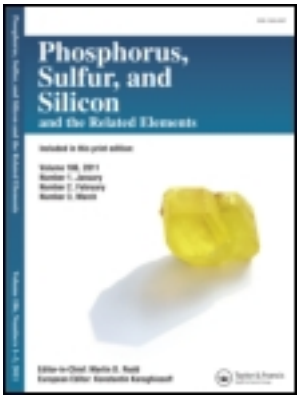

Phosphorus, Sulfur, and Silicon and the Related Elements

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Tungstophosphoric Acid Supported on Zirconia: A Recyclable Catalyst for the Green Synthesis on Quinoxaline Derivatives under Solvent-Free Conditions

Alexis A. Sosa [a] , Toa S. Rivera [a] , Mirta N. Blanco [a] , Luis R. Pizzio [a] & Gustavo P. Romanelli [a]

[a] Centro de Investigación y Desarrollo en Ciencias Aplicadas "Dr. Jorge J.J. Ronco" (CINDECA), Departamento de Química, Facultad de Ciencias Exactas, UNLP-CCT La Plata CONICET , 1900 , La Plata , Argentina

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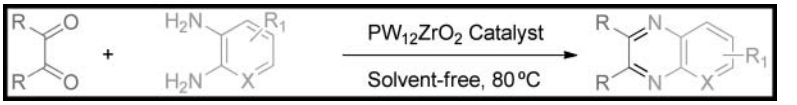
TUNGSTOPHOSPHORIC ACID SUPPORTED ON ZIRCONIA: A RECYCLABLE CATALYST FOR THE GREEN SYNTHESIS ON QUINOXALINE DERIVATIVES UNDER SOLVENT-FREE CONDITIONS

Alexis A. Sosa, Toa S. Rivera, Mirta N. Blanco, Luis R. Pizzio, and Gustavo P. Romanelli

Centro de Investigación y Desarrollo en Ciencias Aplicadas "Dr. Jorge J.J. Ronco" (CINDECA), Departamento de Química, Facultad de Ciencias Exactas, UNLP-CCT La Plata CONICET, 1900 La Plata, Argentina

GRAPHICAL ABSTRACT



Abstract *A green, simple, and fast procedure has been developed for the preparation of quinoxaline derivatives by a condensation of 1,2-diamines with 1,2-dicarbonyl compounds in the presence of zirconium oxide modified with tungstophosphoric acid ($H_3PW_{12}O_{40}$) as a heterogeneous catalyst, in a solvent-free medium using conventional heating. Quinoxaline derivatives were formed in short-time periods and excellent yields (65–100%). The reaction work-up is very simple and the catalyst can be easily separated from the reaction mixture and reused several times in subsequent reactions without appreciable loss of the catalytic activity.*

Supplementary materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfer, and Silicon and the Related Elements *for the following free supplemental files:* Additional text.

Keywords Quinoxalines; tungstophosphoric acid; mesoporous zirconia; ecofriendly process; solvent-free condition

INTRODUCTION

The need for greener techniques in the synthesis of different chemical compounds leads to the use of different environmentally friendly reaction conditions; among them, the replacement of pollutant inorganic acid catalysts, such as sulfuric or hydrochloric acids, by reusable solid acids is yet very necessary.[1] The application of solid acids in organic

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Address correspondence to Centro de Investigación y Desarrollo en Ciencias Aplicadas "Dr. Jorge J. J. Ronco" (CINDECA), Departamento de Química, Facultad de Ciencias Exactas, UNLP-CCT La Plata CONICET-CCT, 47 N° 257, 1900 La Plata, Argentina. E-mail: gpr@quimica.unlp.edu.ar

transformations has an important role, because these materials have many advantages, such as the ease of handling, decreased plant corrosion, and more environmentally safe waste-disposal procedures.[1]

In particular, catalysis by heteropolyacids (HPA) and related compounds is a field of increasing significance worldwide. Many developments have been carried out both in basic research and in fine chemistry processes.[2] The HPA are well-defined molecular arrangements with remarkable and useful applications. Their main technological property is their reusability in heterogeneous catalysis. Diverse electronic and molecular structures of HPA lead to their application in different areas, such as medicine and materials science, among others. Within the wide field of structural possibilities that the HPA have shown,[3] those that present the Keggin-type primary structure deserve to be mentioned. The HPA with Keggin structure are polynuclear complexes mainly constituted by molybdenum, tungsten, or vanadium as polyatoms (M), and phosphorus, silicon, or germanium as central atom or heteroatom (X). The Keggin structure is formed by a central XO_4 tetrahedron, surrounded by 12 MO_6 octahedra. They could be either multielectron oxidants or strong acids, with an acid strength higher than that of the classical acids. Recently, our research group reported green catalytic acid and oxidation procedures using Keggin HPA.[4–8]

