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ORIGINAL PAPER

Novel and chemoselective one-pot synthesis of 4-arylidene-2-phenyl-5(4*H*)-oxazolones starting from benzyl alcohols promoted by $[(C_{14}H_{24}N_4)_2W_{10}O_{32}]$-[bmim]$NO_3$

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Abstract A new and practical promoter system for one-pot, efficient, chemoselective synthesis of 4-arylidene-2-phenyl-5(4*H*)-oxazolones using $[(C_{14}H_{24}N_4)_2W_{10}O_{32}]$-[bmim]$NO_3$ under solvent-free conditions is described. The present work opens up a new and ecofriendly synthetic route to Erlenmeyer–Plöchl adducts from primary benzyl alcohols in a one-pot operation.

Keywords Azlactone · Aryl alcohol · Ionic liquid · One-pot synthesis · Hybrid polyoxometalates

Introduction

The oxazolone core represents an important structural motif frequently found in numerous natural products that exhibit a wide range of biological activities [1–3]. Among them, 4-arylidene-2-phenyl-5(4*H*)-oxazolones (azlactones) occupy a versatile place in the realm of biological sciences [4, 5]. They have served as precursors to a variety of synthetic targets such as peptides [6], amino acids [7], antitumor compounds [8], antimicrobial compounds [9], biosensors [10], and new heterocyclic compounds [11]. Moreover, these systems are employed in the synthesis of hydrogel supports for in vivo cell growth [12]. Recently, almazolone (Fig. 1), an alkaloid bearing an azlactone unit, has been isolated from the Senegalese alga *Haraldiophyllum sp.* and synthesized experimentally [13].

Accordingly, the development of synthetic routes to produce these heterocycles has received considerable attention. One of the general strategies for synthesis of these compounds includes the protic or Lewis acid-assisted condensation reaction of aryl aldehydes, hippuric acid, and acetic anhydride, known as the Erlenmeyer–Plöchl reaction [14–19]. Even though these methods are suitable for many synthetic conditions, all of these methods are restricted to utilizing aryl aldehydes as a key precursor. Moreover, the volatility, toxicity or instability of some aldehydes limits these methods. Therefore, to overcome these problems, there is a need to broaden the scope of this reaction using safer substrates via a one-pot reaction in combination with "green" chemistry. Alcohols are generally considered to be superior to aldehydes in terms of ease of handling, preparation, toxicity, stability, and functionalization [21–23]. Despite advances in heterocyclic synthesis, no attention has so far been paid to using an alcohol as a substrate in azlactone production.

Investigation of hybrid organic–inorganic polyoxometalates (POMs) with a variety of ionic liquids is a new field of modern catalysts [24]. Moreover, these compounds have been used in thermally stable solid lubricants, biocatalysis, and nanoparticle research [25]. A facile synthetic route to new POM-based ionic liquids (ILs) is therefore appealing. Studying applications of this new class of POMs in organic synthesis has reinforced their importance.

Results and discussion

In this report, we describe extension of our investigations to the preparation of another POM based on a dicationic

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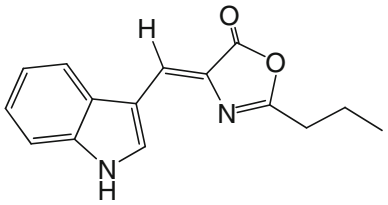


Fig. 1 Almazolone

ionic liquid and investigation of its potential as a new catalyst in azlactone synthesis. Herein we wish to exploit $[(C_{14}H_{24}N_4)_2W_{10}O_{32}]$ (Fig. 2) immobilized on 1-*n*-butyl-3-methylimidazolium nitrate ([bmim]NO_3) for one-pot transformation of aryl alcohols to 4-arylidene-2-phenyl-5(4*H*)-oxazolone derivatives (Scheme 1).

To the best of our knowledge, no report is available in literature using benzylic alcohols as precursors in one-pot azlactone synthesis utilizing hybrid organic–inorganic polyoxometalates immobilized on an ionic liquid. At the outset, we investigated and compared the possibility of forming the product in two ways (Scheme 2).

