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A suitable synthesis of azlactones (4-benzylidene-2-phenyloxazolin-5-ones and 4-alkylidene-2-phenyloxazolin-5-ones) catalyzed by silica–alumina supported heteropolyacids

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ABSTRACT

Eleven examples of azlactones (4-benzylidene-2-phenyloxazolin-5-ones and 4-alkylidene-2-phenyloxazolin-5-ones) were prepared via an Erlenmeyer-type synthesis from aromatic aldehydes, hippuric acid and acetic anhydride was added to the hot solution as a dehydrating agent. Molybdophosphoric or tungstophosphoric acids supported on silica–alumina, obtained by the sol–gel method, catalyze the reaction. The prepared catalysts were characterized by X-ray diffraction and diffuse reflectance spectroscopy. The specific surface area of the catalysts was determined by the nitrogen adsorption/desorption at 196 °C technique, and the catalyst acidity was measured by potentiometric titration with *n*-butylamine. The heteropolyacid amount removed from the catalysts during the leaching with toluene was lower than 1%. The products were obtained with high conversion and selectivity. The yields were in the 87–96% range for the majority of the selected samples, with the exception of the azlactones synthesized from 2-nitrobenzaldehyde and cyclohexanone, which gave yields in the 70–80% range. The same catalysts were used several times without appreciable loss of their catalytic activity. A rational mechanism for the azlactone formation catalyzed by the supported heteropolyacid is proposed.

1. Introduction

Azlactones, anhydrides of N-acyl-α-aminoacids, are interesting intermediates for the synthesis of a variety of bioactive compounds, some of their activities are anticancer, antitumor, and inhibition of the central nervous system [1].

Azlactones are also utilized in the synthesis of N-substituted pyrrols [2], α-acylaminoalcohols [3], heterocyclic compounds [4,5], asymmetric synthesis of aminoacids [6,7], and for the homologation of carboxylic acids [8]. Recently, Zimmermann et al. [9] have reported the use of azlactones for the preparation of methacrylamidopeptide macromonomers, employed in the synthesis of hydrogel supports for in vivo cell growth.

Since the first report on the synthesis of azlactones published in 1883, a number of methods have been developed. The usual method for their preparation is the Erlenmeyer synthesis, consisting in the condensation of an aldehyde with hippuric acid in the presence of acetic anhydride and usually sodium acetate [10].

Different reagents have been used to perform the cyclodehydration of hippuric acid, for example acetic anhydride and sodium acetate or lead acetate [11], perchloric acid [12], polyphosphoric acid [13], anhydrous zinc chloride [14], carbodiimides [15] and SO_3 in dimethylformamide [16]. However, some of these procedures have important drawbacks, such as the use of corrosive acids, or compounds that generate toxic waste streams. Then, there is a need for the development of environmentally benign methods. In recent years, several procedures were developed using heterogeneous conditions. The employed catalysts were mainly basic, nevertheless some solid acids were used, in the presence of a stoichiometric quantity or an excess of acetic anhydride, for example KF-alumina [17], and Bi (III) [18] or calcium acetate under microwave irradiation [19]. The reported advantages are the mild reaction conditions, high yields and easy recovery of products.

On the other hand, there is an increasing interest in the area of heteropolycompound-induced organic transformations. In view of their remarkable catalytic properties, heteropolycompounds are applied both in bulk or supported form, and homogeneous

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or heterogeneous catalysis is possible. The heteropolycompounds (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 tetrahedron XO_4, surrounded by 12 octahedra MO_6. They could be either multi-electron oxidants or strong acids, with an acid strength higher than that of the classical acids [20].

For a long time, our efforts were focused on the development of environmentally benign synthetic methods using supported HPA [20–22]. Within this line, in this paper we report a simplified procedure for the synthesis of 4-benzylidene-2-phenyloxazolin-5-ones and 4-alkylidene-2-phenyloxazolin-5-ones. Heterogeneous conditions were used for the reaction of several aldehydes or cyclohexanone with hippuric acid, using a catalytic amount of molybdophosphoric (MPA) or tungstophosphoric (TPA) acids supported on silica–alumina, in the presence of acetic anhydride in toluene solution (Scheme 1). In addition, a rational mechanism for the azlactone formation catalyzed by the supported heteropolyacid is proposed.

