

## Heteropolyacids accelerated multi-component synthesis of *N*-phenylquinazolin-4-amines by using silica-supported Preyssler nanoparticles in green solvent

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*N*-phenylquinazolin-4-amines derivatives were obtained in high yields with excellent purity from the reaction of 2-aminobenzamide, orthoesters, and substituted anilines in the presence of Silica-Supported Preyssler Nanoparticles and various heteropolyacids (HPAs).

**Keywords:** Silica-Supported Preyssler Nanoparticles (SPNP), *N*-phenylquinazolin-4-amines; Recyclable catalysts; Heteropolyacids; Multi-component; Green.

### INTRODUCTION

In recent years, multicomponent reactions (MCRs) have become important tools in modern preparative synthetic chemistry because these reactions increase the efficiency by combining several operational steps without any isolation of intermediates or change of the conditions [1] and MCRs have recently emerged as valuable tools in the preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds [2]. They showed various applications in organic, medicinal chemistry [3] and in drug discovery as well as 'green chemistry' [4]. On the other hand heteropolyacid (HPA) has been successfully employed as a heterogeneous catalyst in organic synthesis [5]. They are noncorrosive and are environmentally benign, as they can be reused and recycled [6]. Owing to all these characteristic features of multicomponent reaction and heteropolyacid, heterogeneous systems show great potential since the use of toxic solvent is drastically reduced, the chemo selectivity and atom-efficiency are often improved, the product isolation is simplified, and the volume of waste is significantly reduced. Over the last decade, due to the unique properties of nanoparticles along with their novel properties and potential applications in different fields [7] the synthesis and characterization of catalysts with lower dimension has become an

active topic of research. Moreover, due to quantum size effects, nanometresized particles may exhibit unique properties for a wide range of applications [8]. Along this line, polyoxometalates (POMs) are attracting much attention as building blocks for functional composite materials because of their interesting nanosized structures [9]. 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. However, in spite of extensive investigations on synthesis and characterization of Keggin-type nanocatalysts [10], the synthesis of sodium 30-tungstophosphate nanocatalysts has been largely overlooked. 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  $\{\text{PW}_6\text{O}_{22}\}$  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  $C_{5v}$  [11].

Natural and synthetic compounds possessing the quinazoline structural motif display a wide range of

biological activities. Recently, quinazolin-4(3*H*)-ones were prepared via cyclocondensation of 2-aminobenzamides with orthoesters catalyzed by H<sub>2</sub>SO<sub>4</sub>/SiO<sub>2</sub> under anhydrous and microwave conditions [12]. In other work, quinazolin-4(3*H*)-one and quinazolin-2,4-dione derivatives were obtained under microwave irradiation [13]. There has been renewed interest in *N*-phenylquinazolin-4-amines connected with reports on the very high activity of 6,7-dimethoxy-4-(3-bromophenylamino)quinazoline (PD 153035) as a tyrosine kinase inhibitor [14]. Analogues of PD 153035 with more complex structures [15] as well as simple derivatives of 4-phenylaminoquinazoline without, for example, methoxy groups [16], also show interesting biological activity. Despite their biological activities, no recent progress on their syntheses has been made. *N*-phenylquinazolin-4-amines can be obtained via reactions of 4-halo- or 4-mercaptoquinazolines with aromatic amines [17]; however, the yields of these reactions do not usually [18] exceed 50%. *N*-phenylquinazolin-4-amines have also been produced by reactions of 4(3*H*)-quinazolone with aromatic amine hydrochlorides in the presence of phosphorus pentoxide and dimethylcyclohexylamine [19]. 4-Phenylaminoquinazoline was obtained by desulfurization of 4-phenylaminoquinazol-2-thione using Raney nickel W7 [20]. In addition to the reactions mentioned above, *N*-phenylquinazolin-4-amines have been obtained by the reaction of 2-aminobenzonitrile and various anilines in the presence of AlCl<sub>3</sub>, and by subsequent condensation of the products with formic acid [21]. The drawback of this method is that the synthesis of 2-amino-*N*-aryl-benzamidines is limited by the substituents on the anilines. Since the pathogenesis of allergic diseases is associated with elevated levels of immunoglobulin E (IgE), Berger et al, developed a high throughput reporter gene assay in a human B-cell line to screen for low molecular weight IgE inhibitory compounds. Monitoring the IL-4 driven IgE-germline promoter activity (IgE-GLP) [22]. Quinoline, isoquinoline, quinoxaline, and quinazoline derivatives were synthesized using microwave-assisted synthesis and their CB1/CB2 receptor activities were determined using the [<sup>35</sup>S]GTPγS binding assay. Most of the prepared quinoline, isoquinoline, and quinoxalanyl phenyl amines showed low-potency partial CB2 receptor agonists activity [23]. An efficient “one-step” synthesis of cyclic amidines and guanidines has been developed. Treatment of cyclic amides and ureas with benzotriazol-1-yl-oxyltris (dimethyl-