Path A (traditional manner) comprises: (a) conversion of the alcohol to the aldehyde by $[(C_{14}H_{24}N_4)_2W_{10}O_{32}]$-[bmim]$NO_3$, (b) isolation of the aldehyde, (c) purification of the aldehyde, and (d) conversion of the aldehyde to the corresponding azlactone in the presence of $[(C_{14}H_{24}N_4)_2W_{10}O_{32}]$. In path B, these steps were done in a one-pot transformation and the intermediate (aryl aldehyde) trapped without isolation. This procedure alleviated the necessity of isolating the intermediate aldehyde and vastly improved the yield. For instance, benzyl alcohol, employing the stepwise approach, could be converted to the corresponding azlactone in 41% yield (path A). Next, with further investigation we found that a true one-pot reaction was also possible. Benzyl alcohol was treated with $[(C_{14}H_{24}N_4)_2W_{10}O_{32}]$-[bmim]$NO_3$ and allowed to react at 80 °C. Once the oxidation was complete, as determined by thin-layer chromatography (TLC), the mixture of hippuric acid and acetic anhydride was added and allowed to stir at the same temperature (path B). Reaction of the alcohol in this new one-pot oxidation–cyclocondensation procedure led to a dramatic doubling of the yield of the azlactone (88%). Thus, we turned our attention to optimizing the conditions of this one-pot process for synthesis of azlactones from alcohols.

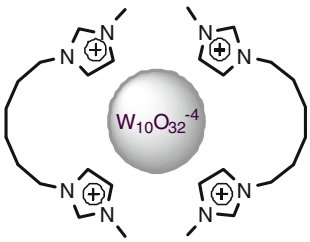
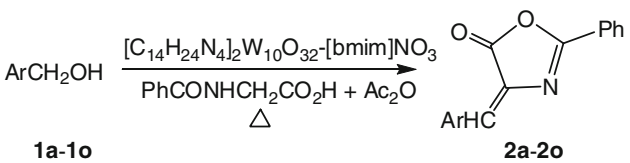
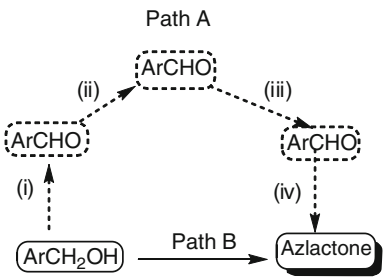


Fig. 2 Di[1,6-bis(3-methylimidazolium-1-yl)hexane] decatungstate



Scheme 1



Scheme 2

The reasonable yield of the desired product indicated that optimization by screening of reaction conditions including the amount of the catalyst, amount of the ionic liquid, and temperature would improve the yield (Table 1).

Initially, the amounts of $[(C_{14}H_{24}N_4)_2W_{10}O_{32}]$ and [bmim]NO_3 were optimized. These results illustrate that the combination of $[(C_{14}H_{24}N_4)_2W_{10}O_{32}]$ with [bmim]NO_3 is essential for this synthesis. Attempts to carry out the reaction in the absence of each of these compounds did not afford the product (Table 1, entries 5 and 6). Further examination confirmed that an oxygen atmosphere is required for this synthesis. In the absence of oxygen, no product was obtained. When the above reaction was carried out with 7 mol% of the POM and 35 mol% of the ionic liquid, the desired product was obtained in excellent yield (Table 1, entry 3). To optimize the reaction temperature, the reactions were carried out at temperatures ranging from 60 to 90 °C. It was found that the highest yield was obtained at 80 °C. Increasing the reaction temperature to 90 °C led to no improvement in yield or reaction time. Therefore, 80 °C was chosen for all reactions.

On the other hand, for proving the effect of the POM and [bmim]NO_3 in the oxidation step, an additional investigation was performed, and the results are summarized in Table 2.

As shown in Table 2, in the presence of $(C_{14}H_{24}N_4)_2W_{10}O_{32}$ using different ionic liquids such as [bmim]PF_6, [bmim]OTf, and TBABr, no aldehyde was detected (entries 1–3). Also, by using KNO_3, *p*-methoxybenzaldehyde was produced in only 40% yield. However, utilization of [bmim]NO_3 surprisingly increased the yield. As shown in the table, $(C_{14}H_{24}N_4)_2W_{10}O_{32}$ catalyzed the

Table 1 Optimization of the reaction conditions

Entry	$[(C_{14}H_{24}N_4)_2W_{10}O_{32}]$/mol%	[bmim]NO_3/mol%	Temperature/°C	Yield/%[a,b]
1	5.5	35	80	75
2	6.5	35	80	90
3	7	35	80	93
4	7.5	35	80	93
5	–	35	80	6
6	7	–	80	0
7	7	25	80	42
8	7	30	80	78
9	7	35	70	90
10	7	35	60	83
11	7	35	90	92

