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$H_6P_2W_{12}O_{62}.24H_2O$ Supported on Silica: A Powerful and Reusable Catalyst for the Synthesis of 4-Arylidene-2-Phenyl-5(4)-Oxazolones (Azlactones)

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Abstract: A simple, efficient and ecofriendly one-pot synthesis protocol has been developed for the synthesis of 4-arylidene-2-phenyl-5(4)-oxazolones (azlactones) by using an efficient and recyclable solid acid silica-supported $H_6P_2W_{18}O_{62}.24H_2O$ catalyst from a condensation of aldehydes, hippuric acid and acetic anhydride in toluene. The reaction using $0.4WDSiO_2$ catalyst was carried out under mild conditions with very high yields of up to 89%-93%. The heterogeneous reaction conditions provided a very simple, environmentally friendly, clean, economical and selective protocol for the preparation of these compounds. The catalyst is easily recycled and reused without loss of the catalytic activity.

Keywords: Heterogeneous catalysis, Wells-Dawson heteropolyacid, Green Chemistry, 4-arylidene-2-phenyl-5(4)-oxazolones, Azlactones.

INTRODUCTION

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 [1, 2]. 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 the heteropolyanion. The reactions catalyzed by both heterogeneous and homogeneous systems have been reviewed by many researchers [3-8].

Although there are many structural types of HPAs, the majority of catalytic applications use the most common Keggin type [9, 10], especially for acid catalysts, owing to its availability and chemical stability. Other catalysts such as Wells-Dawson and Preyssler heteropolyacids have begun to be used [11-14].

In the last two decades, Green Chemistry has become an interesting research field for catalytic and organic chemists. Among the different strategies for achieving this goal, the use of heterogeneous catalysts has received special attention. These suitable methods offer several advantages such as shorter reaction times, lower temperature, higher yields and selectivity, much simpler workup and cleaner products [15, 16].

Azlactones, anhydrides of N-acyl-α-aminoacids, are interesting intermediates for the synthesis of a variety of bioactive compounds, which occupy an important place in the realm of biological and pharmaceutical sciences [17–19]. Azlactones have been used in a wide variety of reactions as precursors [20] for biologically active peptides [21], herbicides and fungicides [22], and as drugs, pesticides and agrochemical intermediates [23]. They have been used in active site titrations of enzymes [24], as antihypertensives [25] and in the asymmetric synthesis of amino acids [26]. Some azlactones are especially active as anticancer [16], antitumor [27] inhibitor of the central nervous system. Recently, Zimmermann et al. have reported the use of azlactones for the preparation of methacrylamidopeptide macromonomers, employed in the synthesis of hydrogel supports for in vivo cell growth, [28].

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 [29]. The reaction goes via a Perkin condensation following the initial cyclization of N-acetylglycine yielding the so-called Erlenmeyer azlactones [20].

Different reagents have been used to perform the cyclodehydration of hippuric acid, for example acetic anhydride and sodium acetate or lead acetate [30], perchloric acid [31], polyphosphoric acid [32], anhydrous zinc chloride [33], carbodiimides [34], SO_3 in dimethylformamide [35], and $POCl_3$ [36]. However, some of these procedures have impor-

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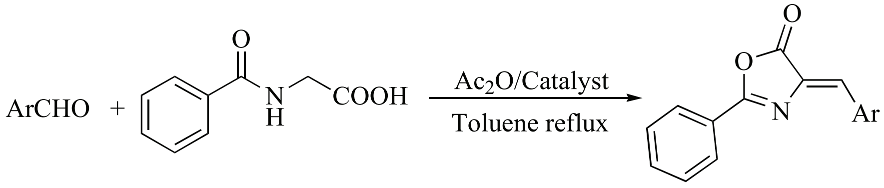


Scheme 1. The azlactone Erlenmeyer synthesis.

tant 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 have been developed using heterogeneous conditions, such as silica-supported heteropolyacids [29] $Yb(OTf)_3$ [37], $Ca(OAc)_2$ [38], organic bases [39], $Bi(OAc)_3$ [40], $Bi(OTf)_3$ [41], Al_2O_3 [20], organic-inorganic hybrid polyoxometalates [16], and the use of microwave and ultrasound as alternative energy source [19, 42], and have been used to perform this condensation [19, 20, 42].

