ₂ O	
21		C ₂ H ₅ NH ₂	u	1	4	82.5	89.5	134–137 [1]
22		C ₂ H ₅ NH ₂	w	1	3.5	80	89.5	136–137 [1]
23		NH ₃	x	2	4.5	78	79	167.2–168.5
24		NH ₃	y	3	5.5	79	81	228–229 [26]
25		NH ₃	z	4	6	82	85	279.1–280.9 [27]
26		NH ₃	Z1	3.5	5	81	83	199–200 [5]
27		NH ₃	Z2	3	4.5	80	81.5	205–206 [28]
28		NH ₃	Z3	2	3	86.5	92	193–194 [27]
29		NH ₃	Z4	3	5	84	92	216.2–217.1 [29]
30		NH ₃	Z5	3	4.5	85	91	212–214 [29]

TABLE 1: Continued.

Entry	Aldehyde (2)	Amine (3)	Product (4)	Time (h)		^a Yield (%)		Mp (°C)
				EtOH	H ₂ O	EtOH	H ₂ O	
31		NH ₃	 Z6	5.5	4.5	76	79	166-167 [30]
32		NH ₃	 Z7	5	4	78	80	187-188 [31]
33		NH ₃	 Z8	5.5	3	81	83.5	249-250 [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 [28]
39		NH ₃	 Z14	5.5	4	82	85	266-267
40		NH ₃	 Z15	5	3	81	88	188-190 [33].

TABLE 1: Continued.

Entry	Aldehyde (2)	Amine (3)	Product (4)	Time (h)		^a Yield (%)		Mp (°C)
				EtOH	H ₂ O	EtOH	H ₂ O	
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

^aIsolated yields.

TABLE 2: The conditions of silica nanostructures production via sol-gel.

4	C ₂ H ₅ OH/TEOS molar ratio	A
2	pH	B
12	Water/TEOS molar ratio	C
20 min	Stirring time	F
220°C	Drying temperature	G
6 h	Drying time	H
4	C ₂ H ₅ OH/TEOS molar ratio	A

2.3. Selected Spectroscopic Data

3-Ethyl-2,3-dihydro-2-(4-hydroxyphenyl)quinazolin-4(1H)-one (4c). IR (KBr, cm⁻¹): 3440, 1680. δ_{H} (300 MHz, CDCl₃): 1.00 (t, J = 7.1 Hz, 3 H, CH₃), 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, CDCl₃): 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 C₁₆H₁₆N₂O₂: C 72.31, H 4.62, N 9.91%. Found C 72.22, H 4.71, N 9.82%. HRMS (EI) Calcd. for C₁₆H₁₆N₂O₂ [M]⁺, 343.1003, Found 343.1008.

2-(4-Nitrophenyl)-3-propyl-2,3-dihydroquinazolin-4(1H)-one (4i). IR (KBr, cm⁻¹): 3420, 1680. δ_{H} (300 MHz, CDCl₃): 0.94 (t, J = 7.3 Hz, 3 H, CH₃), 1.65 (m, 2 H, CH₂), 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, CDCl₃): 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 C₁₇H₁₇N₃O₃: C, 65.63; H, 5.52; N, 13.56. Found: C, 65.52; H, 5.45; N, 13.49. HRMS (EI) Calcd. for C₁₇H₁₇N₃O₃ [M]⁺, 311.1002, Found 311.1005.

2-(4-Chlorophenyl)-3-(4-isopropylphenyl)-2,3-dihydroquinazolin-4(1H)-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 = 8.4 Hz), 7.75 (1H, d, J = 6.9 Hz), 7.64 (1H, d, J = 2.4 Hz), 7.57 (1H, d, J = 8.4 Hz),

SCHEME 1: Synthesized mono- and disubstituted 2,3-dihydroquinazolin-4(1H)-ones using silica-supported preyssler nanoparticles heteropolyacid under reflux conditions.

SCHEME 2: Synthesized disubstituted 2,3-dihydroquinazolin-4(1H)-ones using silica-supported preyssler nanoparticles heteropolyacid under reflux conditions.