All reactions were conducted with 1 equiv *p*-methoxybenzyl alcohol

[a] After 60 min (containing oxidation and azlactone synthesis steps)

[b] Isolated yield

Table 2 Effect of POMs and ILs in the oxidation of *p*-methoxybenzyl alcohol to the corresponding aldehyde

Entry	POM[a]	IL[b]	Yield of oxidation/%
1	$(C_{14}H_{24}N_4)_2W_{10}O_{32}$	[bmim]PF_6	–
2	$(C_{14}H_{24}N_4)_2W_{10}O_{32}$	[bmim]OTf	–
3	$(C_{14}H_{24}N_4)_2W_{10}O_{32}$	TBABr	–
4	$(C_{14}H_{24}N_4)_2W_{10}O_{32}$	KNO_3	40
5	$K_4W_{10}O_{32}$	[bmim]NO_3	75
6	$[bmim]_2W_{10}O_{32}$	[bmim]NO_3	84
7	$(C_{14}H_{24}N_4)_2W_{10}O_{32}$	[bmim]NO_3	99

All reactions were performed at 80 °C after 15 min in the presence of oxygen atmosphere

[a] 7 mol%

[b] 35 mol%

Table 3 Effect of different promoters in the one-pot conversion of *p*-methoxybenzyl alcohol to the corresponding azlactone

Entry	Promoter	Yield/%
1	CAN[a]-[bmim]Cl[b]	60
2	$Bi(NO_3)_3.5H_2O$[a]-[bmim]Cl[b]	52
3	$NaNO_3$[a]-[bmim]Cl[b]	70
4	$(C_{14}H_{24}N_4)_2W_{10}O_{32}$[a]-[bmim]$NO_3$[b]	93

All reactions were performed at 80 °C after 60 min in the presence of oxygen atmosphere

[a] 7 mol%

[b] 35 mol%

oxidation of *p*-methoxybenzyl alcohol with [bmim]NO_3 (entry 7), and the corresponding aldehyde was produced quantitatively; however, $K_4W_{10}O_{32}$-[bmim]NO_3 or $[bmim]_2W_{10}O_{32}$-[bmim]NO_3 performed this transformation in lower yields (entries 5 and 6). So, both the POM and the ionic liquid are required for this step.

After more investigation, we also found that conversion of the aldehyde to the corresponding azlactone is dependent on the POM, since in the absence of the ionic liquid also this final product was obtained. Thus, in the second step (conversion of aldehyde to azlactone), POM is a key factor and the effect of the ionic liquid is slight.

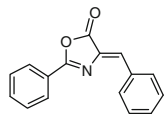
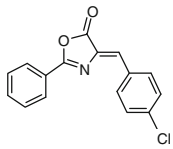
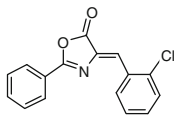
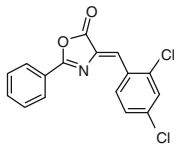
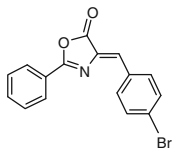
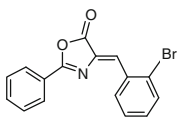
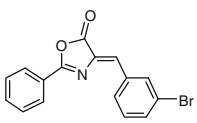
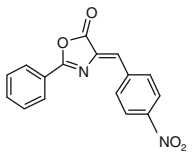
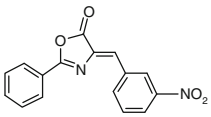
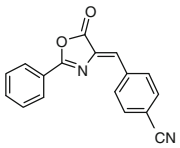
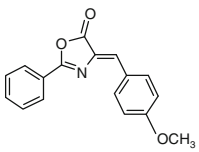
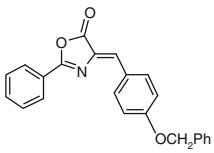
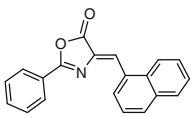
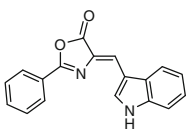
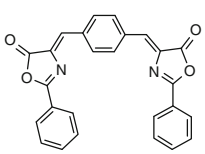
Moreover, to show the ability of other alcohol oxidants in this transformation, we examined the effect of cerium(IV) ammonium nitrate(CAN)-[bmim]Cl, $Bi(NO_3)_3$-[bmim]Cl, and $NaNO_3$-[bmim]Cl in the reaction of *p*-methoxybenzyl alcohol with hippuric acid and acetic anhydride. The obtained results showed that the amount of the corresponding product was 60%, 52%, and 70%, respectively (Table 3).