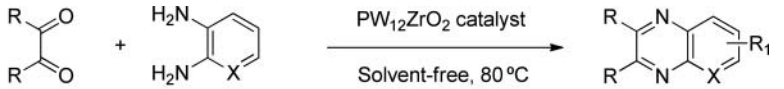
Zirconia is an interesting material to be used as catalyst support due to its thermal stability in different atmospheres. Its acid properties can be modified by addition of cationic or anionic substances, such as sulfate or tungstate.[9] The addition of Keggin heteropolyacids to modify them has been studied to a lesser extent.[10] We recently reported a procedure for the 14-aryl-14*H*-dibenzo[a,j]xanthenes using recyclable mesoporous zirconia modified with tungstophosphoric acid.[11]

On the other hand, quinoxaline derivatives are a very important class of nitrogen-containing heterocycles as they constitute useful intermediates in organic synthesis.[12] This structure plays an important role in the design of a number of heterocyclic compounds with different biological activities, making this type of compounds important in the field of medicine as antitumor, anticonvulsant, antimalarial, anti-inflammatory, antiamoebic, antioxidant, antidepressant, antiprotozoal, antibacterial, and anti-HIV agents.[12–15] Quinoxalines are important in the pharmaceutical industry, with antibiotics such as echinomycin, levomycin, and actinoleutin having quinoxaline as part of their structure.[16]

The most used method for the preparation of quinoxaline is the condensation of a 1,2-dicarbonylic compound with a 1,2-diamino compound. In general, this procedure needs high temperature, the use of a strong acid catalyst, and long reaction times.[17]

A variety of catalysts were tested in these reactions such as acetic acid,[18] iodine,[19] $CuSO_4 \cdot 5H_2O$,[20] nickel nanoparticles,[21] montmorillonite K10,[22] ionic liquids,[23] nano TiO_2,[24] Al_2O_3,[25] zirconium(IV)-modified silica gel,[26] cerium(IV) ammonium nitrate,[27] iron-exchanged molybdophosphoric acid,[28] silica-bonded S-sulfonic acid,[1] among others. However, some of these methods suffer from unsatisfactory yields, problem of recyclability of the traditional acid catalysis, harsh reaction conditions, which limit their use in friendly processes.

As part of our research project directed toward the development of highly suitable methods and the synthesis of diverse heterocyclic compounds, we herein disclose a new, one-pot synthesis of quinoxaline derivatives from 1,2-diaminobenzenes and 1,2-dicarbonyl compounds catalyzed by mesoporous zirconia modified with tungstophosphoric acid under solvent-free conditions with the aim to obtain high yields with an environmentally advantageous procedure (Scheme 1).



R = Ph, 4-CH_3Ph, CH_3CH_2
X = CH, N
R_1 = H, 2-CH_3, 3-Cl, 3-Br, 3-NO_2

Scheme 1

RESULTS AND DISCUSSION

Catalyst Characterization

As a result of the addition of PW_{12} to the zirconia matrix, the FT-IR spectra of the $PW_{12}ZrO_2$ sample displayed a new set of bands overlapped to the zirconia wide band. The presence of the P–O_a, W–O_d, and W–O_b–W stretching vibrations of the $[PW_{12}O_{40}]^{3-}$ anion can be clearly observed. In addition, bands assigned to the $[PW_{11}O_{39}]^{7-}$ anion are also observed in the catalyst if a comparison with the spectrum of the sodium salt of the lacunary anion is made, which presents bands at 1100, 1046, 958, 904, 812, and 742 cm^{-1}, in agreement with the literature.[29]

The ^{31}P MAS-NMR spectra of $PW_{12}ZrO_2$ displayed a wide band with maximum at around −14 ppm, accompanied by a shoulder at −12 ppm. They may be attributed to the $[PW_{12}O_{40}]^{3-}$ anion and to the $[P_2W_{21}O_{71}]^{6-}$ dimeric species, respectively.[30] The downfield shift and the increase of the line width observed, compared to tungstophosphoric acid (−15.3 ppm), can be attributed to the interaction between the anion and the zirconia matrix.[31]

