Recent Applications of Heteropolyacids and Related Compounds in Heterocycles Synthesis

Gustavo P. Romanelli[1,2 *] and Juan C. Autino[2]

[1]*Centro de Investigación y Desarrollo en Ciencias Aplicadas "Dr. Jorge J. Ronco" (CINDECA) Facultad de Ciencias Exactas, Universidad Nacional de La Plata. CCT- CONICET. Calle 47 Nº 257 (B1900AJK) La Plata, Argentina.*

[2] *Cátedra de Química Orgánica, Facultad de Ciencias Agrarias y Forestales, UNLP. Calles 60 y 119, B1904AAN La Plata, Argentina*

Abstract: Heteropolyacids (HPAs) and related compounds have received considerable attention as solid acids in recent years. HPAs possess unique physicochemical properties, with their structural mobility and multifunctionality being the most important for catalysis. They possess a very strong Bronsted acidity and appropriate redox properties that make them excellent catalysts in substoichiometric quantities. This review will focus on describing new developments in the application of HPAs in the organic synthesis of heterocycles. Heterocycles that will be covered include coumarins, flavones, chromones, quinazolidones, dihydropyrimidinones, imidazoles, isoxazoles, pyrimidines, tetrazines, pyrazoles, dihydropyridines, and others.

Keywords: Heteropolyacids, Catalysis, Heterocycles, Green Chemistry.

It is well known that the use of conventional liquid and Lewis acids such as H_2SO_4, HCl, HF, $AlCl_3$, BF_3 and $ZnCl_2$ poses risks in handling, containment, disposal and regeneration due to their corrosive and toxic nature. There is an urgent need to eliminate the aggressive mineral acid-catalyzed processes [1].

There are numerous acid-catalyzed organic reactions and the use of solid acid catalysts is very important in several industrial and environmental processes [2]. The use of solid (heterogeneous) catalysts in organic synthesis and in the industrial manufacture of chemicals is increasingly important since they provide green alternatives to homogeneous catalysts [3].

In recent times, inorganic solid-catalyzed organic transformations are gaining much importance due to the proven advantage of heterogeneous catalysts, such as simplified product isolation, mild reaction conditions, high selectivities, easy recovery and catalyst reuse, and reduction in generation of waste byproducts [1,4,5,6]. Heterogeneous catalysts are used extensively in protection/deprotection process in organic synthesis [7].

Catalysis by heteropolyacids (HPAs) and related compounds is a field of increasing importance worldwide. Numerous developments are being carried out in basic research as well as in fine chemistry processes [8]. HPAs possess, on the one hand, a very strong acidity and, on the other hand, appropriate redox properties, which can be changed by varying the chemical composition of heteropolyanion. The reactions catalyzed by both heterogeneous and homogeneous systems have been reviewed by many researchers [9-17]. The reactions in which they can be used, from dehydration, cyclization or esterification up to amine oxidation or olefin epoxidation, may find wide applications in fine chemical production, such as fragrances, pharmaceutical and food [18,19].

Although there are many structural types of HPAs, the majority of the catalytic applications use the most common Keggin-type HPAs [20], especially for acid catalysts, owing to their availability and chemical stability. Other catalysts such as Wells-Dawson and Preyssler heteropolyacids have began to be used. [21,22].

Heteropolycompounds are known as condensates of different oxoacids. The heteropolycompounds with Keggin-type primary structure are polynuclear complexes principally 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 tetrahedral XO_4 surrounded by 12 octahedral MO_6[21]. The general formula of the Wells–Dawson heteropolyanion is $[(Xn^+)_2M_{18}O_{62}]^{(16-2n)-}$, where X^{n+} represents a central atom, such as phosphorous(V), arsenic(V), sulfur(VI), and fluorine: surrounded by a cage of M addenda atoms, such as tungsten(VI), molybdenum(VI) or a mixture of elements, each of them composing MO_6 (M-oxygen) octahedral units. The structure, known as α isomer, possesses two identical "half units" of the central atom surrounded by nine octahedral units XM_9O_{31} linked through oxygen atoms [22]. The Preyssler polyanion consists of a cyclic assembly of five PW_6O_{22} units, each derived from Keggin anion, $[PW_{12}O_{40}]^{3-}$, by removal of two sets of three corner shared WO_6 octahedra [23].

On the other hand, heterocyclic compounds are important compounds in organic chemistry. Most of the members have wide applications in medicinal chemistry and in the fine chemistry industry.

Due to their wide range of biological activity in synthetic and industrial applications, the synthesis of these compounds has recently received a great deal of attention for the discovery of improved protocols towards clean, milder and high yielding approaches.

This review highlights recent developments and opportunities in the application of heteropolyacids and related compounds to catalytic heterocycle synthesis.

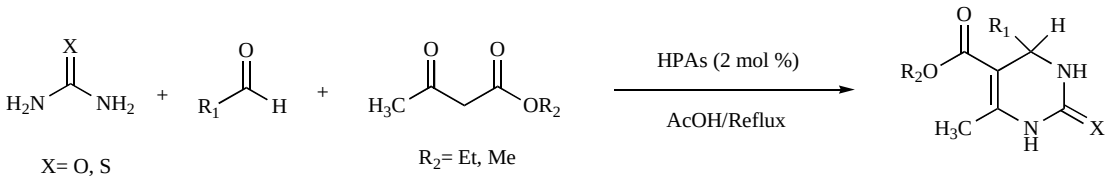
3,4-Dihydropyrimidine-2(1H)-ones are interesting compounds and play an important role in synthetic, therapeutic and bioorganic chemistry, for example calcium channel blockers, antihypertensive agents, α-1a-antagonists, antiviral, antitumor and anti-inflammatory drugs [24]. Synthetic strategies for dihydropyrimidinone derivatives would involve one-pot which multistep approaches. The first one-pot synthesis of 3,4-dihydropyrimidine-2(1H) was reported by Biginelli in 1893, often involves low yields (20-60%), harsh reaction conditions and long reaction times [25-26]. Biginelli reaction consists in the condensation of an aldehyde, a β-ketoester and urea in the presence of an acid catalyst. Due to the importance of Biginelli reaction products, the discovery and introduction of better and milder conditions using a new catalyst have received great attention.

Heravi has demonstrated that 12-molybdophosporic acid, a Keggin heteropolyacid, in refluxing acetic acid is an efficient catalyst for s three component condensation reaction (urea, ethylacetoacetate and aldehydes) to afford the corresponding pyrimidinones in good yields (50-80%, 14 examples) [26].