The optimized one-pot procedure for the synthesis of azlactones from benzyl alcohols involves stirring a mixture of aryl alcohol **1** (1 mmol), $[(C_{14}H_{24}N_4)_2W_{10}O_{32}]$ (7 mol%), and [bmim]NO_3 (35 mol%) at 80 °C until the reaction is completed. Next, addition of 1.2 mmol hippuric acid and 0.027 mol acetic anhydride and further stirring at the same temperature afforded adduct **2** in 87–95% yields (Table 4).

As shown in Table 4, it is clear that, based on the optimized reaction conditions, this procedure is quite general. In most cases, the reaction proceeded with excellent efficiency and broad functional-group tolerance. To expand the scope of benzyl alcohol substrates, various mono- and disubstituted benzyl alcohols containing both electron-withdrawing and electron-donating substituents were used. All displayed high reactivity and afforded the desired products in excellent yields. In addition, polycyclic or heterocyclic methyl alcohols such as 1-naphthalenylmethanol or (1*H*-indol-3-yl)methanol were reactive substrates and provided the desired products **2m** and **2n**, respectively, in excellent yields.

A particularly noteworthy feature of the present protocol is the successful synthesis of bis-azlactone **2o** from 1,4-benzenedimethanol. The wide potential of this promoter makes the proposed procedure an attractive strategy for synthesis of 4-arylidene-2-phenyl-5(4*H*)-oxazolones.

Table 4 One-pot synthesis of 4-arylidene-2-phenyl-5(4*H*)-oxazolones from aryl alcohols promoted by $[(C_{14}H_{24}N_4)_2W_{10}O_{32}]$-[bmim]$NO_3$

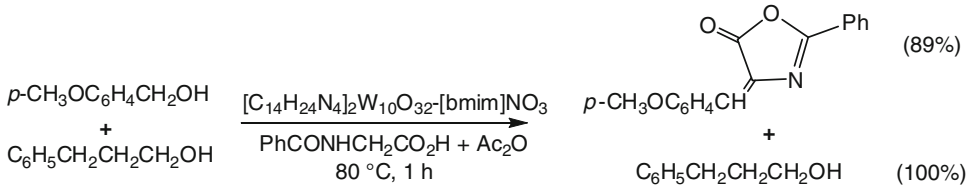
Comp.	Structure	Time/min[a]	Yield/%[b]	M.p./°C	
				Found	Reported
2a		80	88	166	165–166 [27]
2b		140	90	188–190	191 [28]
2c		115	87	162–163	161–163 [27]
2d		120	91	181–183	180–181 [17]
2e		128	90	197–199	197–198 [20]
2f		95	89	141–143	120 [29]
2g		110	94	147–149	147–148 [15]
2h		260	89	237–239	238–240 [19]
2i		250	92	174–176	177 [27]
2j		190	91	285–287	286–288 [30]
2k		60	93	153–155	155 [18]
2l		115	94	152–154	159–161 [31]
2m		68	95	163–165	166–167 [32]
2n		135	92	209–211	210–212 [29]
2o		130	90	280–282	–

[a] Total time (oxidation + azlactone synthesis)

[b] Yields refer to isolated pure products, which were characterized by ^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR, infrared (IR), and CHNS analysis

When aliphatic alcohols such as *n*-butanol were used as substrate in this reaction, only <30% of the corresponding azlactone was produced and some side-products were

Scheme 3



detected in the reaction mixture. These data are consistent with the low yields for preparation of azlactones with aliphatic aldehydes as reported previously. Also, it was found that cinnamyl alcohol or 3-phenylprop-2-yn-1-ol was unchanged under the reaction condition, and no aldehyde or azlactone derivatives were detected after 3 h.

This method was also highly chemoselective. In binary mixtures of benzyl alcohols and alkyl alcohols, the benzyl alcohols were almost quantitatively converted to their azlactone, while other alcohols remained intact and were completely recovered (Scheme 3). These observations may be due to the higher reactivity of benzyl alcohols toward oxidation in comparison with aliphatic alcohols.