amino) phosphonium hexafluorophosphate (BOP), base, and nitrogen nucleophiles leads to the formation of the corresponding cyclic amidines and guanidines, typically in good to excellent yields. This method has also been used to prepare heteroaryl ethers and thioethers using phenol and thiophenol nucleophiles. [24]. A new multi-component synthesis of 4-arylaminquinazolines from the reaction of 2-aminobenzamide, orthoesters and substituted anilines in presence of catalytic amounts of sodium 30-tungstopentaphosphate, so-called Preyssler heteropolyacid, is reported [25]. Also, some 4-*N*-(3'- or 4'-substituted-phenyl)amino-6,7-dimethoxyquinazolines and the corresponding unsubstituted compounds were synthesized from 2-amino-4,5-dimethoxybenzoic acid and the appropriate substituted anilines [26].

## EXPERIMENTAL

### *Chemicals and Apparatus*

All the chemicals were obtained from Merck Company and used as received. The melting points were obtained using an Electrothermal IA 9100 digital melting point apparatus. The IR spectra were recorded on a Bruker (4000–400 cm<sup>-1</sup>) spectrometer. <sup>1</sup>H NMR spectra were recorded on a 400 MHz spectrometer using TMS as internal standard (in most spectra trimethylsilane (TMS) is used to reference the signal to a zero (0.00) and all other signals are relative to this standard).

### *Catalyst Preparation*

Heteropolyacid Preyssler was prepared according to the procedure reported before [29-31]. Supported heteropolyacid catalysts were prepared by impregnating a support in the form of powder (nanoSiO<sub>2</sub>) with an aqueous solution of the heteropolyacid with different concentrations. Samples were dried at 120-140°C, and the catalysts were calcined at 220°C in a furnace prior to use. H<sub>14</sub>[NaP<sub>5</sub>W<sub>30</sub>O<sub>110</sub>]/SiO<sub>2</sub> nanoparticles, H<sub>4</sub>[PMo<sub>11</sub>VO<sub>40</sub>], H<sub>5</sub>[PMo<sub>10</sub>V<sub>2</sub>O<sub>40</sub>], H<sub>6</sub>[PMo<sub>9</sub>V<sub>3</sub>O<sub>40</sub>], H<sub>14</sub>[NaP<sub>5</sub>W<sub>30</sub>O<sub>110</sub>]/SiO<sub>2</sub>(40%), H<sub>3</sub>[PMo<sub>12</sub>O<sub>40</sub>]/SiO<sub>2</sub>(40%), H<sub>4</sub>[PMo<sub>11</sub>VO<sub>40</sub>]/SiO<sub>2</sub>(40%), and H<sub>3</sub>[PW<sub>12</sub>O<sub>40</sub>]/SiO<sub>2</sub>(40%) and H<sub>3</sub>[PMo<sub>12</sub>O<sub>40</sub>] were prepared according to reports in the literature [29, 30]. Melting points were measured using Barnstead Electro thermal. Yields are based on GC/mass analysis using an Agilent 6890 GC system Hp-5 capillary 30 m × 530 μm × 1.5 μm nominal.