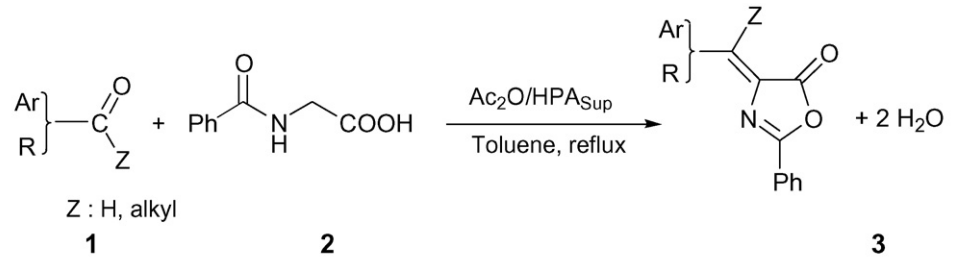
2. Experimental

2.1. Support preparation

A solution of tetraethyl orthosilicate (TEOS) in ethanol was prepared. Then commercial alumina, about 10 μm in particle size, was added. Hydrolysis of TEOS, by a stepwise water addition at 45 °C, led to a silica sol–gel [20]. After 24 h, the solid and the solution were separated by decantation. Afterward, the solid was dried at 60 °C for 24 h, and then at 100 °C for 2 h.

2.2. Catalyst preparation

The synthesized support was impregnated with ethanol–water solutions (50%, v/v) of TPA ($H_3PW_{12}O_{40}$) or MPA ($H_3PMo_{12}O_{40}\cdot H_2O$) of 0.14 mmol HPA/ml concentration, using the pore filling method. Then, the samples were dried at room temperature (r.t.) for 24 h. The HPA concentration on support was 0.10 mmol TPA (MPA)/g support. In order to evaluate the HPA retention in the support, the catalysts were leached with toluene under continuous stirring for



Carbonyl Compound 1	R'	Azlactone 3
a-h	a H b 4-N(CH3)2 c 4-CH3 d 2-Cl e 4-Cl f 2-NO2 g 4-NO2 h 3-CH3O-4-HO	
i		
j		
k		

Scheme 1. Preparation of 4-benzylidene-2-phenyloxazolin-5-ones and 4-alkylidene-2-phenyloxazolin-5-ones.

two periods of 24 h. The solids were then dried and calcined at 150 °C. They will be named MPA_{Sup} or TPA_{Sup}.

2.3. Catalyst characterization

The specific surface area (S_{BET}) of the catalysts was determined by the nitrogen adsorption/desorption at −196 °C technique, using Micromeritics Accusorb 2100E equipment.

The diffuse reflectance spectra (DRS) were obtained in the 200–600 nm range, using UV–vis Varian Super Scan equipment, to which a diffuse reflectance chamber with an internal surface of $BaSO_4$ is attached. The samples were pressed in a teflon sample holder in order to obtain a 2 mm sample thickness.

Besides, the catalysts were characterized by X-ray diffraction (XRD) employing Philips PW-1732 equipment. The measuring conditions were: Cu Kα radiation, Ni filter; 30 mA and 40 kV; scanning angle between 5 and 50°2θ, and scanning rate 1°/min.

The catalyst acidity was measured by potentiometric titration with *n*-butylamine. A known mass of solid was suspended in acetonitrile (Baker) with stirring. Then, the suspension was titrated with a 0.05-N acetonitrile solution of *n*-butylamine (Carlo Erba), at a flow rate of 0.05 ml/min. The electrode potential variation was measured with a digital Instrumentalia pH-meter, using a Ag/AgCl electrode.