7.26 (7H, m), 6.73 (2H, m), 6.27 (1H, d, $J = 2.4$ Hz), 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 $\text{C}_{23}\text{H}_{21}\text{ClN}_2\text{O}$ $[\text{M}]^+$, 376.1000, Found 376.1006; Anal. Calcd for $\text{C}_{23}\text{H}_{21}\text{ClN}_2\text{O}$ 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(1H)-one (4I). 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- d_6) 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 $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_2$ $[\text{M}]^+$, 372.2003, Found 372.1007. Anal. Calcd for $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_2$: 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-isopropylphenyl)-2,3-dihydroquinazolin-4(1H)-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 $\text{C}_{24}\text{H}_{22}\text{N}_2\text{O}_3$ $[\text{M}]^+$, 386.2001, Found 386.1006. Anal. Calcd for $\text{C}_{24}\text{H}_{22}\text{N}_2\text{O}_3$: 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(1H)-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 $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_3$ $[\text{M}]^+$, 360.1004, Found 360.1008. Anal. Calcd for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_3$: 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(1H)-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- d_6) 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 $\text{C}_{17}\text{H}_{14}\text{N}_4\text{O}_3\text{S}$: C 57.63, H 3.97, N 15.80%. Found C 57.52, H 3.90, N 15.72%. HRMS (EI) Calcd. for $\text{C}_{17}\text{H}_{14}\text{N}_4\text{O}_3\text{S}$ $[\text{M}]^+$, 360.1002, Found 360.1006.

2,3-Dihydro-2-(4-hydroxyphenyl)-3-(thiazol-2-yl)quinazolin-4(1H)-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 $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}_2\text{S}$: C 62.75, H 4.65, N 12.92%. Found C 62.81, H 4.73, N 12.82%. HRMS (EI) Calcd. for $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}_2\text{S}$ $[\text{M}]^+$, 325.1002, Found 325.1005.

2-(4,5-Dihydrothiazol-2-yl)-3-p-tolyl-2,3-dihydroquinazolin-4(1H)-one (4Z19). IR (KBr, cm^{-1}): 3406, 3045, 1635, 1507, 1453, 1393. δ_{H} (300 MHz, DMSO- d_6) 2.15 (s, 3H, CH_3), 7.65 (m, 10H, Ar-H), 7.35 (d, $J = 3.27$, 1H, CH), 8.15 (d, $J = 3.27$ Hz, 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 $\text{C}_{18}\text{H}_{17}\text{N}_3\text{OS}$: C 66.85, H 5.31, N 12.98%. Found C 66.80, H 5.22, N 12.80%. HRMS (EI) Calcd. for $\text{C}_{18}\text{H}_{17}\text{N}_3\text{OS}$ $[\text{M}]^+$, 325.1002, Found 325.1005.

2,3-Dihydro-2-(4-nitrophenyl)-3-(thiazol-2-yl)quinazolin-4(1H)-one (4Z20). IR (KBr, cm^{-1}): 3325, 3103, 1637, 1615, 1510, 1445,

SCHEME 3: Synthesis of Monosubstituted 2,3-dihydroquinazolin-4(1H)-ones by using ammonium carbonate and silica-supported preyssler nanoparticles heteropolyacid under reflux conditions in water as solvent.

SCHEME 4: Synthesis of Bis-2,3-dihydroquinazolin-4(1H)-ones derivatives using silica-supported preyssler nanoparticles and primary amine and terephthalaldehyde under reflux conditions.

1393. δ_{H} (300 MHz, CDCl_3) 7.96 (m, 1H, 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 $\text{C}_{17}\text{H}_{14}\text{N}_4\text{O}_3\text{S}$: C 66.85, H 5.31, N 12.98%. Found C 66.80, H 5.22, N 12.80%. HRMS (EI) Calcd. for $\text{C}_{17}\text{H}_{14}\text{N}_4\text{O}_3\text{S} [\text{M}]^+$, 354.1001, Found 354.1006.

2-(4-Chlorophenyl)-2,3-dihydro-3-(thiazol-2-yl)quinazolin-4(1H)-one (**4Z21**). IR (KBr, cm^{-1}): 3360, 3333, 3078, 1624, 1613, 1508, 1433. δ_{H} (300 MHz, CDCl_3): 7.75 (m, 1H, Ar-H), 8.16 (d, $J = 3.72$ Hz, NH). δ_{C} (300 MHz, CDCl_3): 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 $\text{C}_{17}\text{H}_{14}\text{ClN}_3\text{OS}$: C, 59.38, H, 4.11, N, 12.22%. Found C 59.21, H, 4.01, N, 12.11%. HRMS (EI) Calcd. for $\text{C}_{17}\text{H}_{14}\text{ClN}_3\text{OS} [\text{M}]^+$, 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(1H)-one (**2a**). IR (KBr, cm^{-1}): 3293, 1644. δ_{H} (300 MHz, $\text{DMSO}-d_6$) 2.25 (s, 6H, CH_3), 6.13 (d, $J = 1.8$ Hz, 2H, CH), 7.35–7.40 (m, 20H, ArH), 7.55 (d, $J = 1.8$ Hz, 2H, NH). δ_{C} (300 MHz, $\text{DMSO}-d_6$) 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 $\text{C}_{36}\text{H}_{30}\text{N}_4\text{O}_2$: C, 78.50; H, 5.50; N, 10.10. Found: C, 78.41; H, 5.45; N, 9.78. HRMS (EI) Calcd. for $\text{C}_{36}\text{H}_{30}\text{N}_4\text{O}_2 [\text{M}]^+$, 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(1H)-one (**2c**). IR (KBr, cm^{-1}): 3322, 1616. δ_{H} (300 MHz, $\text{DMSO}-d_6$)