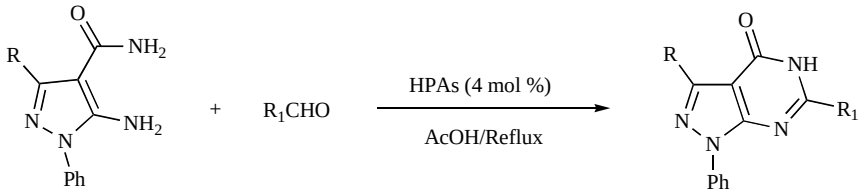
The best reaction conditions to prepare the dihydropyrimidinones were achieved when 2 mol % of $H_3PMo_{12}O_{40}$, 1.5 equivalent

*Address correspondence to this author at the Centro de Investigación y Desarrollo en Ciencias Aplicadas "Dr. Jorge J. Ronco" (CINDECA) Facultad de Ciencias Exactas, Universidad Nacional de La Plata. CCT- CONICET. Calle 47 Nº 257 (B1900AJK) La Plata, Argentina; E-mail: gpr@quimica.unp.edu.ar

1570-193X/09 $55.00+.00



Scheme 1.



Scheme 2.

of aldehydes was heated under reflux for 4-7 h, affording the desired product in good yields (Scheme **1**).

Similarly, Amini has described that $H_3PW_{12}O_{40}$ is an efficient catalyst for the one-pot synthesis of dihydropyrimidine-2(1H)-ones. The HPA bulk or supported on silica gel catalyzed the three component condensation reaction of aldehyde, 1-3 dicarbonyl compound, and urea or thiourea to afford the corresponding 3,4-dihydropyrimidine-2(1H)-ones in high yields under solvent free conditions (87-93%, 25 examples). The catalyst is also efficient for the cyclic β-diketones, β-diester and β-diamide derivatives such as dimedone, Meldrum´s acid and barbituric acid derivatives [24].

Raffiee *et al.* have described a simple procedure for the synthesis of dihydropyrimidinones using Keggin heteropolyacids. The HPAs used were: $H_3PW_{12}O_{40}$ $H_3PMo_{12}O_{40}$ and $H_4SiW_{12}O_{40}$. The HPAs in bulk form catalyzed the three component condensation reaction between aldehyde, 1,3-dicarbonyl compounds and urea in acetonitrile at 80°C in 1 h. to afford the corresponding 3,4-dihydropyrimidine-2(1H)-ones in good yields (47-97%, 35 examples). Aliphatic aldehydes such as propanal and pentanal also reacted well (48-67%). Such aldehydes normally show extremely poor yields in the Biginelli reaction.

It is interesting to note that in the case of acid-sensitive aldehydes, such as furfural and cinnamaldehyde, DHPMs were achieved in excellent yields without the formation of any side products [28].

Fazaeli *et al.* have described a similar procedure using $H_3PW_{12}O_{40}$ and $H_3PMo_{12}O_{40}$ in bulk and deposited on different supports. Supported heteropolyacid catalyst have much greater surface areas. The reaction of aldehyde, ethyl acetoacetate and urea in the presence of catalytic amounts of HPAs in bulk and supported on KSF-montmorillonite, Al_2O_3, SiO_2, TiO_2, and carbon in refluxing acetonitrile resulted in the formation of dihidropirimidone. (80-98%, 17 examples) [29].

Recently, our group found a procedure for the Biginelli reaction in acetonitrile and under solvent free conditions, using 1% milimol of a Wells-Dawson heteropolyacid ($H_6P_2W_{18}O_{62}.24H_2O$). Both aromatic and aliphatic aldehydes, different β-dicarbonyl compounds and urea or thiourea were used as starting materials. Seventeen examples of dihydropyrimidinones and dihydropyrimidinethiones were prepared by heating the reactants either by refluxing acetonitrile 8h. or in the ausence of solvent 1h. Operational simplicity, the reusable catalyst, and the very good yields (83-97%, 17 examples) are the main advantages of the method [30].

The Perumal groups have described a variant of the Biginelli reaction to obtain novel 4-pyrazolyl-2-oxo-1,2,3,4-tetrahydropyrimidines promoted by phosphotungstic acid ($H_3PW_{12}O_{40}$). The reaction was carried out using pyrazole aldehyde, ethyl acetoacetate and urea to obtain with excellent yields the corresponding pyrazolyl derivatives [31].

Pyrazolo[3,4-d] pyrimidines have attracted considerable attention because of their pharmacological importance, anti-tumor and anti-leukemia activities [32]. Heravi has presented the synthesis of some derivatives of 1H-pyrazolo[3,4-d] pyrimidine-4(5H)-ones, using Keggin-type $H_3PMo_{12}O_{40}$ and Preyssler-type $H_{14}[NaP_5W_{30}O_{110}]$ $H_{14}[NaP_5W_{29}MoO_{110}]$ heteropolyacids as solid acid catalyst. When the mixture of 5-amino-1-phenyl-1-H-pyrazolo-4-carboxamide 1 and aromatic aldehyde 2 in acetic acid was refluxed in the presence of catalytic amounts of the adobe mentioned heteropolyacids for 1 h, 6-aryl-1H-pyrazolo[3,4-d] pyrimidine-4(5H)ones 3 were obtained in good yields (70-86%, 14 examples) (Scheme **2**). Comparison of yields of the reaction for three catalysts show little better yields when the Preyssler heteropolyacid $H_{14}[NaP_5W_{29}MoO_{110}]$ were doped with molybdenum [32,33].

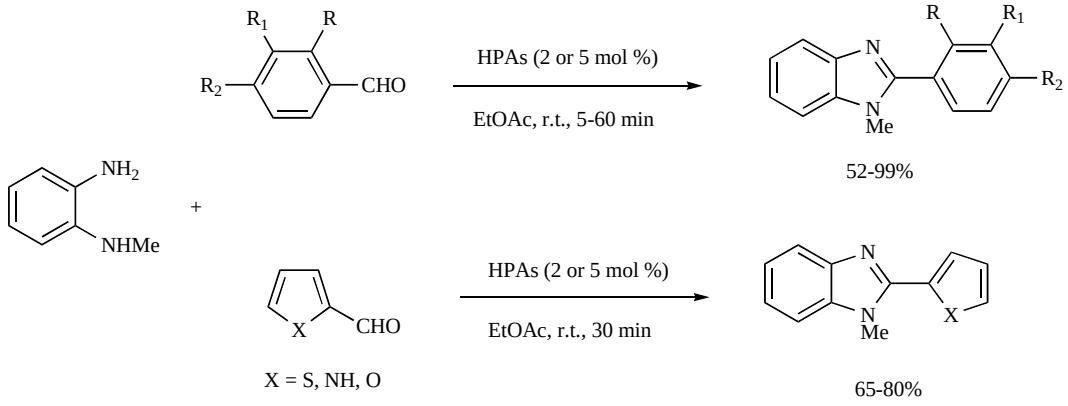
Benzimidazoles are pharmaceuticals, that are used as anthelmintics in veterinary medicine and display significant anticancer, antiviral, antiallergic, antiulcer and anticoagulant properties in human therapeutics [34].