2.4. Azlactone synthesis

The reactions were carried out in a glass batch reactor at atmospheric pressure. The aldehyde or cyclohexanone (1 mmol) and hippuric acid (1 mmol) were dissolved in toluene (2 ml), and the catalyst (0.0013 or 0.0065 mmol) was added to the solution. The resulting mixture was stirred and refluxed for 5 min. Acetic anhydride (1 mmol) was added to the hot solution, as a dehydrating agent, and the mixture was further refluxed for 1 h. The reaction mixture was cooled, the catalyst was separated by filtration, and the solvent was removed in vacuum. The crude reaction product, a yellow or orange solid, was purified by recrystallization from 95% ethanol to give the corresponding 4-benzylidene-2-phenyloxazolin-5-one or 4-alkylidene-2-phenyloxazolin-5-one.

All the products were characterized by comparison (thin layer chromatography and physical constants) with standard samples prepared by conventional methods. All the yields were calculated from the amount of crystallized product.

In order to study the reuse of the catalyst, it was washed with toluene after its filtration from the reaction medium, and it was dried in vacuum at 40 °C up to constant weight.

3. Results and discussion

3.1. Catalyst characterization

The TPA_{Sup} and MPA_{Sup} catalysts presented a low specific surface area ($S_{BET} < 3.6\ m^2/g$), TPA(MPA)/g support. The amount of TPA(MPA) removed from the catalyst during the leaching with toluene was lower than 0.1% of the initial content. This fact indicates that the $[PW(Mo)_{12}O_{40}]^{3-}$ anion impregnated in the synthesized silica–alumina support is very poorly soluble in toluene.

The diffuse reflectance spectra of the TPA_{Sup} and MPA_{Sup} catalysts are shown in Fig. 1. The charge transfer absorption spectra of most nonreduced polyanions appear between 200 and 500 nm, and consist of bands that may be ascribed to oxygen-to-metal transfers. Molybdenum and tungsten in octahedral coordination exhibit two absorption bands approximately at 220 and 260 nm. The last band broadens and extends up to near 530 nm for bulk MPA [23], whereas for bulk TPA it extends up to near 450 nm [24], being somewhat less extended for dried bulk HPA. The spectra of both catalysts showed a band near 200 nm and a broad band extended up to 490 and 400 nm for MPA- and TPA-based catalysts, respectively. They presented the broad band sufficiently extended, which can be assigned to undegraded $[PW(Mo)_{12}O_{40}]^{3-}$ species. The absorption slightly increase near 600 nm in the MPA_{Sup} spectrum is due to the presence of the so-called heteropoly blue, which is the result of a fast and reversible reduction of Mo^{VI} to Mo^{V}.

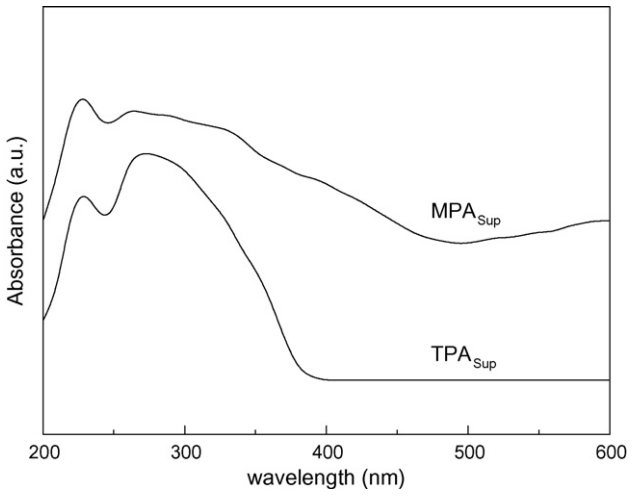


Fig. 1. Diffuse reflectance spectra of the heteropolyacids supported on the synthesized silica–alumina.