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 (azlactones). Heterogeneous conditions were used for the reaction of several aldehydes with hippuric acid, using a catalytic amount of bulk and silica-supported Wells-Dawson in the presence of acetic anhydride in reflux toluene (Scheme **1**). The azlactones were produced with 100% selectivity without appreciable formation of any other side product under mild reaction conditions. The catalyst can be recovered and reused without loss of its activity, which makes this methodology environmentally benign.

EXPERIMENTAL

All the chemicals were purchased from Aldrich and used without further purification. Melting points of the compounds were determined in open capillary tubes and are uncorrected. Thin layer chromatography (TLC) was performed on UV-active aluminum-backed plates of silica gel (TLC Silica gel 60 F254). ^{1}H-NMR and ^{13}C-NMR spectra were measured on a Bruker 200 MHz spectrometer in $CDCl_3$ with chemical shift given in ppm relative to TMS as internal standard.

CATALYST PREPARATION

The Dawson acid ($H_6P_2W_{18}O_{62}.24H_2O$.) was prepared by the Drechsel/ Drechsel's method from an α/β $K_6P_2W_{18}O_{62}.10H_2O$ isomer mixture. This Dawson-type salt was prepared according to the technique reported by Lyon et al. [43]. Concentrated H_3PO_4 in a 4:1 acid/salt ratio was added to a boiling aqueous solution of $Na_2WO_4.2H_2O$, and the mixture was kept boiling in a reflux system for 8 h. The salt was precipitated by adding KCl, then purified by recrystallization and cooled overnight to 278 K. The product, which is a mixture of the α and β isomers, was filtered, washed and then vacuum-dried for 8 h. The acid was obtained from an aqueous solution of α/β $K_6P_2W_{18}O_{62}.10H_2O$ salt, which was treated with ether and concentrated HCl (37%) solution. The Dawson acid so released formed an addition compound with the ether, which allows it to be separated from the solution. After obtaining the ether solution with the acid, the ether was eliminated by flowing dry air and the remaining solution was placed in a vacuum-desiccator until crystallization.

Silica-supported Wells-Dawson acid ($WD40/SiO_2$) was prepared by wet impregnation of Grace Davison silica (Grade 59, specific area = 250 m^2/g) with an aqueous solution of the synthesized WD acid. A catalyst containing 40 wt% of WD was prepared. After impregnation, samples were dried at room temperature in a vacuum-desiccator for 8h.

CATALYST CHARACTERIZATION

The ^{31}P-MAS-NMR was carried out and the results match literature values [44].

GENERAL PROCEDURE FOR THE SYNTHESIS OF 4-ARYLIDENES-2-PHENYL-5(4)-OXAZOLONES

The reactions were carried out in a glass batch reactor at atmospheric pressure. The aldehyde (1 mmol) and hippuric acid (1 mmol) were dissolved in toluene (3 ml), and the catalyst (1 mmol %) was added to the solution. The resulting mixture was stirred and refluxed for 5 min. Acetic anhydride (1.5 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-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 and ^{1}H-NMR and ^{13}C-NMR. The separation and quantification of reactant and products were performed by preparative liquid chromatography.

CATALYST REUSE

In order to study the reuse of the catalyst, it was washed with toluene (3 ml) after its filtration from the reaction medium, and it was dried in vacuum at 40ºC up to constant weight.

^{13}C-NMR SPECTRAL DATA FOR SELECTED COMPOUNDS

4-Benzylidene-2-phenyloxazol-5-one (Table **6**, entry 1). Yellow needles, 93%, mp 168–169°C (lit. mp 167–168 [20]).^{13}C NMR (100 MHz, $CDCl_3$) = 110.0, 125.6, 128.4, 128.8, 128.9, 131.2, 131.8, 132.4, 133.3, 133.5, 163.6, 167.6.

4-(4-Methylbenzylidene)-2-phenyloxazol-5-one (Table **6**, entry 2). Yellow solid, 92%, mp 142–144ºC (lit. mp 143-144ºC [20]). ^{13}C NMR (100 MHz, $CDCl_3$) = 21.3, 125.6, 128.0, 128.6, 128.9, 129.6, 132.1, 133.1, 133.4, 133.6, 139.0, 163.5, 167.7.