The Chakrabarty group has developed an expeditious, one-pot synthesis of several 1-methyl-2-(hetero)arylbenzimidazoles directly from N-methyl-1,2-phenylenediamine and (hetero) aryl aldehydes in ethyl acetate at room temperature using the Keggin heteropolyacid silicotungstic acid ($H_4SiW_{12}O_{40}$), as the catalyst [34] (Scheme **3**).

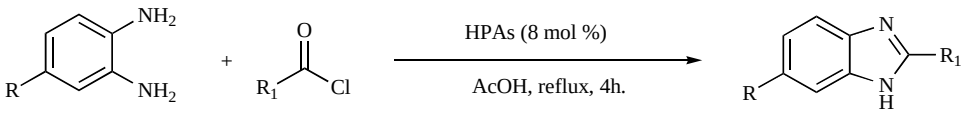
The reaction was carried out under mild reaction conditions (room temperature) short reaction periods (5-60 min), high yields (52-99%) and an easily available, inexpensive and eco-friendly catalyst. Additionally, the catalyst was effective for the reaction of 1,2-phenylenediamine and N-phenyl-1,2-phenylenediamine.

Benzimidazoles are also synthesized from condensation of o-phenylenediamine and acyl chlorides in the presence of a catalytic amount of various heteropolyacids (Wells-Dawson, Keggin and Keggin-doped with vanadium) (Scheme **4**).

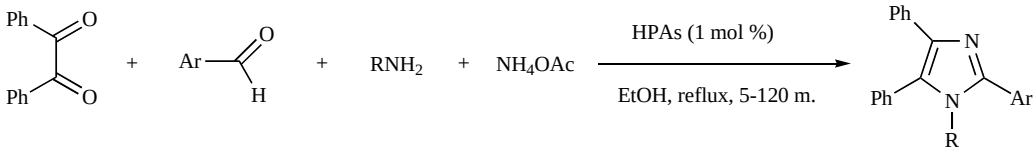
In the reaction a 1:1 mixture of *o*-phenylenediamine, acyl chloride and heteropolyacid (8 mol %) in acetic acid as solvent was refluxed for 4 h. Benzimidazoles were obtained in excellent yields (76-98%, 4 examples, using different heteropolyacids) [35]. The catalyst can be reused after a simple work-up, and the filtered catalyst is ready for its immediate reutilization, without decrease of its activity.



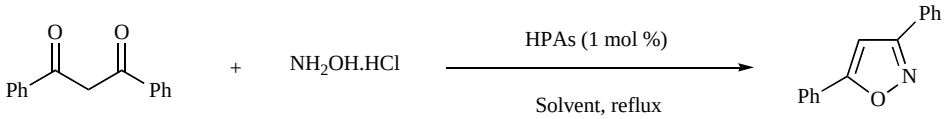
Scheme 3.



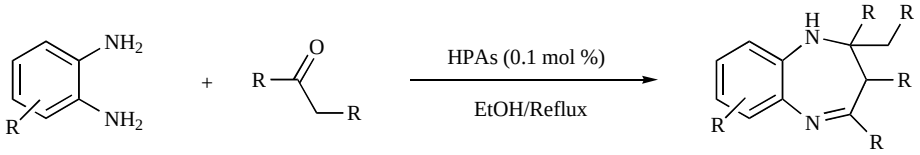
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

The multicomponent coupling reactions are emerging as a useful source for accessing small drug-like molecules with several levels of structural diversity. Heravi *et al.* have reported the four-component condensation of benzyl, benzaldehyde derivatives, primary amines and ammonium acetate catalyzed by Keggin heteropolyacids such as $H_3PW_{12}O_{40}$, $H_4SiW_{12}O_{40}$, $H_4PMo_{11}VO_{40}$, $Na_2HPMo_{12}O_{40}$ as efficient and facile one-pot synthesis of tetrasubstituted imidazoles (Scheme **5**).

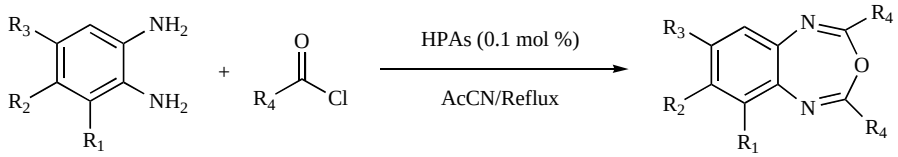
In the reaction a stoichiometric mixture of benzil, amine, aldehyde, ammonium acetate and heteropolyacid (1 mol %) was refluxed in ethanol. After completion of the reaction, the mixture was cooled to room temperature and the precipited products were separated by filtration. Tetrasubstituted benzylimidazoles were obtained with good yields (68-90%, 7 examples) (Scheme **5**) [36].

Heteropolyanions with different structures, including Keggin, Wells-Dawson, Preyssler mixed addenda, and sanwich types, catalyzed the formation of 1,3-diphenyl-isoxazole from the condensation of 1,3-diphenyl propane 1,3-dione and hydroxylamine hydrochloride under different solvent and heating conditions (Scheme **6**).

The $H_3PW_{11}CuO_{40}$ is the most active catalyst and can catalyze the synthesis of other isoxazole derivatives in high yields and good selectivities.

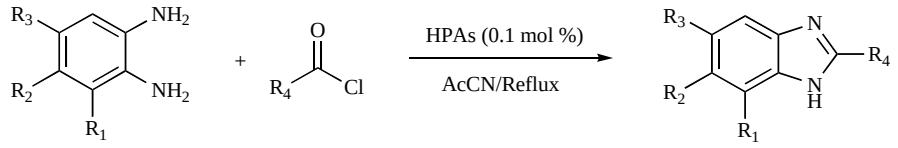
The compounds with 1,5-benzodiazepine scaffold have recently received considerable attention because of their pharmacological properties. Many members of benzodiazepines are widely used as antianxiety, analgetic, sedative, antidepressive and hypnotic agents. These compounds also have commercial use as dyes for acrylic fibers and as anti-inflammatory agents. Particularly, 1,5-benzodiazepines are useful precursors for the synthesis of some fused-ring benzodiazepine derivatives such as triazolo-, oxadiazolo- or furanobenzodiazepines [37].