### *General Procedure*

Synthesis of *N*-phenylquinazolin-4-amine derivatives from the reaction of 2-aminobenzamide,

orthoester (trimethoxymethane) with substituted aniline: A mixture of 2-aminobenzamide (10 mmol), orthoester (10 mmol), and substituted aniline (15 mmol) and heteropolyacid (0.03 mmol) was refluxed in proper solvent (10 mL). The progress of the reaction was monitored by TLC and GC. After completion of the reaction, the catalyst was filtered off. The pure products were obtained by column chromatography. All products were identified by comparison of their physical and spectroscopic data with those reported for authentic samples [21, 24].

#### Selected spectral data

*N*-phenylquinazolin-4-amine (**3a**): mp: 220 °C, <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>, δ/ppm): 9.15 (s, 1H, NH) 8.67 (s, 1H, CH=N), 7.44 (m, 5H), 7.76 (m, 4H); <sup>13</sup>C-NMR (400 MHz, DMSO-*d*<sub>6</sub>, δ/ppm): 169.6 (C-1), 156.4 (C-2), 149.9 (C-3), 140.8 (C-4), 132.2 (C-5), 129.5 (C-6), 128.6 (C-7), 127.8 (C-8), 126.5 (C-9), 122.5 (C-10), 117.9, 116.7. IR (KBr, cm<sup>-1</sup>): 3325, 1604; Anal. Calc. for C<sub>14</sub>H<sub>11</sub>N<sub>3</sub>: C, 76.00; H, 5.02; N, 18.99%. Found: C, 75.93; H, 4.98; N, 18.96%. HRMS (EI) Calcd. for C<sub>14</sub>H<sub>11</sub>N<sub>3</sub> [M]<sup>+</sup>, 221.1005, Found 221.1008;

*N*-*p*-tolylquinazolin-4-amine (**3e**): Mp: 192 °C, <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>, δ/ppm): 9.15 (s, 1H, NH), 8.65 (s, 1H, CH=N), 7.22 (m, 4H), 7.80 (m, 4H), 2.31 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C-NMR (400 MHz, DMSO-*d*<sub>6</sub>, δ/ppm): 169.6 (C-1), 156.4 (C-2), 149.7 (C-3), 137.9 (C-4), 132.3 (C-5), 131.5 (C-6), 132.1 (C-7), 129.8 (C-8), 128.8 (C-9), 127.5 (C-10), 127.8 (C-10), 126.6 (C-11), 120.5 (C-11), 116.6 (C-12). IR (KBr, cm<sup>-1</sup>): 3327, 1602; MS: m/z 235 [M<sup>+</sup>]. HRMS (EI) Calcd. for C<sub>15</sub>H<sub>13</sub>N<sub>3</sub> [M]<sup>+</sup>, 235.1002, Found 235.1004; Anal. Calc. for C<sub>15</sub>H<sub>13</sub>N<sub>3</sub>: C, 76.57; H, 5.57; N, 17.86%. Found: C, 76.53; H, 5.51; N, 17.85%.

*N*-(4-nitrophenyl)quinazolin-4-amine (**3g**): Mp: 212 °C, <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>, δ/ppm): 9.20 (s, 1H, NH), 8.45 (s, 1H, CH=N), 8.11 (t, 1H, CH), 7.78 (m, 4H), 7.55 (m, 4H); <sup>13</sup>C-NMR (400 MHz, DMSO-*d*<sub>6</sub>, δ/ppm): 169.7 (C-1), 156.2 (C-2), 149.8 (C-3), 147 (C-4), 137.9 (C-5), 132.1 (C-6), 131.5 (C-7), 128.8 (C-8), 127.7 (C-9), 126.5 (C-