The recovered $[(C_{14}H_{24}N_4)_2W_{10}O_{32}]$ could also be reused without any significant loss of its high catalytic performance. The catalyst was separated by simple filtration and washed with ethanol. This catalytic system was easily recyclable after activation at 80 °C under reduced pressure. $[(C_{14}H_{24}N_4)_2W_{10}O_{32}]$ retained its activity after four consecutive reactions.

In summary, we have developed a new, efficient, chemoselective one-pot procedure for synthesis of azlactones via sequential oxidation of alcohols to aldehydes and their Erlenmeyer–Plöchl reaction. The present work opens up a novel one-pot synthetic route to Erlenmeyer–Plöchl adducts starting directly from benzyl alcohols. To the best of our knowledge, this is the first examination of $[(C_{14}H_{24}N_4)_2W_{10}O_{32}]$-[bmim]$NO_3$ as a new promoter in heterocyclic synthesis. Finally, the simple experimental procedure combined with the ease of work-up of the product in the absence of any toxic organic solvents make this method quite convenient and environmentally benign for synthesis of azlactones. Further synthetic study of the present method is underway in this laboratory.

Experimental

All chemicals were purchased from Merck chemical company. 1,6-Bis(3-methylimidazolium-1-yl)hexane chloride $[C_6(MIm)_2Cl_2]$ was synthesized according to the literature [26]. $[(C_{14}H_{24}N_4)_2W_{10}O_{32}]$ was completely characterized by Fourier-transform infrared (FTIR), thermogravimetry (TG), X-ray diffraction (XRD), and scanning electron microscopy (SEM) techniques. All known organic products were identified by comparison of their physical and spectral data with those of authentic samples. Thin-layer chromatography (TLC) was performed on ultraviolet (UV)-active aluminum-backed plates of silica gel (TLC silica gel 60 F254). ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were measured on a Bruker DPX 400 MHz spectrometer in $CDCl_3$ or dimethyl sulfoxide (DMSO)-d_6 with chemical shifts (δ) given in ppm relative to tetramethylsilane (TMS) as internal standard. Coupling constants are given in Hz. Low-resolution mass spectra (LRMS) were recorded on a Bell and Howell 21-490 spectrometer. IR spectra were taken on a FT-IR-Tensor 27 spectrometer in KBr pellets and are reported in cm^{-1}. Melting points were determined using a Stuart Scientific SMP2 apparatus.

Synthesis of di[1,6-bis(3-methylimidazolium-1-yl)hexane]-decatungstate ($[(C_{14}H_{24}N_4)_2W_{10}O_{32}]$)

To a solution of $Na_2WO_4{\cdot}2H_2O$ (5 mmol) in 10 cm^3 H_2O was added 9 cm^3 3 M aqueous HCl, following by boiling until a clear yellow solution was obtained. An aqueous solution of 1,6-bis(3-methylimidazolium-1-yl)hexane chloride $[C_6(MIm)_2Cl_2]$ (10 mmol; dried at 80 °C) was added to this solution, and the precipitate was filtered, washed with water, and dried overnight at 80 °C in vacuum.

General procedure for the synthesis of adducts ***2***

A mixture of aryl alcohol **1** (1.00 mmol) and [bmim]NO_3 (0.33 mmol) in the presence of $[(C_{14}H_{24}N_4)_2W_{10}O_{32}]$ (0.07 mmol) was stirred at 80 °C until the aldehyde was consumed, then hippuric acid (1.2 mmol) and 2.5 cm^3 acetic anhydride were added and the mixture was stirred at the same temperature. After completion of the reaction as indicated by TLC, 5 cm^3 ethanol was added and the mixture stirred for 10 min until a yellow solid precipitated. The mixture was allowed to stand overnight, and then it was cooled in an ice bath. The crude azlactones were obtained after filtration and washing with hot water. Recrystallization from ethanol/water afforded the pure product in 87-95% yield.

(Z,Z)-4,4′-(1,4-Phenylenedimethylidyne)bis(2-phenyl-5 (4H)-oxazolone) (**2o**, $C_{26}H_{16}N_2O_4$)

IR (KBr): $\bar{\nu}$ = 3,039, 1,789, 1,762, 1,653, 1,548, 1,327, 1,159 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.60 (5H, m), 7.65–7.69 (2H, m), 8.21–8.27 (4H, m), 8.32 (5H, s)

ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 125.41$, 128.60, 129.06, 130.08, 132.68, 133.72, 134.64, 135.86, 164.28, 167.38 ppm; MS (EI): $m/z = 420.18$, 287.78, 104.89, 76.88.

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