On the other hand, the XRD patterns of the catalysts, shown in Fig. 2, presented the main diffraction lines of the corresponding HPA, placed at 26, 35 and 43°2θ. Assuming that the interaction between the heteropolyanions and the surface groups of the support is of electrostatic type, the presence of HPA diffraction lines may be attributed to the low specific surface area of the support, leading to the presence of heteropolyacid with and without interaction with the surface hydroxyl groups of the support.

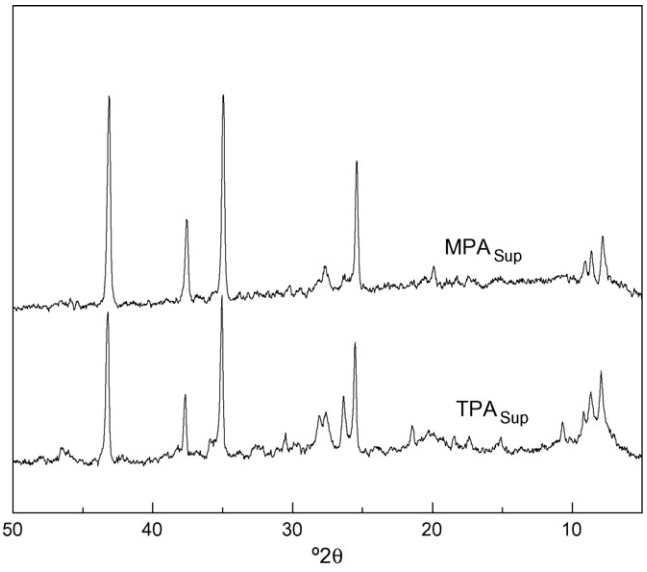


Fig. 2. X-ray diffraction patterns of the heteropolyacids supported on the synthesized silica–alumina.

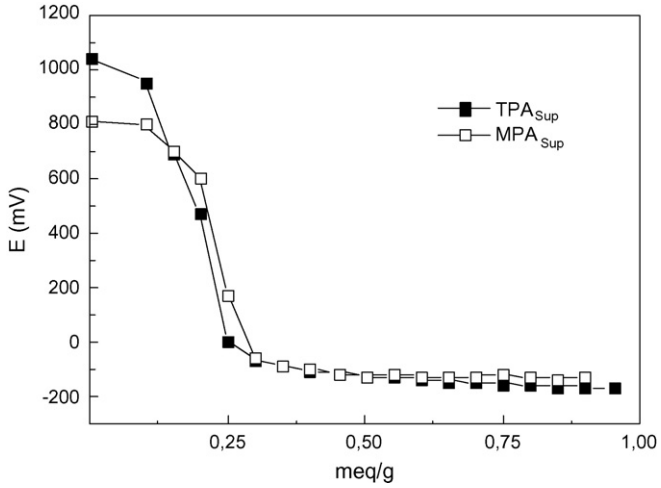


Fig. 3. Potentiometric titration curves of the heteropolyacids supported on the synthesized silica–alumina.

In order to estimate the strength and the number of acid sites present in the catalysts, the potentiometric titration with *n*-butylamine method was used. The initial electrode potential (Ei) is considered indicative of the maximum strength of the acid sites, and the value (meq amine/g catalyst) from which the plateau is reached is indicative of the total number of acid sites of the solid. The strength of the acid sites can be classified according to the following scale: Ei > 100 mV (very strong sites); 0 < Ei < 100 mV (strong sites); −100 < Ei < 0 mV (weak sites), and Ei < −100 mV (very weak sites) [25]. The potentiometric titration curves of the TPA_{Sup} and MPA_{Sup} catalysts are presented in Fig. 3. It can be observed that the initial electrode potential Ei is 1040 and 815 mV, for TPA_{Sup} and MPA_{Sup}, respectively. Therefore, the obtained catalysts present very strong acid sites. In addition, the number of acid sites is similar for both catalysts.