2,3-Dihydro-1H-1,5-benzodiazepines are synthesized by condensation of o-phenylenediamine and various ketones in the presence of Preyssler heteropolyacids as a recyclable catalyst in refluxing ethanol. In the reaction a mixture of ketone (2.2 mmol), *o*-phenylenediamine derivative (1 mmol) and $H_{14}[NaP_5W_{30}O_{110}]$ (0.1 mol%) was refluxed in ethanol at 78°C for 60-105 min. Under these conditions 2,3-dihydro-1H-1,5-benzodiazepines are obtained in a simple more convenient and environmentally benign (80-95%, 10 examples). The catalyst can be washed with a portion of dichloromethane and reused in another reaction (Scheme **7**) [38].



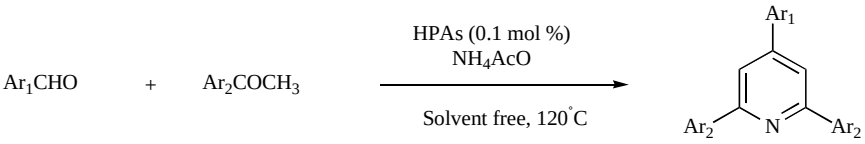
R_1, R_2, R_3 H or CH_3

Scheme 8.

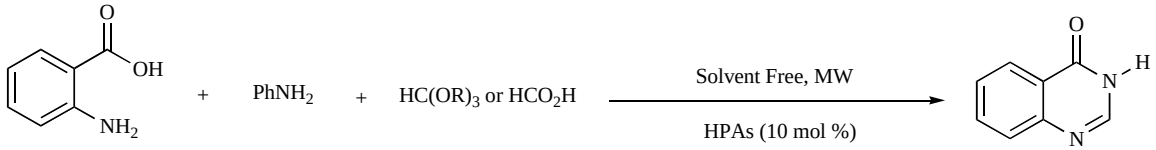


R_1, R_2, R_3 H or NO_2

Scheme 9.



Scheme 10.



Scheme 11.

3,1,5-Benzoxadiazepines are synthesized by condensation of *o*-phenylenediamine and different acyl chlorides in the presence of a catalytic amount of various HPAs ($H_{14}[NaP_5W_{30}O_{110}]$, $H_6[NaP_5W_{30}O_{110}]$, and $H_5[PMo_{10}V_2O_{40}]$). In the reaction *o*-phenylenediamine was dissolved in acetonitrile and the acyl chloride and the catalyst (0.1 mol %) were heated at reflux temperature for 4 h (60-86%, 2 examples) (Scheme **8**). [39].

When 4-nitrophenylenediamine and 3,5-dinitrophenylenediamine and acyl chloride were used as substrates, in this reaction the corresponding benzyimidazoles were obtained instead of 3,1,5-benzoxadiazepines (77-98%, 4 examples) (Scheme **9**).

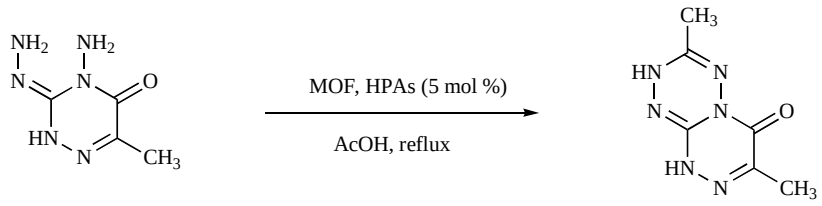
The pyridine ring system is present in various natural products, and many pyridine derivatives exhibit a broad range of biological activities, such as antimalarial, vasodilator, anesthesic, anticonvulsant, fungicidal, pesticidal and herbicidal. The Preyssler-type heteropolyacid ($H_{14}[NaP_5W_{30}O_{110}]$) is found to be an efficient catalyst for the synthesis of 2,4,6-triarylpyridines in good yields. A 1:2:1.3 mixture of aldehyde, acetophenone, NH_4OAc as ammonia source and HPAs (100 mg) was heated at 120°C under solvent-free conditions for 3.5-5 h. Under these conditions 2,4,6- triarylpyridines are obtained with a yield of 50-98%, (8 examples) (Scheme **9**). The recycled catalyst was used for three reactions without observation of appreciable loss in the catalytic activities [40].

The quinazolinone core and its derivatives form an important class of compounds, as they are present in a large family of products with broad biological activities. They generally display useful therapeutic and pharmacological properties such as anti-inflammatory, anticonvulsant, antihypertensive and antimalarial activity [41].

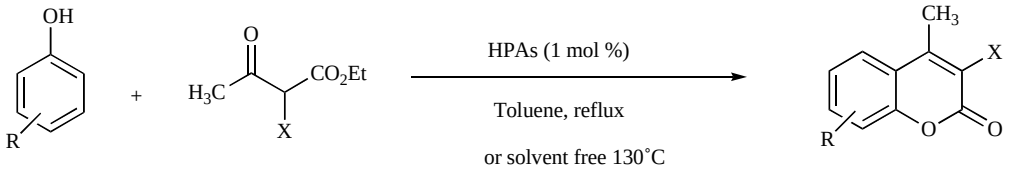
Hamdi´s group has investigated a microwave-assisted synthesis of 4(3H)-quinazolinones by condensation of anthranilic acid, orthoesters (or formic acid) and substituted anilines using Keggin-type heteropolyacids ($H_3PW_{12}O_{40}.13H_2O$, $H_4SiW_{12}O_{40}.13H_2O$, $H_3Mo_{12}O_{40}.13H_2O$ or $H_4SiW_{12}O_{40}.13H_2O$) as catalyst. We found that the use of $H_3PW_{12}O_{40}.13H_2O$ acid coupled to microwave irradiation allows a solvent free, rapid (approx. 13 min) and high-yielding reaction. Under these conditions 4(3H)-quinazolinones were obtained in good yields (30-80%, 10 examples). Compared to the conventional methods, microwave activation in the presence of solvent led to lower yields, where activation without solvent afforded equivalent or slightly increased yields. It should be noted that the reaction time was ten fold shorter (13 min for microwave irradiation versus 120 min for conventional heating) (Scheme **11**) [41].