Table 1. Effect of Temperature on Azlactone Yields (%)

Entry	Temperature (°C)	Yield^a (%)
1	60	36
2	80	55
3	105	71
4	110	85

Reaction conditions: aldehyde, 1 mmol; hippuric acid, 1 mmol; acetic anhydride, 1.5 mmol; 0.01 mmol WD bulk; toluene, 3 ml, 60 min. ^{a}Isolated yield.

Table 2. Effect of Silica-Supported Catalyst on Azlactone Yields (%)

Entry	Catalyst	Yield^a (%)
1	WD_{Sop20}	78
2	WD_{Sop40}	93 (85)^b
3	WD_{Sop60}	91

Reaction conditions: aldehyde 1 mmol; hippuric acid, 1 mmol; acetic anhydride, 1.5 mmol; 0.01 mmol WD bulk or supported; toluene 3 ml, 60 min, 110°C ^{a}Isolated yield. ^{b}In bulk condition (comparative purpose).

Table 3. Effect of Amount of Silica-Supported Catalyst on Azlactone Yields (%)

Entry	Catalyst Amount, Mmol (%)	Yield^a (%)
1	0.1	28
2	0.5	54
3	1	93
4	3	94

Reaction conditions: aldehyde, 1 mmol; hippuric acid, 1 mmol; acetic anhydride, 1.5 mmol; 0.4$WDSiO_2$; toluene 3 ml, 60 min, 110°C.

4-(4-Methoxybenzylidene)-2-phenyloxazol-5-one (Table **6**, entry 4). Orange Solid, 92%, mp 157–158 °C (lit. mp 157-158 [20]).^{13}C-NMR (100 MHz, $CDCl_3$) 55.4, 114.5, 125.9, 126.6, 128.1, 128.9, 131.1, 131.9, 133.0, 134.6, 162.2, 162.5, 167.9

RESULTS AND DISCUSSION

The overall process defined as cyclodehydration–condensation reaction was initially studied using benzaldehyde as the substrate (Table **1**). Different reaction conditions were checked, such as reaction temperature, reaction time and catalyst reuse for prepared catalysts (bulk and silica-supported).

The influence of the reaction temperature on azlactone synthesis was investigated using the bulk catalyst (WD_{bulk}), and the results are illustrated in Table **1**. In order to obtain the optimal temperature, four temperatures (110, 105, 80, and 60 °C, Table **1**) were tested. The experimental reaction conditions were: benzaldehyde, 1 mmol; hippuric acid, 1 mmol; acetic anhydride, 1.5 mmol; 0.01 mmol WD_{bulk}; toluene, 3 ml, 1 h. No reaction was observed at 20ºC. A temperature increase leads to a higher azlactone yield. The yield of azlactone for a reaction time of 1 h at 60°C is only 36%, whereas at 110°C the conversion is 85%, which is 2.5 times higher than at 60°C. For this reason, 110°C (toluene reflux) was employed as the ideal temperature to continue with the analysis of other reaction variables.

Table 4. Effect of Time of Reaction on Azlactone Yields (%)

Entry	Reaction Time (min)	Yield^a (%)
1	5	32
2	15	58
3	30	75
4	60	93
5	120	94

Reaction conditions: aldehyde, 1 mmol; hippuric acid, 1 mmol; acetic anhydride, 1.5 mmol; 0.4$WDSiO_2$; toluene, 3 ml, 60 min, 110ºC.