3.2. Azlactone synthesis

The overall process defined as cyclodehydration–condensation reaction was initially studied using benzaldehyde **1a** as the substrate (Table 1). Different reaction conditions were checked, reaction temperature, catalyst, catalyst/reagent molar ratio, and reaction time, for both prepared catalysts. The best results were obtained using toluene as solvent at 110 °C, and a catalyst/reagent molar ratio of 0.0013. Under these conditions, product **3a** was obtained with high selectivity and free of by-products in 60 min (Table 1, entries 4 and 9).

For a TPA_{Sup}/benzaldehyde molar ratio of 0.0013, the conversion of benzaldehyde **1a** into the azlactone **3a** increased from 45% to 96% between 5 and 60 min at 110 °C (Table 1, entries 1 and 4). However, the yield was the same for an increase of the reaction time to 180 min (Table 1, entries 4 and 5). For the same ratio and temperature, the MPA_{Sup} catalyst led to a yield increase from 46% to 95% between 5 and 60 min (Table 1, entries 7 and 9). The catalytic behavior of both catalysts is alike, in line with their similar characteristics, especially their acidic properties.

When the catalyst/benzaldehyde molar ratio was increased to 0.0065, the observed conversion of benzaldehyde into the azlactone was comparable to the results obtained with a molar ratio of 0.0013 using both catalysts (MPA_{Sup} and TPA_{Sup}) (see Table 1 entries 6 and 4, 10 and 9).

For MPA_{Sup} catalyst, when the reaction temperature was decreased to 80 °C, the yield decreased 10% (Table 1, entries 9 and 11). This yield was the same when the reaction time increases to 180 min (Table 1, entries 11 and 12), as it has been mentioned above regarding to other reaction conditions.

When the reaction between benzaldehyde **1a**, and hippuric acid **2**, was carried out in absence of catalysts, formation of azlactone **3a** was not observed.

Using the optimized conditions, a molar ratio of reagents and catalyst (**1:2:HPA**) of 1:1:0.0013, 110 °C (toluene reflux) for 1 h, several aldehydes and cyclohexanone (**1b–1k**) were tested (Table 2). The yield of the reaction was comparable for both catalysts. In all the experiments, the desired products were

Table 1
Preparation of unsubstituted azlactone (**3a**): 4-benzylidene-2-phenyloxazolin-5-one[a].