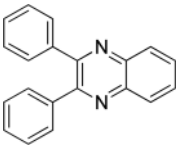
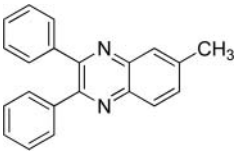
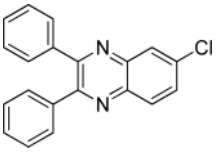
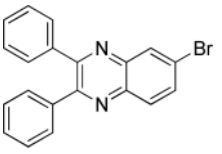
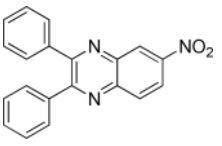
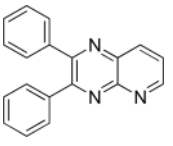
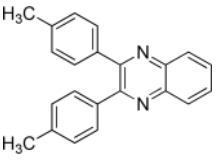
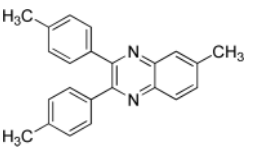
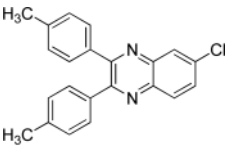
The acidity measurements of the catalyst by means of potentiometric titration with *n*-butylamine let us to estimate the number of acid sites and their acid strength. It was suggested that the initial electrode potential (Ei) indicates the maximum acid strength of the sites, and the value of meq amine/g solid where the plateau is reached indicates the total number of acid sites. The acid strength of these sites may be classified according to the following scale: Ei > 100 mV (very strong sites), 0 < Ei < 100 mV (strong sites), −100 < Ei < 0 (weak sites), and Ei < −100 mV (very weak sites).[32,33] The acid strength of the modified sample $PW_{12}ZrO_2$ (Ei = 397 mV) was markedly higher than that of the unmodified zirconia (Ei = 140 mV), but lower than that of bulk PW_{12} (Ei = 620 mV).[34] The lower acid strength of the $PW_{12}ZrO_2$ sample compared to bulk PW_{12} could be assigned to the fact that the protons in the $H_3PW_{12}O_{40}\cdot 6H_2O$ are present as $H^+(H_2O)_2$ species, whereas in the $PW_{12}ZrO_2$ sample they are interacting with the oxygen of Zr–OH groups or in a higher hydration state ($H^+(H_2O)_n$), as previously reported.[35]

Synthesis of Quinoxaline Derivative

As a continuation of our interest in the application of HPA catalysts for the development of a useful synthetic methodology, a simple and efficient approach for the preparation of quinoxaline derivatives is here reported, using mesoporous zirconia modified with tungstophosphoric acid as an eco-friendly catalyst with high catalytic activity under solvent-free conditions at 80 °C.

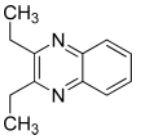
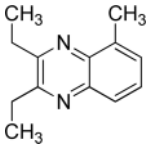
The reaction between 1,2-diaminobenzene and benzyl (PhCOCOPh) was first studied (Table 1, entry 1) to screen the reaction conditions, in order to determine the best conditions.

Table 1 Synthesis of quinoxaline derivatives catalyzed by $PW_{12}ZrO_2$[a]

Entry	Product	Time (min)	Yields[b] (%)	Product (ref.)
1		5	100 (100, 99, 99)[c]	[1,34,36]
2		5	99	[1,34,36]
3		10	91	[1,34]
4		20	92	[34]
5		300	65	[1,34,36]
6		120	95	[34]
7		3	93	[19,36]
8		10	94	[19,36]
9		3	78	[19]

(Continued on next page)

Table 1 Synthesis of quinoxaline derivatives catalyzed by $PW_{12}ZrO_2$[a] (*Continued*)

Entry	Product	Time (min)	Yields[b] (%)	Product (ref.)
10		5	88	[36]
11		5	95	[36]

[a]All reactions were performed at 1 mmol scale using 1 mmol % of $PW_{12}ZrO_2$ in solvent-free conditions at 80 °C.

[b]Column-isolated yields.