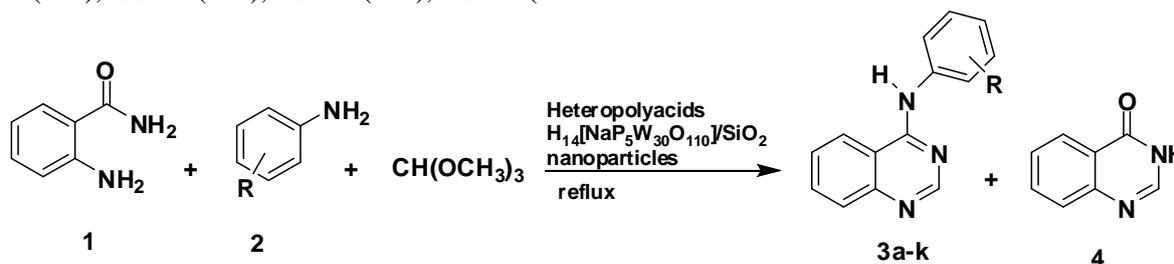
10), 124.6 (C-11), 119.1 (C-12), 116.3 (C-12). IR (KBr, cm<sup>-1</sup>): 3320, 1552, 1350; MS: m/z 266 [M<sup>+</sup>]. HRMS (EI) Calcd. for C<sub>14</sub>H<sub>10</sub>N<sub>4</sub>O<sub>2</sub> [M]<sup>+</sup>, 266.1001, Found 266.1003; Anal. Calc. for C<sub>14</sub>H<sub>10</sub>N<sub>4</sub>O<sub>2</sub>: C, 63.17; H, 3.79; N, 21.05%. Found: C, 63.43; H, 3.84; N, 21.23%.

*N*-(2-nitrophenyl)quinazolin-4-amine (**3h**): Mp: 219 °C, <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>, δ/ppm): 9.40 (s, 1H, C-NH), 8.46 (s, 1H, CH=N), 8.20 (t, 1H, CH), 7.80 (m, 4H), 7.57 (m, 4H); <sup>13</sup>C-NMR (400 MHz, DMSO-*d*<sub>6</sub>, δ/ppm): 169.7 (C-1), 156.2 (C-2), 149.8 (C-3), 147 (C-4), 137.9 (C-5), 132.2 (C-6), 128.7 (C-7), 127.9 (C-8), 126.5 (C-9), 125.6 (C-10), 119.5 (C-11), 116.1 (C-12), 110.4 (C-12). IR (KBr, cm<sup>-1</sup>): 3322, 1585, 1364; MS: m/z 266 [M<sup>+</sup>]. HRMS (EI) Calcd. for C<sub>14</sub>H<sub>10</sub>N<sub>4</sub>O<sub>2</sub> [M]<sup>+</sup>, 266.1001, Found 266.1003; Anal. Calc. for C<sub>14</sub>H<sub>10</sub>N<sub>4</sub>O<sub>2</sub>: C, 63.17; H, 3.79; N, 21.05%. Found: C, 63.43; H, 3.84; N, 21.23%.

*N*-(2-methoxyphenyl)quinazolin-4-amine (**3i**): Mp: 208 °C, <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>, δ/ppm): 9.40 (s, 1H, NH), 8.48 (s, 1H, CH=N), 8.12 (t, 1H, CH), 7.82 (m, 4H), 7.57 (m, 4H); <sup>13</sup>C-NMR (400 MHz, DMSO-*d*<sub>6</sub>, δ/ppm): 169.8 (C-1), 156.1 (C-2), 149.9 (C-3), 147.2 (C-4), 137.9 (C-4), 132.7 (C-5), 132.1 (C-6), 128.8 (C-7), 127.6 (C-8), 126.6 (C-9), 122.6 (C-10), 121.7 (C-11), 116.3 (C-12). IR (KBr, cm<sup>-1</sup>): 3329, 1288; MS: m/z 251 [M<sup>+</sup>]. HRMS (EI) Calcd. for C<sub>15</sub>H<sub>13</sub>N<sub>3</sub>O [M]<sup>+</sup>, 266.1001, Found 266.1003; Anal. Calc. for C<sub>15</sub>H<sub>13</sub>N<sub>3</sub>O: C, 71.70; H, 5.21; N, 16.72%. Found: C, 71.65; H, 5.15; N, 16.79%.

## RESULTS AND DISCUSSION

Herein we wish to report a simple method for the synthesis of *N*-phenylquinazolin-4-amine derivatives from reaction of 2-aminobenzamide, orthoesters, and various substituted anilines using silica-supported Preyssler nanoparticles, H<sub>14</sub>[NaP<sub>5</sub>W<sub>30</sub>O<sub>110</sub>]/SiO<sub>2</sub> and three different Keggin types of HPAs including, H<sub>5</sub>[PMO<sub>10</sub>V<sub>2</sub>O<sub>40</sub>], H<sub>4</sub>[PMO<sub>11</sub>VO<sub>40</sub>] and H<sub>3</sub>[PMO<sub>12</sub>O<sub>40</sub>] as the catalysts (Scheme 1).