Triazinotetrazines are a class of heterocyclic systems, that have not received much attention. The catalytic performance of Keggin $H_3PW_{12}O_{40}$ and Preyssler $H_{14}NaP_5W_{30}O_{110}$ catalysts both pure and supported on silica, have been studied in the cyclocondensation of amino-3-hydrazino-6-methyl -1,2,4-triazin-5(2H)-one (4-AHMT) with orthoesters. Amino-3-hydrazino-6-methyl-1,2,4-triazin-5(2H)-one (2 mmol) was dissolved in an appropriate solvent (acetic acid, ethanol, acetonitrile and n-butanol). Orthoester 1 ml was added to the solution and the catalyst (0.1 mmol) was subsequently added to the reaction mixture, the reaction mixture was stirred at reflux temperature for 1-6 h. The best yield, 95 % in 6 h. was obtained using methyl orthoformate (MOF) as orthoester, acetic acid as solvent at reflux temperature and bulk Preyssler HPAs as catalyst [42] (Scheme **12**).

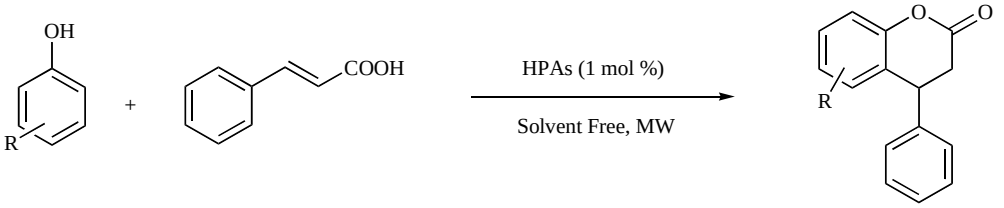
Coumarins and their derivative compounds are widely applied. They are mainly used as active components in the formulation of



Scheme 12.



Scheme 13.



Scheme 14.

pesticides and additives in the manufacture of pharmaceuticals, food and cosmetics. Coumarins have also been used as an optical brightening agent, laser dyes and fluorescent markers for derivatize and further analize diverse compounds, for example, alcohols, carboxylic acid and type-A trichothecenes. Coumarins have varied bioactivity, for example inhibition of platelet aggregation, antibacterial, anticancer, inhibitory of steroid 5α-reductase and inhibition of HIV-1 protease [43].

The Pechman reaction is the most widely used method for preparing 4-substituted coumarins since it proceeds from very simple starting materials, phenols, β-ketoesters or α,β unsaturated carboxylic acids (Scheme **13**). In a previous paper we reported the catalytic activity of $H_6P_2W_{18}O_{62}.24H_2O$ in the sustainable, simple preparation of substituted coumarins.

The experiment carried out in refluxing toluene with of the starting material (in 1:1 molar ratio) in the presence of 1% of the catalyst, for 3-9 h to give the corresponding coumarins (6-82%, 10 examples). The nature of the substituent in the starting phenols seems to have relevant effects. The reaction performed on not very activated phenols led to poor yields of coumarins (e.g. m-cresol 39% and 3,4-dimethylphenol only 6%). The reaction performed under solvent free conditions by heating the reaction mixture at 130°C showed a substantial reduction of the reaction times (0.5-1.8 h.), usually giving higher yields (97-31%, 17 examples).

Other phenols were checked for the reaction, resacetophenone, and m-aminophenol failed to give the expected coumarins. As expected β-naphthol was less reactive than alpha-isomer, yielding no more than 7% 4-methylbenzo[*f*] coumarin in refluxing o-xylene. The recyclic of the catalyst was checked in two consecutive batches after the first use; the cataltst showed almost constant activity [43].

Our research group has recently developed a procedure to prepare coumarins and dihydrocoumarins, using Wells-Dawson heteropolyacids, under solvent-free conditions and microwave irradiation [44]. We performed the sustainable solvent-free preparation of substituted coumarins from phenols and β-ketoesters/3-phenyl-2-propynoic acid by the Pechmann reaction (Scheme **1**). Silica-supported Wells-Dawson acid (WD/SiO_2) was tested as catalyst. The employed β-ketoesters were ethyl acetoacetate, ethyl α-methylacetoacetate and ethyl α-fluoroacetoacetate.

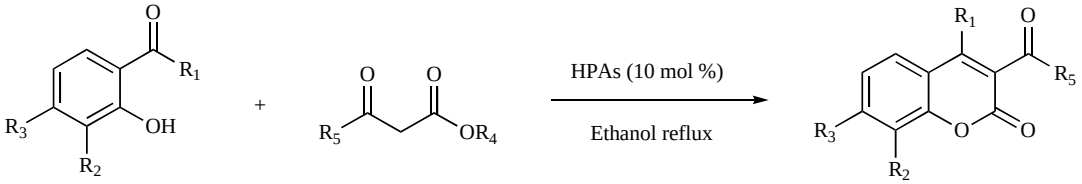
The experiments were carried out employing conventional and microwave heating, in the presence of 1% mmol catalyst, till consumption of the phenol or until no changes in the composition of the reaction mixture were observed. In general high yields of coumarins were attained, almost free of secondary products. The yields obtained by microwave heating were similar to those obtained by conventional heating (yields 54-99%, 9 examples). However, a reduction of the reaction times, can be observed.

Similarly, dihydrocoumarins were obtained by carriyng out, the sustainable solvent-free synthesis of 3,4-dihydrocoumarins from an α,β-unsaturated acid and a phenol using the same catalyst (WD/SiO_2) Scheme **14**.

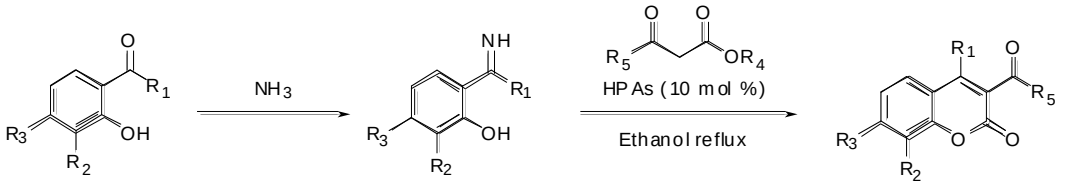
Good yields of dihydrocoumarins were attained, again free of secondary products (yields 38-82%, 6 examples). The conventional heating gives null or poor results. The time decreases notably with microwave irradiation on the reaction (5-15 min), and the excess of reaction time results in a yield decrease.

The steric hindrance is important for this reaction, as in the case of using phloroglucinol, were the yield decreased remarkably.