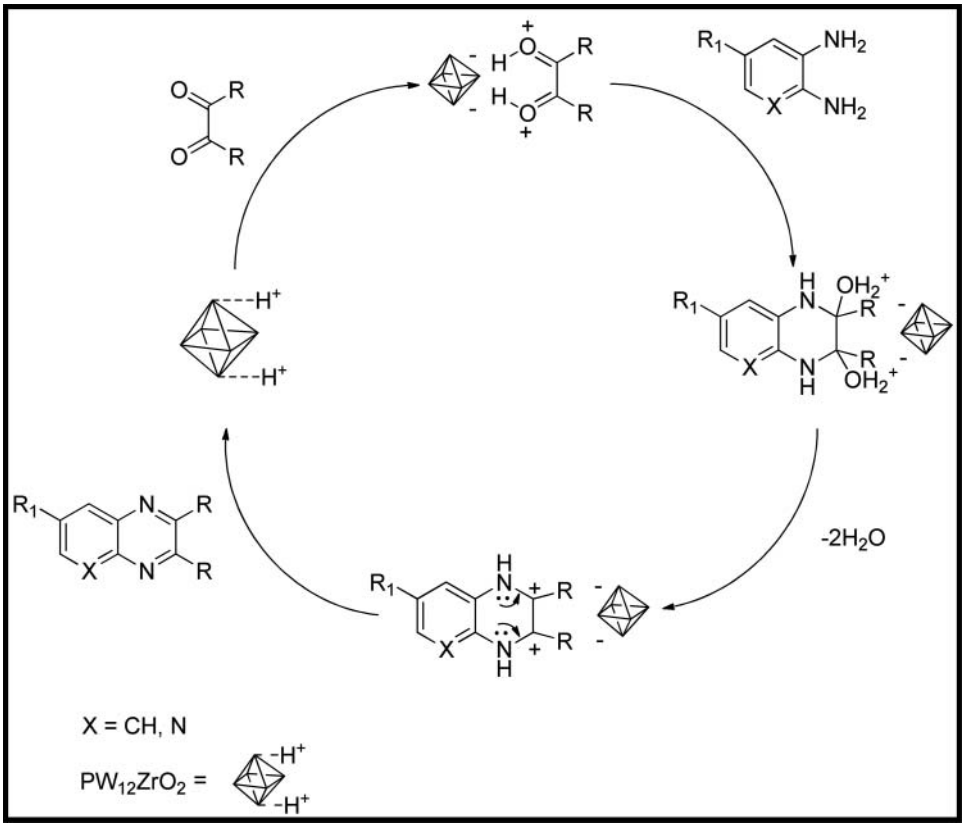
[c]First, second, and third reuse.

The influence of the reaction temperature, the reaction time, the molar ratio of substrates, and the amount of catalyst were all examined. For a typical experiment, 1,2-diaminobenzene, benzyl, and the catalyst were mixed at 80 °C. The condensation was completed in the formation of quinoxaline ring after 5 min (Table 1, entry 1, 100%).

The excellent preliminary result encouraged us to extend the generality of the novel catalytic system to various 1,2-diamines and 1,2-dicarbonyls. Most of the reaction took 5 min to be completed at 80 °C. The experiments were run until benzyls were consumed or until no changes in the composition of the reaction mixture were observed. In all the cases, the desired products were obtained with high selectivity, almost free of secondary products.

The result presented in Table 1 shows that electron-donating groups at the phenyl ring of the 1,2-diamine favored the formation of the product (Table 1, entry 2) to give quantitative yields. In contrast, electron-withdrawing groups such as chloro and bromo gave slightly lower yields (91–92%) in a longer time, 10 and 20 min, respectively (Table 1, entries 3 and 4). The presence of a nitro group, a strong electron-withdrawing group, reduced the yield to 65% (Table 1, entry 5), and the reaction was not complete. However, the unchanged starting materials were recovered nearly quantitatively (Table 1, entry 6). In Table 1, entry 6 and, it can be observed that, when a 2,3-diamine pyridine was used as substrate, a pyrazine was obtained as reaction product in excellent yields (95%). On the other hand, the substituents at the 1,2-diketone had no significant effects on the yield to the corresponding products. Since only symmetric 1,2-diketones were used for the condensation reaction, no regioisomers were generated as the products (Table 1, entries 7–11).

The possibility of recycling the catalyst ($PW_{12}ZrO_2$) was examined. For this reason, the reaction of 1,2-diaminobenzene and benzyl was studied in solvent-free conditions at 80 °C in the presence of $PW_{12}ZrO_2$. When the reaction was complete, the reaction mixture was cooled to room temperature (20 °C), toluene (5 mL) was added, and then the mixture was stirred for 15 min, filtered to separate the catalyst, and the catalyst was dried in a vacuum oven at room temperature for 4 h prior to reuse. No appreciable loss of catalytic activity was observed after four cycles (Table 1, entry 1).