**Scheme 1.** Synthesis of *N*-phenylquinazolin-4-amine derivatives using Preyssler nanoparticles, H<sub>14</sub>[NaP<sub>5</sub>W<sub>30</sub>O<sub>110</sub>]/SiO<sub>2</sub>

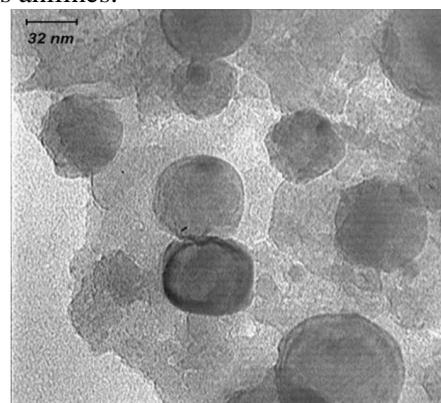
In connection with our program of using heteropolyacid in organic reactions [27], we wish to report the result of a study on the use of silica-supported Preyssler nanoparticles,  $H_{14}[NaP_5W_{30}O_{110}]/SiO_2$  and three Keggin types of HPAs including  $H_4[PMo_{11}VO_{40}]$ ,  $H_5[PMo_{10}V_2O_{40}]$  and  $H_3[PMo_{12}O_{40}]$  in the synthesis *N*-phenylquinazolin-4-amine derivatives and the effects of reaction parameters such as the type, amount of HPA and solvent on the yield of reaction. The results of synthesis of *N*-phenylquinazolin-4-amines from reaction of 2-aminobenzamide, orthoesters, and various anilines using  $H_{14}[NaP_5W_{30}O_{110}]/SiO_2$  nanoparticles are summarized in Table 1. In all the reactions, 3-quinazolin-4-one, 4, was obtained as a byproduct in low yield (Scheme 1). To investigate the effect of silica-supported Preyssler nanoparticles, we carried out comparative experiments with some silica-gel-supported heteropolyacids, and the comparative results are summarized in Table 2.

Comparison of silica-supported Preyssler nanoparticles,  $H_{14}[NaP_5W_{30}O_{110}]/SiO_2$ ,  $H_3[PMo_{12}O_{40}]$ ,  $H_5[PMo_{10}V_2O_{40}]$ ,  $H_4[PMo_{11}VO_{40}]$ ,  $H_6[PMo_9V_3O_{40}]$ ,  $H_3[PW_{12}O_{40}]$ ,  $H_{14}[NaP_5W_{30}O_{110}]/SiO_2$  (40%),  $H_3[PMo_{12}O_{40}]/SiO_2$  (40%),  $H_4[PMo_{11}VO_{40}]/SiO_2$  (40%), and  $H_3[PW_{12}O_{40}]/SiO_2$  (40%) shows that silica-supported Preyssler nanoparticles led to greater yields.

Silica nanostructures were obtained through a sol-gel method. All of the conditions are shown in the experimental section. The BET surface area, pore volume, and average pore size of nanosized  $SiO_2$  were obtained as  $287\text{ m}^2/\text{g}$ ,  $0.28\text{ cm}^3/\text{g}$ , and  $0.25\text{ nm}$ , respectively. After the impregnation of HPA (with 30% being the best loading), the BET surface area, pore volume, and average pore size were obtained as  $201\text{ m}^2/\text{g}$ ,  $0.10\text{ cm}^3/\text{g}$ , and  $0.21\text{ nm}$ , respectively. The BET surface area and pore volume decreased, indicating that the pores of nanosized silica are being filled and the supported HPA blocked some pores of the support. The obtained nano structures were characterized by TEM as shown in Fig. 1. This figure shows 40 nm spheres. The XRD pattern of nano- $SiO_2$  with sharp peaks in the  $2\theta$  range from  $7^\circ$  to  $36^\circ$  confirmed the crystalline nature of  $SiO_2$ . In addition, lack of an XRD peak centered at  $2\theta$  angle  $22^\circ$  (typical for amorphous  $SiO_2$ ) confirmed the crystallinity. The patterns of the spherical products confirm the  $SiO_2$  structure.