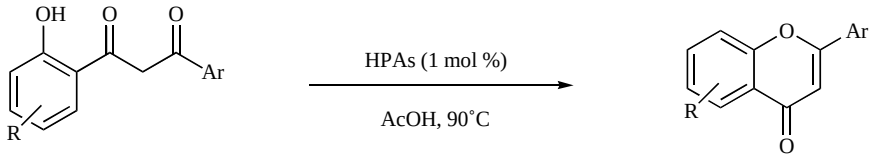
Torviso *et al.* have reported the use of different Keggin heteropolyacids in the synthesis of coumarins from phenols and ethyl acetoacetate [45]. The catalysts used $H_3PMo_{12}O_{40}$, $H_3PW_{12}O_{40}$ and the corresponding aluminum salt, bulk and supported on silica. In the reaction ethyl acetoacetate or toluene were used as solvent of the reaction, phenol was dissolved and the the solid HPA catalyst was added to the solution in a phenol:HPA molar ratio of 1:0.03. The resulting mixture was heated to reflux to 110°C, or a domestic microwave oven at 210 W was employed for microwave irradiation. The catalytic activity using several phenols such as resorcinol, 3,5-dimethylphenol, 1- and 2-naphthol was determined, and high product yields of the corresponding coumarins were obtained in the case of 4-methyl-7-hydroxycoumarin (80-95%), 4-methyl-5,7-dimethoxycoumarin (60-92%) and 4-methyl-7,8-benzocoumarin (90%9. The yield to 4-methyl-5,6-benzocoumarin was low, and the



Scheme 15.



Scheme 16.



Scheme 17.

use of microwave irradiation as power supply increased the reaction yields and fundamentally decreased the reaction time [45].

In a recent paper a variety of heteropolyanions including Keggin, Wells-Dawson, Preyssler, mixed addenda and sandwich types, catalyzed the formation of a coumarins from the condensation of 1-naphthol and ethyl acetoacetate, in a solvent free system and under heating conditions. In the reaction a mixture a 1-naphthol (1 mmol) and ethyl acetoacetate (1 mmol) was made with a catalytic amount of heteropolyacid (1 mol %) and stirred at 130°C. Comparison of $H_3PW_{12}O_{40}$, $H_4SiW_{12}O_{40}$, $HNa_2PMo_{12}O_{40}$ (Keggin series), $K_7PW_{11}CuO_{40}$, $K_7PW_{11}CuO_{40}$ (mixed addenda Keggin), $H_{14}NaP_5W_{30}O_{110}$ (Preyssler), $H_6P_2W_{18}O_{62}$ (Wells-Dawson) and $K_{10}P_2W_{18}Co_4(H_2O_2)_2O_{62}.20H_2O$ (sandwich type) showed that the highest activity and selectivity could be achieved using $H_{14}NaP_5W_{30}O_{110}$. The catalyst is more efficient than others and gave the highest yields of the desired product in the shortest reaction time, 30 min. To show the generality of this method, $H_{14}NaP_5W_{30}O_{110}$, the best catalyst, was used for the synthesis of other coumarins derivatives in solvent free conditions at 130°C. (Yields 70-98%, 7 examples). This method is efficient for the preparation of coumarins from both electron rich and electron deficient phenols [46].

Coumarin 3-carboxylic acids and 3-acetyl-coumarins were obtained in high yields from ortho-hydroxybenzaldehydes and 1-ethylacetoacetate or malonic acid after a 2 h reflux in ethanol in the presence of a catalytic amount of differents type of HPAs including, $H_{14}NaP_5W_{30}O_{110}$, $H_4PMo_{11}VO_{40}$, $H_5PMo_{10}V_2O_{40}$ and $H_6P_3W_{18}O_{62}$. (Scheme **15**).

The Preyssler catalyst ($H_{14}NaP_5W_{30}O_{110}$) was used to prepared six differents coumarins (yields 59-98%, six examples). The less reactive 1-(2-hydroxy)-phenyl etanone was first reacted with alcoholic ammonia to form ketimines, which were then condensed with 1-ethylacetoacetate or malonic acid to generate 4-methyl coumarin-3-carboxylic acid and 4-methyl-3-acetyl coumarin in moderate yields. (Scheme **16**).

Compounds containing the chromone skeleton (4H-benzopyran-4-one) are widely distributed in the plant kingdom; they constitute a group of compounds in the flavonoids family. These compounds have multiple biological properties, for example anti-inflamatory, antibacterial, antitumor, antioxidant, anti HIV, vasodilator, antiviral, antiallergic and neuroprotective. Some flavonoids inhibit the histamine release from human basophils and rat mast cell. Moreover, it is know that some flavonoids have antifeedant activity agains some phytophagous insects a a coptotermes sp. Subterranean termite [47].

Vázquez and coworked reported the cyclization reaction of substituted 1-2(-hydroxyphenyl-3-aryl-1,3-propanodiones to obtain flavones and 2-arylchromones at 90°C. $H_3PW_{12}O_{40}$ and $H_3PMo_{12}O_{40}$ acids were used as catalyst, both bulk or supported on silica (Scheme **17**).

The conversion to flavones and substituted chromones at different reaction times and molar ratios of heteropolyacid to inicial ketone was evaluated. The desired products were obtained in all cases with good yields (40-69%, 5 examples).

The conversion to flavones and substituted chromones was in general higher in homogeneous phase than that observed for the supported catalyst. Neverthelees, the use of the supported catalyst enabled an easy separation and recovery of the catalysts to immediate reuse without any important decrease of the catalytic activity. In addition, the unchanged starting material may be recycled because it was almost quantitatively recovered and secondary product were not practically formed.

Our research group reported a simple a clean procedure for the preparation of functionalized flavones and chromones using commercial Keggin heteropolycid in reflux acetonitrile medium. Sixteen examples of flavones and naphthyl and furyl chromones are reported (60-91%, 17 examples). Five substituted 2-naphthylchromones are prepared for the first time [19].

Similarly, we report the use of bulk and silica-supported Wells-Dawson acid ($H_2P_2W_{18}O_{62}.24H_2O$ as reusable, heterogeneous catalyst to obtained flavones and chromones. The reaction experiment were performed using toluene as solvent at reflux and in absence of solvent, at 110°C. under these conditions eleven examples were obtained with very good yields (82-91%) and high selectivity. The catalysts were easily recycled and reused without loss of their catalytic activity. The reactions are complete in 4-5 h. using toluene as solvent and the 0.5-0.8 h in solvent free conditions [49].

Finally our research group has developed recently a procedure to prepare flavones and chromones, using Wells-Dawson hetero-

polyacids, in solvent-free conditions and microwave irradiation [44].

In conclusion, heteropolyacids and derivatives are very attractive catalyst to be used in the heterocyclic synthesis, important compounds for derivatives that have biological activities. So, they constitute an important contribution to perform acid reactions applying new clean technologies.