Scheme 2

Niknam and coworkers[1] proposed that the reaction follows a mechanism of acid-catalyzed condensation reactions. In our case, $PW_{12}ZrO_2$ catalyst acts as a Brønsted acid and the mechanism can be rationalized in four stages: (1) the coordination of the diketone to the acid sites of $PW_{12}ZrO_2$, (2) the nucleophilic attack on the carbonyl intermediate, (3) the dehydration to give a carbocation intermediate, and (4) the elimination of a proton to give the quinoxaline product (Scheme 2).[1]

CONCLUSIONS

In conclusion, tungstophosphoric acid supported on zirconia ($PW_{12}ZrO_2$), which can simply be prepared from commercially available and relatively cheap starting materials, is an efficient, thermally stable, and easily recoverable catalyst for the synthesis of quinoxaline derivatives. The present procedure provides a simple, efficient, selective, and recyclable methodology for the preparation of quinoxaline derivatives in high yields with an easy work-up procedure. The catalyst can be recovered and reused over several reaction cycles without considerable loss of reactivity. Moreover, this methodology introduces a practical and viable green technology for quinoxaline preparation. We are currently exploring further applications of this solid to other types of heterocycles.

EXPERIMENTAL

General

All chemical reagents and solvents were obtained from Merck and Aldrich and were used without further purification. All products are known compounds and were identified by comparison of their physical and spectral data with those of the authentic samples. The purity of the substances and the progress of the reaction were monitored by thin layer chromatography (TLC) on silica gel, and yields refer to isolated products. Flash column chromatography was performed with 230–400 mesh silica gel. Melting points of the compounds were determined in sealed capillary tubes on a Bioamerican Bs 448 apparatus and were uncorrected. The ^{13}CNMR and ^{1}H NMR spectra were recorded at room temperature on Varian-200 spectrometer using TMS as internal standard.

Synthesis of Supported Catalysts

Zirconium propoxide (26.6 g) was mixed with absolute ethanol (336.1 g) and stirred for 10 min to obtain a homogeneous solution under N_2 at room temperature. Then, 0.5 mL of HCl 0.28 M aqueous solution was dropped slowly into the above mixture to catalyze the sol–gel reaction. After 3 h, an appropriate amount of polyethylene glycol (PEG)–alcohol–water solution (1:5:1 weight ratio) was added to the hydrolyzed solution under vigorous stirring to act as pore-forming agent. The amount of added solution was fixed in order to obtain a PEG concentration of 10% by weight in the final material. A tungstophosphoric acid ($H_3PW_{12}O_{40}\cdot 6H_2O$) ($PW_{12}$) solution, of adequate concentration in order to obtain a PW_{12} concentration of 60% w/w in the solid, was added together with the template addition ($PW_{12}ZrO_2$ sample). The gel was then kept in a beaker at room temperature to dryness. The solid was ground into powder and extracted with distilled water for three periods of 8 h, in a system with continuous stirring, to remove PEG. Afterwards, the solid was thermally treated at 100 °C for 24 h.

Catalyst Characterization

In a previous paper, we reported the full characterization of the catalysts by X-ray diffraction (XRD), Fourier transformed infrared spectroscopy (FT-IR), the ^{31}P magic angle spinning-nuclear magnetic resonance (^{31}P MAS-NMR), and the acidity of the solids was estimated by means of potentiometric titration. We present here only the result necessary to confirm the catalyst structure.[37]

General Procedure for the Synthesis of Quinoxalines Using $PW_{12}ZrO_2$ Catalyst

A mixture of the corresponding benzil (1.2 mmol), diamine, and $PW_{12}ZrO_2$ (1 mmol %, ca 30 mg) was stirred at 80 °C for the appropriate time according to Table 1. Completion of the reaction was indicated by TLC. The reaction mixture was cooled to 25 °C, toluene (5 mL) was added, and then the mixture was stirred for 15 min and filtered to separate the catalyst, which was subsequently washed twice with toluene (3 mL). The combined toluene extracts were washed twice with water (5 mL), dried over anhydrous Na_2SO_4, and

evaporated in vacuo. The solid obtained was recrystallized from ethyl alcohol to afford the pure quinoxaline derivative.

Recycling of the Catalyst

After the reaction, the catalyst was filtered, washed thoroughly with toluene, dried in a vacuum oven (80 °C, 4 h), and reused for the next reaction, following the procedure described above.

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