We compared three bulk and supported catalysts with different charges of WD prepared in our laboratory. The experimental reaction conditions were: benzaldehyde, 1 mmol; hippuric acid, 1 mmol; acetic anhydride, 1.5 mmol; 0.01 mmol (active phase) WD bulk or supported; toluene, 3 ml, 1 h and 110ºC. The substrate conversion was analyzed, and additional runs were made in order to see if the supported catalyst presents a deactivation process. Table **2** shows the results obtained for the cyclodehydration reaction to azlactone using supported catalysts with different WD loadings (0.2$WDSiO_2$, 0.4$WDSiO_2$ and 0.6$WDSiO_2$). Additional tests carried out with the support as catalyst indicate that the support has a very low catalytic activity, only 30% after 1 h of reaction. A slight increase in catalytic activity for supported catalysts can be observed (93% and 85%, respectively). An increase in WD loading produces a conversion increment following the sequence 0.2$WDSiO_2$ < 0.4$WDSiO_2$ ≈ 0.6$WDSiO_2$. For the highest WD content, the catalytic activity is similar to that of the 0.4$WDSiO_2$ sample. On the other hand, catalytic tests keeping the amount of active phase constant were done. For this purpose we used a variable mass of catalyst. It can be determined that the conversion values are similar for samples with an acid content in the range 0.4-0.6.

Table **3** displays the effect of the amount of catalyst (0.4$WDSiO_2$) on the yield of azlactone in the reaction. The experimental reaction conditions were: benzaldehyde, 1 mmol; hippuric acid, 1 mmol; acetic anhydride, 1.5 mmol; toluene 3 ml, 1 h, 110ºC, and a variable amount of 0.4$WDSiO_2$ catalyst (0.1%, 0.5%, 1% and 3%, respectively). It can be seen that the conversion of yields increased from 54% to 93% when the amount of 0.4$WDSiO_2$ increased from 0.5% to 1% (Table **3**, entries 2 and 3). A further increase in the amount of 0.4$WDSiO_2$ (3%) caused a very slight increase in azlactone yields (94%, Table **3**, entry 4). Thus 1% of 0.4$WDSiO_2$ is a suitable amount in this reaction.

Table **4** shows the result for azlactone synthesis as a function of reaction time using 0.4$WDSiO_2$ catalyst at a reaction temperature of 110ºC. The experimental reaction conditions were: benzaldehyde, 1 mmol; hippuric acid, 1 mmol; acetic anhydride, 1.5 mmol; 0.4$WDSiO_2$, 0.01 mmol; toluene 3 ml and 110ºC. It can be observed that the yields of azlactone increased with the reaction time up to 1 h and then stayed at a constant level.

The reusability of the catalysts was investigated in the sequential reaction of benzaldehyde with hippuric acid and

Table 5. Catalyst Reuse on 4-Benzylidene-2-Phenyloxazol-5-One Yields (%)

Entry	Cycle	Yield[a] (%)
1	0	93
2	1	90
3	2	90

Reaction conditions: benzaldehyde, 1 mmol; hippuric acid, 1 mmol; acetic anhydride, 1.5 mmol, and 0.01 mmol 0.4WDSop (active phase), temperature 110ºC, toluene, 3 ml, 60 min.
[a]Isolated yield.