ACKNOWLEDGEMENTS

We thank Agencia Nacional de Promoción Científica y Tecnológica (Argentina), Universidad Nacional de La Plata, and CONICET for financial support.

REFERENCES

[1] Reddy, B.M.; Sreekanth, P.M.; Lakshmanan, P. Sulfated zirconia as an efficient catalyst for organic synthesis and transformation reactions. *J. Mol. Catal. A: Chem.*, 2005, *237*, 93-100.

[2] Corma, A.; García, H. Lewis acids: From conventional homogeneous to green homogeneous and heterogeneous catalysis. *Chem. Rev.*, 2003, *103*, 4307-4365.

[3] Ledneczki, I.; Darányi, M.; Fulop, F.; Molnár, A. SAC-13 silica nanocomposite solid acid catalyst in organic synthesis. *Catal. Today*, 2005, *100*, 437-440.

[4] Clark, J. H. Solid acids for green chemistry. *Acc. Chem. Res.*, 2002, *35*, 791-797.

[5] Okuhara, T. Water-tolerant solid acid catalysts. *Chem. Rev.*, 2002,*102*, 3641-3666.

[6] Wilson, K.; Clark, J. H. Solid acids and their use as environmentally friendly catalysts in organic synthesis. *Pure Appl. Chem.*, 2000, *72*, 1313-1319.

[7] Sartori, G.; Ballini, R.; Bigi, F.; Bosica, G.; Maggi, R.; Righi, P. Protection (and Deprotection) of functional groups in organic synthesis by heterogeneous catalysis. *Chem. Rev.*, 2004,*104*, 199-250.

[8] Misono, M.; Nojiri, N. Recent progress in catalytic technology in Japan. *Appl. Catal. A: Gen.*,1990, *64*, 1-30.

[9] Okuhara, T. New catalytic functions of heteropoly compounds as solid acids. *Catal. Today*, 2002, *73*, 167-176.

[10] Mizuno, N.; Misono, M. Heterogeneous catalysis. *Chem. Rev*., 1998, *98*, 199-217.

[11] Kozhevnikov, I. V. Catalysis by heteropoly acids and multicomponent polyoxometalates in liquid-phase reactions. *Chem. Rev.*, 1998, *98*, 171-198.

[12] Yadav, G. Synergism of clay and heteropoly acids as nano-catalysts for the development of green processes with potential industrial applications. *Catal. Surveys from Asia*, 2005, *9*, 117-137.

[13] Kozhevnikov, I. V. Sustainable heterogeneous acid catalysis by heteropoly acids. *J. Mol. Catal. A: Chem.*, 2007, *262*, 86-92.

[14] Yarmo, M. A.; Shariff, R. S. R.; Omar, S. R.; Ching, J. J.; Haron, R. New perspective in recent solid acid catalyst. *Mat. Science Forun*, 2006, *517*, 117-122.

[15] Misono, M.; Ono, I.; Koyano, G.; Aoshima, A. *Pure and Appl. Chem.*, 2002, *72* 1305-1311.

[16] Misono, M. Acid catalysts for clean production. Green aspects of heteropolyacid catalysts. *Comptes Rend de l´academie des Sciences- Series II c: Chemistry*, 2000, *3*, 471-473.

[17] Mizuno, N.; Misono, M. Heteropolyacid catalysts. *Curr. Opin. Solid Stat Mater. Sci.*, 1997, *2*, 84-89.

[18] Pizzio, L. R.; Vázquez, P. G.; Cáceres, C. V.; Blanco, M. N. Supported Keggin type heteropolycompounds for ecofriendly reactions. *Appl. Catal. A: Gen.*, 2003, *256*, 125-139.

[19] Vázquez, V.; Pizzio, L.; Romanelli, G.; Autino, J.; Cáceres, C.; Blanco, M. Mo and W heteropolyacid based catalysts applied to the preparation of flavones and substituted chromones by cyclocondensation of o-hydroxyphenyl aryl 1,3-propanediones. *Appl. Catal A: Gen.*, 2002, *235*, 233-240.

[20] Kozhevnikov, I. V. Heteropoly acids and related compounds as catalysts for fine chemical synthesis. *Catal. Rev. Sci. Eng.*, 1995, *37*, 311-352.

[21] Pope, M. *Heteropoly and Isopoly Oxometalates*, Springer, Berlin, 1983.

[22] Briand, L.; Baronetti, G. T., Thomas, H. J. The state of the art on Wells-Dawson heteropoly-compounds: A review of their properties and applications. *Appl. Catal. A: Gen.*, 2003, *256*, 37-50.

[23] Hu, C. ; Zang, Y. ; Xu, L.; Peng, G. Continuous syntheses of octyl phenol or nonane phenol on supported heteropoly acid catalysts. *Appl. Catal. A : Gen.*, 1999, *177*, 237-244.

[24] Amini, M. M.; Shaabani, A.; Bazgir, A. Tangstophosphoric acid ($H_3PW_{12}O_{40}$): An efficient and eco-friendly catalyst for the one-pot synthesis of dihydropyrimidin-2(1H)-ones. *Catal. Commun.*, 2006, *7*, 843-847, and references cited herein.

[25] Kappe, C. O. Recent advances in the Biginelli dihydropyrimidine synthesis. New tricks from an old dog. *Acc. Chem. Res.*, 2000, *33*, 879-888.

[26] Folkers, K.; Harwood, H.J.; Johnson, T.B. Research on pyrimidines. CXXX. Synthesis of 2-keto-1,2,3,4-tetrahydropyrimines. *J. Am. Chem. Soc*., 1932, *54*, 3751-3758.

[27] Heravi, M.M.; Bakhtiari, K.; Bamoharram, F.F. 12-Molybdophosphoric acid: A recyclable catalyst for the synthesis of Biginelli-type 3,4-dihydropyrimidine-2(1H)-ones *Catal. Commun.*, 2006, *7*, 373-376.

[28] Rafiee, E.; Jafari, H. A practical and green approach towards synthesis of dihydropyrimidinones: Using heteropoly acids as efficient catalysts. *Biorg. Med. Chem., Lett.* 2006, *16*, 2463-2466.

[29] Fazaeli, R.; Tangestaninejad, S.; Aliyan, H.; Moghadam, M. One-pot synthesis of dihydropyrimidinones using facile and reusable polyoxometalate catalysts for the Biginelli reaction. *Appl. Catal. A: Gen.*, 2006, *309*, 44-51.