The synthesis of *N*-phenylquinazolin-4-amine derivatives show that reaction of 2-

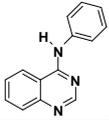
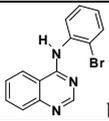
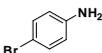
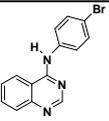
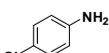
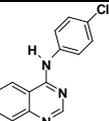
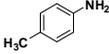
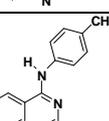
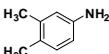
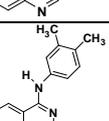
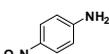
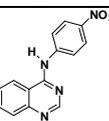
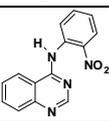
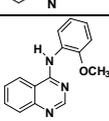
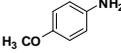
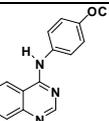
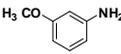
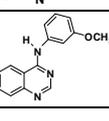
aminobenzamide, orthoesters, and various anilines using heteropolyacids under refluxing conditions leads to better yields and anilines with electron-donating groups gave slightly better yields than anilines with electron-withdrawing groups. The synthesis of *N*-phenylquinazolin-4-amine derivatives from the reaction of 2-aminobenzamide, orthoesters, and various anilines using silica-supported Preyssler nanoparticles,  $H_{14}[NaP_5W_{30}O_{110}]/SiO_2$  as catalyst was selected as a model reaction. The results are summarized in Tables 1 and 2. As shown in this table the sever condition is required for synthesis of *N*-phenylquinazolin-4-amine derivatives from the reaction of 2-aminobenzamide, orthoesters, and various anilines.



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

The efficiency of silica-supported Preyssler nanoparticles,  $H_{14}[NaP_5W_{30}O_{110}]/SiO_2$ ,  $H_3[PMo_{12}O_{40}]$ ,  $H_4[PMo_{11}VO_{40}]$ ,  $H_5[PMo_{10}V_2O_{40}]$ ,  $H_6[PMo_9V_3O_{40}]$ ,  $H_3[PW_{12}O_{40}]$ ,  $H_3[PMo_{12}O_{40}]/SiO_2$  (50%),  $H_4[PMo_{11}VO_{40}]/SiO_2$  (50%), and  $H_3[PW_{12}O_{40}]/SiO_2$  (50%) were also studied. Among silica-supported Preyssler nanoparticles,  $H_{14}[NaP_5W_{30}O_{110}]/SiO_2$  and the Keggin heteropolyacids,  $H_3[PMo_{12}O_{40}]$  and Keggin-type vanadium-substituted heteropolymolybdates: silica-supported Preyssler nanoparticles,  $H_{14}[NaP_5W_{30}O_{110}]/SiO_2$ ,  $H_4[PMo_{11}VO_{40}]$  and  $H_5[PMo_{10}V_2O_{40}]$ , the last one gave the best results in the reactions. The Keggin anions have an assembly of 12 corner-shared octahedral  $MoO_6$  from trimetallic groups  $[Mo_3O_{13}]$  around a heteroatom tetrahedron  $PO_4$ . The introduction of vanadium (V) into the Keggin framework of  $[PMo_{12}O_{40}]^{3-}$  is beneficial for catalysis reactions. Usually positional isomers are possible and coexist when two or more vanadium atoms are incorporated into the Keggin structure. Studies on these isomers in catalytic reactions indicate that

**Table 1.** Synthesis of various *N*-phenylquinazolin-4-amine derivatives in the presence of silica-supported Preyssler nanoparticles,  $H_{14}[NaP_5W_{30}O_{110}]/SiO_2$  and under reflux conditions in water (as green solvent) for 1.5 hours.