Table 6. Preparation of Azlactone from Different Aldehydes

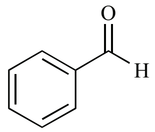
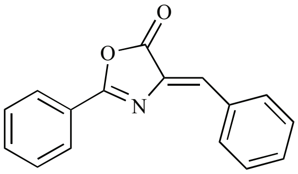
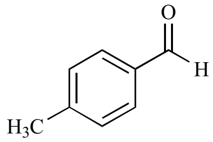
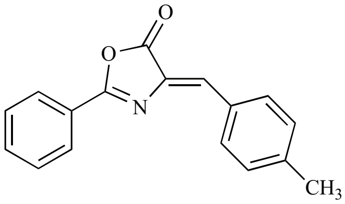
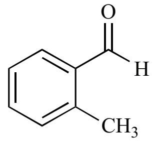
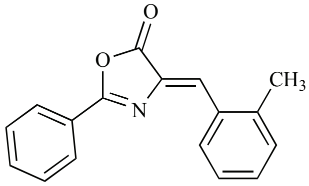
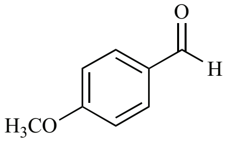
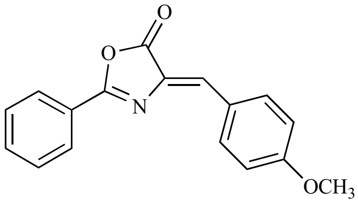
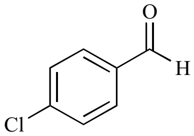
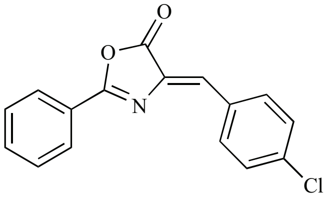
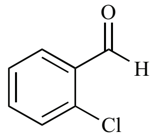
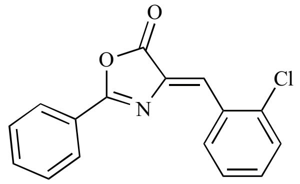
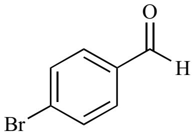
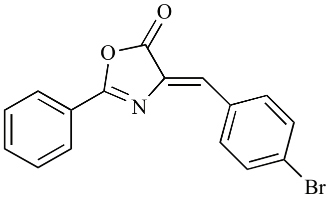
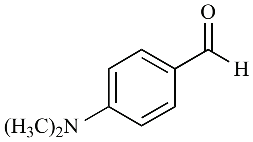
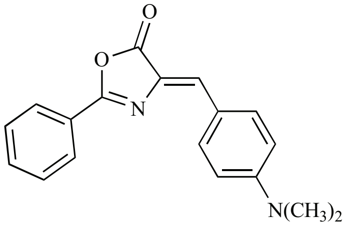
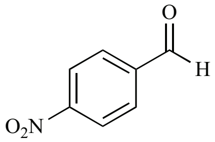
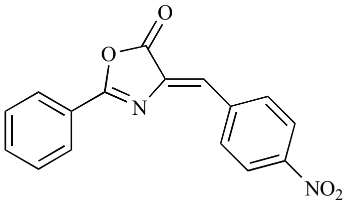
Entry	Aldehyde	Product	Time (min)	Yield[a] (%)
1			60	93
2			60	92
3			90	90
4			30	92
5			75	91
6			90	89

Table 6. cont….

7			75	92
8			30	90
9			120	70

Reaction conditions: the molar ratio of reagents and catalyst was 1:1:1.5:0.01: Reactions were run at 110ºC (toluene reflux). ^{a}Isolated yield

acetic anhydride. At the end of each run the catalyst was removed, washed with toluene, dried in vacuum at 40°C and reused. The results, which are summarized in Table **5**, showed that the catalyst was reused three consecutive runs and no appreciate loss of its catalytic activity was observed. Execution of the reactions under the same conditions using $0.4WDSiO_2$ as catalyst showed 93%, 90% and 90% of azlactone yield, respectively.

Using the optimized conditions, aldehyde, 1 mmol; hippuric acid, 1 mmol; acetic anhydride, 1.5 mmol; $0.4WDSiO_2$, 0.01 mmol; toluene 3 ml and 110ºC, several aldehydes were tested (Table **6**). The yield of the reaction was comparable for both catalysts. In all the experiments, the desired products were obtained with high selectivity. When aldehydes, hippuric acid and acetic anhydride were treated with the supported WD catalysts for 1 h, the azlactones were obtained with very good yields (89%–93%), except for the azlactone substituted with a nitro group (Table **6**, entry 9: 70%). That is to say that in general, no substituent group has a specific effect on the yield. However, a difference in the yield is observed when a para-nitro group is present in the aldehyde molecule. The yield of p-nitro-substituted azlactone is significantly lower than that of the other selected examples. This could be due to the close proximity of both basic oxygen atoms behaving as carbonyl and nitrophenyl groups, respectively [29]. A probable mechanism for the reaction of azlactone synthesis has been described for us in the bibliography [29].

CONCLUSION

In conclusion, we have developed a mild, efficient and environmentally friendly protocol for the synthesis of 4-arylidene-2-phenyl-5(4)-oxazolones (azlactones) *via* condensation of aldehyde, hippuric acid and acetic anhydride in the presence of $H_6P_2W_{18}O_{62}.24H_2O/SiO_2$ ($0.4WDSiO_2$) as recyclable solid acid catalyst. The azlactones were produced with 100% selectivity without appreciable formation of any other side product under mild reaction conditions. The catalyst can be recovered and reused without loss of its activity, which makes this methodology environmentally benign.

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