[30] Romanelli, G.P.; Sathicq, A.G.; Autino, J.C.; Baronetti, G.; Thomas, H.J., Solvent-free approach to 3,4-dihydropyrimidin-2(1H)-(thio)ones: Biginelli reaction catalyzed by a Wells-Dawson reusable heteropolyacid. *Synth. Commun*., 2007, *37*, 3907-3916.

[31] Sivaprasad, G.; Perumal, P.T. Synthesis of novel 4-pyrazolyl-2-oxo-1,2,3,4-tetrahydropyrimidines promoted by phosphotungstic acid. *J. Heter. Chem.*, 2005, *42*, 863-866.

[32] Heravi, M.M.; Motamedi, R.; Seifi, N.; Bamoharram, F.F. Catalytic synthesis of 6-aryl-1H-pyrazolo[3,4-d]pyrimidin-4[5H]-ones by heteropolyacid: $H_{14}[NaP_5W_{30}O_{110}]$ and $H_3PW_{12}O_{40}$. *J. Mol. Catal. A Gen.*, 2006, *249*, 1-3.

[33] Heravi, M.M.; Motamedi, R.; Bamoharram, F.F.; Seify, N. A catalytic method for synthesis of 6-aryl-1H-pyrazolo[3,4-d]pyrimidin-4[5H]-ones by heteropolyacids: $H_{14}[NaP_5W_{29}MoO_{110}]$ and H3PMo12O40. *Catal. Commun.* 2007, *8*, 1467-1471.

[34] MChakrabarty, M.; Mukherji, A.; Mukherjee, R.; Arima, S.; Harigaya, Y. A Keggin heteropoly acid as an efficient catalyst for an expeditious, one-pot synthesis of 1-methyl-2-(hetero)arylbenzimidazoles. *Tetrahedron Lett., 2007, 48, 5239-5242* and references cited hereim.

[35] Heravi, M.M.; Sadjadi, S.; Oskooie, H.A.; Shoar, R.H.; Bamoharram, F.F. Heteropolyacids as heterogeneous and recyclable catalysts for the synthesis of benzimidazoles . *Catal. Commun*., 2008, *9*, 504-507.

[36] Heravi, M.M.; Derikvand, F.; Bamoharram, F.F. Highly efficient, four-component one-pot synthesis of tetrasubstituted imidazoles using Keggin-type heteropolyacids as green and reusable catalysts. *J. Mol. Catal. A: Chem.*, 2007, *263*, 112-114.

[37] Yadav, J.S.; Reddy, B.V.S.; Eshwaraiah, B.; Anuradha, K. Amberlyst-15®: A novel and recyclable reagent for the synthesis of 1,5-benzodiazepines in ionic liquids. *Green Chem*., 2002, *4*, 592-594

[38] Bamoharram, F.F.; Heravi, M.M.; Roshani, M.; Abrishami, F. J. Catalytic N-oxidation of picolinic acid in the presence of heteropolyacids including Mo and W. *Mol. Catal. A: Chem.*, 2007, *267*, 241-244.

[39] Heravi, M.M.; Sadjadi, S.; Oskooie, H.A.; Shoar, R.H.; Bamoharram, F.F. Heteropolyacids as green and reusable catalysts for the synthesis of 3,1,5-benzoxadiazepines. *Molecules*, 2007, *12*, 255-262.

[40] Heravi, M.M.; Bakhtiari, K.; Daroogheha, Z.; Bamoharram, F.F. An efficient synthesis of 2,4,6-triarylpyridines catalyzed by heteropolyacid under solvent-free conditions. *Catal. Commun*., 2007, *8*, 1991-1994.

[41] Ighilahriz, K.; Boutemeur, B.; Chami, F.; Rabia, C.; Hamdi, M.; Hamdi, S.M. microwave-assisted and heteropolyacids-catalysed cyclocondensation reaction for the synthesis of 4(3H)-quinazolinones. *Molecules*, 2008, *13*, *779-789.*

[42] Heravi, M.M., Zadsirjan, V., Behbahani, F.K., Oskooie, H.A. Catalytic synthesis of 2,3-dihydro-1H-1,5-benzodiazepines by ferric perchlorate. *J. Mol. Catal A: Chem.*, 2006, *259*, 201-204.

[43] Romanelli, G.P.; Bennardi, D.; Ruiz, D.M.; Baronetti, G.; Thomas, H.J.; Autino, J.C. A solvent-free synthesis of coumarins using a Wells-Dawson heteropolyacid as catalyst. *Tetrahedron Lett.*, 2004, *45*, 8935-8939 and references cited hereim.

[44] Bennardi D.; Ruiz D.; Romanelli G.P.; Autino J.C.; Baronetti G.; Thomas H. J. Efficient Microwave Solvent-Free Synthesis of Flavones, Chromones, Coumarins and Dihydrocoumarins. *Lett. Org. Chem.*, 2008, *5*, 607-615.

[45] Torviso, R.; Mansilla, D.; Belizán, A.; Alesso, E.; Moltrasio, G.; Vázquez, P.; Pizzio, L.; Blanco M.; Cáceres, C. Catalytic activity of Keggin heteropolycompounds in the Pechmann reaction. *Appl. Catal. A: Gen*., 2008, *339*, 53-60.

[46] Heravi, M.M.; Khorasani, M.; Derikvand, F.; Oskooie, H.A.; Bamoharram, F.F. Highly efficient synthesis of coumarin derivatives in the presence of $H_{14}[NaP_5W_{30}O_{110}]$ as a green and reusable catalyst. *Catal. Commun.*, 2007, *8*, 1886-1890.

[47] Heravi, M.M.; Sadjadi, S.; Oskooie, H.A.; Shoar, R.H.; Bamoharram, F.F. The synthesis of coumarin-3-carboxylic acids and 3-acetyl-coumarin derivatives using heteropolyacids as heterogeneous and recyclable catalysts. *Catal. Commun.*, 2008, *9*, 470-474.

[48] Bennardi, D.O.; Romanelli, G.P.; Jios, J.L.; Vázquez, P.G.; Cáceres, C.V.; Autino, J.C. Synthesis of substituted flavones and arylchromones using P and Si Keggin heteropolyacids as catalysts. *Heterocycl. Commun.*, 2007, *13*, 77-81.

[49] Bennardi, D.O.; Romanelli, G.P.; Jios, J.L.; Autino, J.C.; Baronetti, G.T.; Thomas, H.J. Synthesis of substituted flavones and chromones using a Wells-Dawson heteropolyacid as catalyst. *Arkivoc*, 2008, *11*, 123-130.

Received: September 22, 2008 Revised: November 25, 2008 Accepted: November 28, 2008