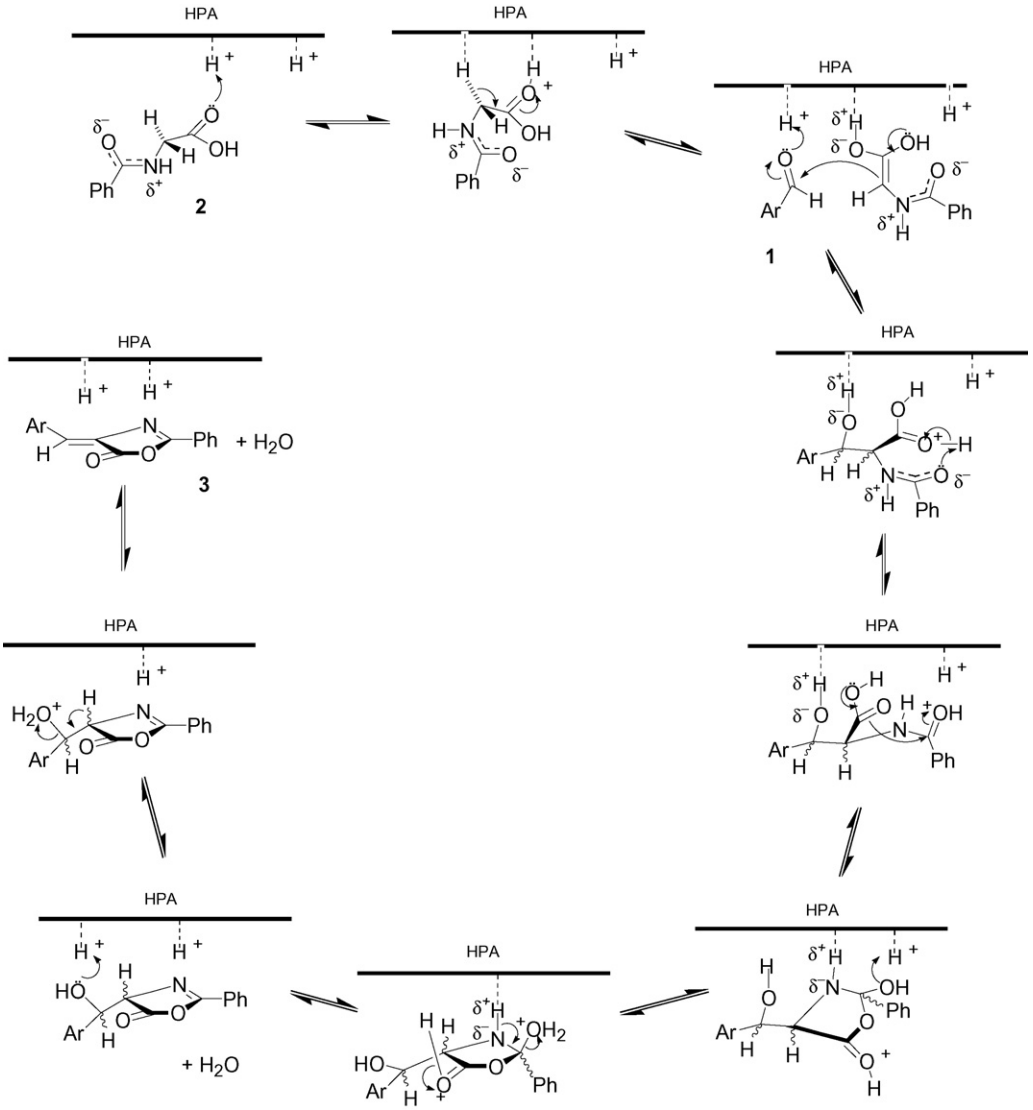
Entry	Catalyst	HPA/reagent molar ratio (%)	Time (min)	*T* (°C)	Yield (%)
1	TPA_{Sup}	0.13	5	110	45
2	TPA_{Sup}	0.13	15	110	63
3	TPA_{Sup}	0.13	30	110	75
4	TPA_{Sup}	0.13	60	110	96 (95, 95)[b]
5	TPA_{Sup}	0.13	180	110	95
6	TPA_{Sup}	0.65	60	110	97
7	MPA_{Sup}	0.13	5	110	46
8	MPA_{Sup}	0.13	30	110	74
9	MPA_{Sup}	0.13	60	110	95 (95, 94)[b]
10	MPA_{Sup}	0.65	60	110	95
11	MPA_{Sup}	0.13	60	80	85
12	MPA_{Sup}	0.13	180	80	86

[a] Molar ratio of reagents (**1:2**): 1:1, content HPA on the catalysts: 0.10 mmol TPA (MPA)/g support.
[b] Yields in parentheses correspond to the first and second re-utilization of the catalyst.

Table 2
Preparation of 4-benzylidene- (or 4-alkylidene-) 2-phenyloxazolin-5-ones from different aldehydes and cyclohexanone[a].

Entry	Carbonyl compound	Catalyst	Yield of 3 (Scheme 1) (%)
1	Benzaldehyde **1a**	TPA_{Sup}	96
2		MPA_{Sup}	95
3	4-Dimethylaminobenzaldehyde **1b**	TPA_{Sup}	94
4		MPA_{Sup}	95
5	4-Methylbenzaldehyde **1c**	TPA_{Sup}	90
6		MPA_{Sup}	91
7	2-Chlorobenzaldehyde **1d**	TPA_{Sup}	90
8		MPA_{Sup}	92
9	4-Chlorobenzaldehyde **1e**	TPA_{Sup}	93
10		MPA_{Sup}	94
11	2-Nitrobenzaldehyde **1f**	TPA_{Sup}	70
12		MPA_{Sup}	74
13	4-Nitrobenzaldehyde **1g**	TPA_{Sup}	93
14		MPA_{Sup}	94
15	3-Methoxy-4-hydroxybenzaldehyde **1h**	TPA_{Sup}	88
16		MPA_{Sup}	89
17	Furfuraldehyde **1i**	TPA_{Sup}	89
18		MPA_{Sup}	89
19	Crotonaldehyde **1j**	TPA_{Sup}	87
20		MPA_{Sup}	89
21	Cyclohexanone **1k**	TPA_{Sup}	80
22		MPA_{Sup}	80