d_6) 6.18 (s, 2H, CH), 7.16–7.45 (m, 22H, $20 \times \text{ArH}$, $2 \times \text{NH}$). δ_{C} (300 MHz, $\text{DMSO}-d_6$) 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 $\text{C}_{34}\text{H}_{24}\text{Cl}_2\text{N}_4\text{O}_2$: C, 69.0; H, 4.0; N, 9.40. Found C, 68.85, H, 3.89; N, 9.22. HRMS (EI) Calcd. for $\text{C}_{34}\text{H}_{24}\text{Cl}_2\text{N}_4\text{O}_2 [\text{M}]^+$, 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(1H)-one (**2d**). IR (KBr, cm^{-1}): 3321, 1616. δ_{H} (300 MHz, $\text{DMSO}-d_6$) 6.94–7.89 (m, 20H). δ_{C} (300 MHz, $\text{DMSO}-d_6$) 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 $\text{C}_{28}\text{H}_{20}\text{N}_6\text{O}_2\text{S}_2$: C, 62.70, H, 3.80; N, 15.64. Found: C, 62.57; H, 3.69; N, 15.58. HRMS (EI) Calcd. for $\text{C}_{28}\text{H}_{20}\text{N}_6\text{O}_2\text{S}_2 [\text{M}]^+$, 536.1004, Found 536.1007.

3-Ethyl-2-[4-(3-ethyl-1,2,3,4-tetrahydro-4-oxoquinazolin-2-yl)phenyl]-2,3-dihydroquinazolin-4(1H)-one (**2f**). IR (KBr, cm^{-1}): 3305, 2977, 1625. δ_{H} (300 MHz, $\text{DMSO}-d_6$) 1.04 (t, $J = 7.0$ Hz, 6H, CH_3), 2.77 (dt, $J = 13.6$, 7.0 Hz, 2H, CH), 3.83 (dt, $J = 13.6$, 7.0 Hz, 2H, CH), 5.85 (s, 2H, CH), 7.05–7.30 (m, 14 H, $12 \times \text{ArH}$, $2 \times \text{NH}$). δ_{C} (300 MHz, $\text{DMSO}-d_6$) 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 $\text{C}_{22}\text{H}_{26}\text{N}_4\text{O}_2$: C, 73.24; H, 6.10; N, 13.12. Found: C, 73.10; H, 5.98; N, 13.03. HRMS (EI) Calcd. for $\text{C}_{22}\text{H}_{26}\text{N}_4\text{O}_2 [\text{M}]^+$, 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(1H)-one (**2g**). IR (KBr, cm^{-1}): 3290, 1644. δ_{H} (300 MHz, $\text{DMSO}-d_6$) 3.77 (d,

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

TABLE 3: Synthesis of 2-Substituted 2,3-dihydroquinazolin-4(1H)-ones derivatives by in the presence of silica-supported preyssler nanoparticles 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]

^aIsolated yield.

TABLE 4: Synthesis of bis-2,3-dihydroquinazolin-4(1H)-ones in the presence of Silica-Supported Preyssler Nanoparticles catalyst in water and/or ethanol solvents under reflux conditions.

Entry	Aldehyde	Amine	Product	Time (h)		^a Yield (%)	
				H ₂ O	EtOH	EtOH	H ₂ O
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 ₃ CH ₂ NH 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

TABLE 4: Continued.

Entry	Aldehyde	Amine	Product	Time (h)		^a Yield (%)	
				H ₂ O	EtOH	EtOH	H ₂ O
9		NH ₃		3.5	7.5	62.5	67.5

^aIsolated yield.TABLE 5: Solvent effects in the reaction of C₂H₅NH₂, isatoic anhydride, and terephthalaldehyde for the synthesis of (2,2'-(1,4-phenylene)bis(3-(4-ethylphenyl)-2,3-dihydroquinazolin-4(1H)-one)) (Table 4, Entry 2, product 2b) in the presence of silica-supported preyssler nanoparticles catalyst.

Entry	Solvent	^b Yield (%)	Time (h)
1	H ₂ O	73.5	3
2	TBAB	61	8
3	C ₂ H ₅ OH	70	6
4	CH ₃ OH	37	12
5	CH ₃ CN	27	20
6	CH ₂ Cl ₂	—	—
7	C ₆ H ₅ CH ₃	—	—
8	CCl ₄	—	—

^bIsolated yield.