Entry	Aniline	Product (3)	<sup>a</sup> Yield (%)	Mp (°C)	
				Found	Reported(lit. 13)
1		 a	93.5	219-220	220-221
2		 b	85	130-131	131-132
3		 c	88.5	190-191	189-190
4		 d	90.5	193-194	194-195
5		 e	93	192-194	191-193
6		 f	96.5	196-197	196.5-198
7		 g	87.5	185-187	-
8		 h	85.5	181-183	-
9		 i	97.5	177-178	-
10		 j	98	174-175	165 [28]
11		 k	91.5	171-173	170-172 [22]

<sup>a</sup>Yields isolated.

different isomers cause different reactivities to show. With respect to the catalytic performances for these catalysts and the overall effects of all isomers, for synthesizing them, we cannot control the reaction conditions for the synthesis of positional vanadium-substituted isomers separately, revealing the relationship between the structures of

$H_{3+x}PMo_{12-x}V_xO_{40}$  ( $x = 1, 2, 3$ ) and hence study of their catalytic activity is difficult. The abundance of different isomers may also play an important role in catalytic performance. In addition, different positional Mo atom(s) substituted by the V atom(s) in  $[PMo_{12}O_{40}]^{3-}$  may create different vanadium chemical environments, thus causing these catalysts

to exhibit varying catalytic performances. The introduction of vanadium (V) into the Keggin framework is beneficial for redox catalysis, shifting its reactivity from acid-dominated to redox-dominated. In addition the amount of introduced vanadium (V) has a dramatic effect on the yields. One of the difficulties encountered in interpreting data obtained from reactions of vanado-molybdophosphate anions is that in solution, a mixture of heteropoly anions are usually present. In addition positional isomers of the polyvanadium anions are also apparent. Another complication inherent in the study of multielectron oxidations by polyvanadium-containing anions is the capacity of these oxidants to be reduced by one or more electrons (reduction of each V(V) ion to V(IV)). However it is difficult to clarify the different activities between these catalysts in this reaction. We believe there is a complex relationship between the activity and structure of polyanion. Transition metal cations have an important effect on the catalytic properties of these compounds when they substitute molybdenum cations in the Keggin units.

**Table 2.** Comparative study of various heteropolyacids catalysts for the preparation of *N*-phenylquinazolin-4-amine (**3a**) under reflux conditions.

Entry	Catalyst	Time (h)	<sup>a</sup> Yield (%)
1	H <sub>14</sub> [NaP <sub>5</sub> W <sub>30</sub> O <sub>110</sub> ]/SiO <sub>2</sub> Nanoparticles	1.5	93.5
2	H <sub>14</sub> [NaP <sub>5</sub> W <sub>30</sub> O <sub>110</sub> ]/SiO <sub>2</sub> (40%)	1.5	90.5
3	H <sub>3</sub> [PMo <sub>12</sub> O <sub>40</sub> ]	3	81
4	H <sub>4</sub> [PMo <sub>11</sub> VO <sub>40</sub> ]	3	84
5	H <sub>5</sub> [PMo <sub>10</sub> V <sub>2</sub> O <sub>40</sub> ]	3	85.5
6	H <sub>6</sub> [PMo <sub>9</sub> V <sub>3</sub> O <sub>40</sub> ]	2	89
7	H <sub>3</sub> [PW <sub>12</sub> O <sub>40</sub> ]	3	82.5
8	H <sub>3</sub> [PMo <sub>12</sub> O <sub>40</sub> ]/SiO <sub>2</sub> (40%)	3	80
9	H <sub>4</sub> [PMo <sub>11</sub> VO <sub>40</sub> ]/SiO <sub>2</sub> (40%),	3	82.5
10	H <sub>3</sub> [PW <sub>12</sub> O <sub>40</sub> ]/SiO <sub>2</sub> (40%)	3	81

<sup>a</sup>Yields isolated.

The case of vanadium, which can occupy both anionic and cationic positions, is more complex. It is suggested that the interactions of the polarized polyanion with substrate and the number of vanadium atoms are important factors in catalytic activity in our reaction.

#### Selection of the solvent type

Due to the increase in environmental consciousness in chemical research and industry, the challenge for a sustainable environment calls for clean procedures that avoid the use of harmful organic solvents. One of the most important principles of the green chemistry is the elimination of hazardous solvents in chemical synthesis and avoids using toxic solvent and the generation of waste.