[a] Molar ratio of reagents and catalyst (**1:2:HPA**) was 1:1:0.0013. Reaction was run at 110 °C (toluene reflux) for 1 h.



Scheme 2. Rational mechanism for the azlactone formation, heteropolyacid-catalyzed.

obtained with high selectivity. When the aldehydes (**1a–j**), hippuric acid (**2**) and the acetic anhydride were treated with the supported HPA catalysts for 1 h, the 4-benzylidene-2-phenyloxazolin-5-ones and 4-alkylidene-2-phenyloxazolin-5-ones (**3a–j**) were obtained with very good yields (87–96%), except for the azlactone **3f** (70–74%). That is to say that in general, no substituent group has a specific effect on the yield. This could be because the protonable sites at the substrate or proposed intermediates, or the intramolecular addition synthons (for example, in the cyclization step, see Scheme 2, 4th and 5th formulae) are located relatively remote from the substituted (formerly aldehyde) aryl ring.

Initially, hippuric acid is activated by protonation and enolyzed, and the enol attacks the protonated aldehyde (1st–3rd formulae). Afterward, a deprotonation/protonation involving the carboxyl and the amido groups prepares the nucleophilic intramolecular attack. This behavior leads to the cyclization. Later protonation and deprotonation steps, with the elimination of two molecules of water (Scheme 2, 6th–10th formulae), give the product **3**.

However, a difference in the yield was observed when an *ortho*- or a *para*-nitro group is present in the aldehyde molecule. The yield of *o*-nitro-substituted azlactone (**3f**) is significantly lower than that of the other selected examples (Table 2, entries 11 and 12). This could be due to the close proximity of both basic oxygen atoms behaving as carbonyl and nitrophenyl groups, respectively. Then, these atoms could compete for the same acid sites, as it can be seen in 3rd formulae.

Besides, cyclohexanone gave the corresponding azlactone (**3k**) under the above-mentioned reaction conditions with a yield of 80%.

The experiments performed involving the bulk acids afforded yields similar to those above-mentioned obtained using the heteropolyacid-based catalysts supported on silica–alumina (Table 2, entries 1 and 2). However, the use of the supported catalysts allows an easy separation and recovery of the catalyst for its immediate re-utilization, without a significant decrease in its activity. For the checked examples, the yields were practically the same over three cycles (Table 1, entries 4 and 9)

4. Conclusions

4-Benzylidene-2-phenyloxazolin-5-ones and 4-alkylidene-2-henyloxazolin-5-ones can be synthesized via the Erlenmeyer

synthesis from aromatic aldehydes, hippuric acid, and acetic anhydride was added to the hot solution as a dehydrating agent at reflux, using supported catalysts. Molybdophosphoric or tungstophosphoric acids were supported on a synthesized silica–alumina obtained by the sol–gel method and they were used as catalysts. The reactions were clean, their work-up was very simple and the yields were good to excellent. Crotonaldehyde and cyclohexanone also gave the corresponding azlactones in very good yield under the above-mentioned reaction conditions. The possibility of a simple reaction work-up with excellent yield, and the reuse of these catalysts are noteworthy advantages compared to traditional process.

In conclusion, the present work provides a suitable and useful method for the preparation of azlactones (4-benzylidene-2-phenyloxazolin-5-ones and 4-alkylidene-2-phenyloxazolin-5-ones) with high yield using mild reaction conditions.

Studies are in progress in our laboratory in relation to the synthesis of azlactones under solvent-free conditions.

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