$J = 15.4$ Hz, 2H, CH), 5.25 (d, $J = 15.4$ Hz, 2H, CH), 5.74 (d, $J = 2.3$ Hz, 2H, CH), 7.0–7.56 (m, 22H, 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 C₃₆H₃₀N₄O₂: C, 78.53; H, 5.56; N, 10.14. Found: C, 78.42; H, 5.45; N, 9.92. HRMS (EI) Calcd. for C₃₆H₃₀N₄O₂ [M]⁺, 550.2005, Found 550.2008.

2,3-Dihydro-2-(1,2,3,4-tetrahydro-4-oxoquinazolin-2-yl)quinazolin-4(1H)-one (3h). IR (KBr, cm⁻¹): 3354, 3300, 1638. δ_H (300 MHz, DMSO- d_6) 4.83 (m, 2H, CH), 6.89–7.70 (m, 10H, 8 × ArH, 2 × NH), 8.44 (2H, 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 C₁₆H₁₄N₄O₂: C, 65.33; H, 4.82; N, 19.06. Found: C, 65.23; H, 4.71; N, 18.89. HRMS (EI) Calcd. for C₁₆H₁₄N₄O₂ [M]⁺, 294.1004, Found 294.1007.

2,3-Dihydro-2-[4-(1,2,3,4-tetrahydro-4-oxoquinazolin-2-yl)phenyl]quinazolin-4(1H)-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 C₂₂H₁₈N₄O₂: C, 71.34; H, 4.95; N, 15.16. Found: C, 71.26; H, 4.89; N, 14.98. HRMS (EI) Calcd. for C₂₂H₁₈N₄O₂ [M]⁺, 370.1001, Found 370.1006.

3. Results and Discussion

We synthesized mono- and disubstituted 2,3-dihydroquinazolin-4(1H)-ones. Water as 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 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 shorter time compared to 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 next explored. The results obtained are listed in Table 1.

Following the obtained results, other derivatives of 2,3-dihydroquinazolin-4(1H)-one were synthesized by using different types of amines and aldehydes under aqueous or solvent-free conditions (Scheme 1). Like aliphatic and aromatic amines, heteroaromatic model compounds also afforded the desired products successfully (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 in the container and the time at which the solution ceases to discernibly flow under the influence of gravity. The conditions used were shown in Table 2 (experimental section).

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

The heteropolyacid H₁₄[NaP₅W₃₀O₁₁₀] in the SiO₂ 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 C_{5v} symmetry anion. These bands demonstrate that H₁₄[NaP₅W₃₀O₁₁₀] is preserved in the HPA/SiO₂ nanoparticles. In addition, the protonated water of H₁₄[NaP₅W₃₀O₁₁₀] also remained in the nanoparticles at 1730 cm⁻¹. It could be confirmed that the heteropoly acid H₁₄[NaP₅W₃₀O₁₁₀] was successfully immobilized into the SiO₂ nanoparticles since the heteropolyacid does not react with SiO₂ or with water, but it can remain in the silica nanoparticles without appreciable change of the structures.

Given the importance of such activities, a number of synthetic methods for their synthesis from isatoic anhydride (path 1) and anthranilamide (path 2) have been reported (Schemes 1 and 2).

Monosubstituted 2,3-dihydroquinazolin-4(1H)-ones were also synthesized successfully using ammonium carbonate as an ammonia source (Scheme 3).

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 desired products **4b–h** in high yields. With other primary amines having an aromatic ring, 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(1H)-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(1H)-ones **7** were synthesized efficiently when ammonium carbonate (**6**), isatoic anhydride (**1**), and an aromatic aldehyde **5** were treated with Silica-Supported Preyssler Nanoparticles 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 anticancer compounds. For the preparation of our potential target compounds **2** and **3**, isatoic anhydride was treated with primary amine and terephthaldehyde (**4**) or glyoxal (**5**) in the presence of silica-supported preyssler nanoparticles (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 previously mentioned advantages are the simple work-up procedure, which makes this process environmentally friendly, and the easy purification, which requires only filtration of the products followed by recrystallization from ethanol (Table 4).

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, by Wilkes [37]. Tetra-*n*-butylammonium bromide (TBAB) was investigated as solvent for the above reaction. Ethanol proved to be 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, by Pratt and Pohorille [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 and 5).

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).

4. Conclusion

In conclusion, a simple and environmentally friendly and novel 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 by Pandey et al. [25]. 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 drive towards green chemistry due to high yields, atomic 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.

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