The use of water, the most abundant chemical on earth, as a solvent has been neglected for many

**Table 3.** Effect of varying the solvent on the yield of *N*-phenylquinazolin-4-amine (**3a**)

Entry	Solvent	Product (3)	Time (h)	<sup>a</sup> Yield (%)
1	Water		1.5	93.5
2	C <sub>2</sub> H <sub>5</sub> OH		2	90.5
3	CH <sub>3</sub> CN		2	87.5
4	CH <sub>3</sub> OH		2.5	88.5
5	CHCl <sub>3</sub>		2.5	88
6	THF		2.5	84
7	DMF		2.5	73.5

<sup>a</sup>Yields isolated. <sup>b</sup>Yields were analyzed by GC. In the presence of silica-supported Preyssler nanoparticles, H<sub>14</sub>[NaP<sub>5</sub>W<sub>30</sub>O<sub>110</sub>]/SiO<sub>2</sub> and water as green solvent.

years by organic chemists since water has been traditionally considered to have destructive effects on many reagents and synthetic reactions, unless water is used as a reagent or in workup procedures. To investigate the effect of solvent in these reactions, the reactions were done in different solvents. The results are reported in Tables 2 and 3.

The results show that the efficiency of solvents vary as water>ethanol>methanol>chloroform>acetonitril>THF >>DMF.

#### Reusability of Catalyst

At the end of the reaction, the catalyst could be recovered by a simple filtration. The recycled catalyst could be washed with dichloromethane and subjected to a second run of the reaction process. In Table 4 the comparison of efficiency of silica-supported Preyssler nanoparticles, H<sub>14</sub>[NaP<sub>5</sub>W<sub>30</sub>O<sub>110</sub>]/SiO<sub>2</sub> in the synthesis of *N*-phenylquinazolin-4-amine derivatives from reaction

of 2-aminobenzamide, orthoester, and substituted aniline after five times is reported. The results indicated that the catalysts were not soluble in the solvent, and the yields of reactions using silica-supported Preyssler nanoparticles,  $H_{14}[NaP_5W_{30}O_{110}]/SiO_2$  catalyst over three runs indicated only a slight loss of activity (Table 4).

**Table 4.** Reuse of the catalyst for synthesis of N-phenylquinazolin-4-amine (**3a**) using silica-supported Preyssler nanoparticles heteropolyacid catalyst,  $H_{14}[NaP_5W_{30}O_{110}]/SiO_2$  at reflux conditions in 1.5 h and water as green solvent

Run	<sup>a</sup> Yield (%)
1	93
2	92
3	92
4	90.5
5	90

<sup>a</sup> Yields refer to isolated product.

## CONCLUSION

In conclusion, we have presented use of Silica-supported Preyssler nanoparticles as a catalyst for efficient synthesis of N-phenylquinazolin-4-amine derivatives and the yields are excellent. For all the presented reactions, the water solvent was used which is relatively environmentally benign and supporting to Green Chemistry. The advantages of the reported method are the use of cheap, mild, and easily available catalyst, easy work-up, and better yields. The catalyst can be reused after a simple work-up, a gradual decline of its activity being observed. High yields, shorter reaction times, simplicity of operation and easy work-up are some of the advantages of this protocol.

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**УСКОРЕНА МНОГО-КОМПОНЕНТНА СИНТЕЗА НА N-ФЕНИЛХИНАЗОЛИН-4-АМИНИ ИЗПОЛЗВАЙКИ PREYSSLER'ОВИ НАНОЧАСТИЦИ ВЪРХУ НОСИТЕЛ ОТ СИЛИЦИЕВ ДИОКСИД И ХЕТЕРОПОЛИКИСЕЛИНИ В "ЗЕЛЕН" РАЗТВОРИТЕЛ**

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(Резюме)

Получени са производни на N-фенилхиназолин-4-амините с високи добиви и отлична чистота чрез реакции на 2-аминобензамид, орто-естери и субституирани анилини в присъствие на Preyssler'ови наночастици върху носител от силициев диоксид и различни хетерополикиселини (HPAs).