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Ultrasound Assisted An Efficient Synthesis of Azlactone Derivatives Catalyzed by Ionic Liquid

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Abstract: 2A convenient and environmentally benign route has been developed for the synthesis of 4-Arylidene-2-phenyl-5(4)-oxazolones (Azlactone) derivatives from the condensation of aromatic aldehydes and hippuric acid in acetic unhydride medium in the presence of catalytic amount of 1-benzyl-3-methylimidazolium dihydrogen phosphate ([bnmim]H_2PO_4) acidic ionic liquid under ultrasound at room temperature in moderate to good yields via the Erlenmeyer synthesis. This method affords the present method are mild reaction conditions, short reaction time. Additionally, the ionic liquid was successfully reused for four cycles without significant loss of activity.

Keywords: Azlactone, Ionic liquid,, aldehyde, hippuric acid, Ultrsound

Introduction:

Azlactones, substituted azlactones are important precursor for the synthesis of several biologically active moieties.[1] Erlenmeyer azlactones have been used in a wide variety of reactions as precursors for biologically active peptides [2a] herbicides and fungicides, [2b] and as drugs, pesticides and agrochemical intermediates.[2c] It is also used as precursors for the synthesis of aminoacid,[3] peptides,[4] heterocycles,[5] biosensors,[6] and anti-tumor[7] or anticancer[8] compounds. Due to their widespread applicability, research are continued to search new methods which is most suitable in terms of pollution abatement, yield and time. Generally azlactones are synthesized by Erlenmeyer method, which involve the direct condensation of aldehydes with hippuric acid in the presence of stoichiometric amounts of fused anhydrous sodium acetate as a basic catalyst in acetic anhydride.[9] In recent years, some new reagents have become available for the synthesis of azlactones, such as Al_2O_3-H_3BO_3,[10] supported KF,[11] $Bi(OAc)_3$,[12] $Bi(OTf)_3$,[13] $ZnCl_2$,[14] $Ca(OAc)_2$,[15] and MgO/Al_2O_3.[16] However, many of these acetylation catalysts also suffer from certain drawbacks. The reported catalyst

can cause many problems such as corrosion; while the Lewis acids are often expensive, toxic and unrecoverable. Hence, there is still a great demand for the development of efficient and recoverable acid catalysts to generate azlactones under mild conditions.

Organic chemists from both academia and industry have started giving serious thought to the detrimental effect of non-green processes and chemicals on the environment. As green alternative catalyst, acidic ionic liquids have been studied extensively for use in acid catalyzed reactions.[17] In particular, imidazolium ionic liquids has been successfully used in many organic transformations includes Diels–Alder, [18a] Wittig, [18b] Suzuki cross-coupling, [18c] Hantzsch condensation [16d] In additionally, ionic liquids with acidic counterions like 1-hexyl-3-methylimidazolium dihydrogen phosphate ([hmim]H_2PO_4) [19a] and 1-butyl-3-methylimidazolium chloroaluminate ([bmim] $Cl._2AlCl_3$) [19b] can be used as good acid catalysts. Our group has reported that one-pot synthesis of 3,4 dihydropyrimidin-2-(1H)-ones catalyzed by 1-benzyl-3-methylimidazolium dihydrogen phosphate ([bnmim]H_2PO_4) acidic ionic liquid. [20]

Ultrasound accelerated chemical reactions are well known and proceed *via* the formation and adiabatic collapse of transient cavitation bubbles. Ultrasound irradiation has been demonstrated as an alternative energy source for organic reactions ordinarily accomplished by heating. Many homogeneous and heterogeneous reactions can be conducted smoothly by sonication to provide improved yields and increased selectivities, [21] therefore ultrasound irradiation has been established as an important technique in organic synthesis.

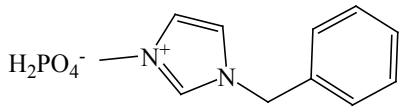
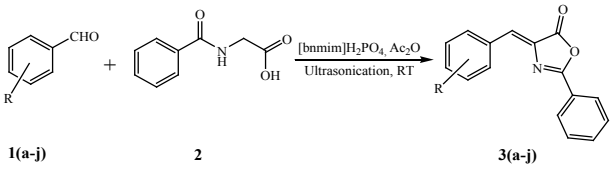


Figure 1: 1-benzyl-3-methylimidazolium dihydrogen phosphate ([bnmim]H_2PO_4)



Scheme

Experimental procedure

Melting points were determined in an open capillary in a paraffin bath apparatus and are uncorrected. The reactions were monitored by TLC and visualized with UV light. IR spectra were recorded on a matrix of KBr with FTIR-4100 (Jasco, Japan) spectrometer. ^{1}H NMR spectra were recorded on Varian NMR spectrometer, Model Mercury Plus (400 MHz) and the chemical shifts are given in ppm relative to TMS as an internal standard.

General Procedure 3(a-j):

A mixture of aromatic aldehyde **1(a-j)** (5 mmol), hippuric acid **2** (5 mmol), acetic anhydride (Ac_2O) (15 mol%) and [bnmim]H_2PO_4 (10 mol%) were taken in a single neck round bottom flask and the flask with the reaction mixture was immersed into the water bath of an ultrasonic cleaner at room temperature for the prescribed time (Table **2)**. The completion of the reaction was monitored by TLC. The product was extracted from diethyl ether (2 × 20 mL), leaving behind [bnmim]H_2PO_4. Organic layer washed by brine solution (2 × 10 mL) and dried over sodium sulfate and removed the solvent on rotary evaporator under reduced pressure. The solid obtained was recrystallized by proper solvent to get pure product. All the products were characterized by IR, ^{1}H NMR and mass spectra and by comparison of their physical characteristics with those of the authentic compounds.

Spectral data of representative compound: 4-Benzylidene-2-phenyloxazol-5-one (3a)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 – 8.20 (m, 2H), 8.20 – 8.17 (m, 2H), 7.61 (t, *J* = 7.4, 1H), 7.53 (t, *J* = 7.7, 2H), 7.51 – 7.42 (m, 3H), 7.25 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 110.0, 125.6, 128.4, 128.8, 128.9, 131.2, 131.8, 132.4, 133.3, 133.5, 163.6, 167.6; IR (KBr) 1784.58, 1724.79, 1648.08, 1553.87, 1449.25, 1295.45, 984.00, 865.88, 767.05 cm^{-1}.

4-(4-Methylbenzylidene)-2-phenyloxazol-5-one (3b)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 – 8.16 (m, 2H), 8.10 (d, *J* = 8.1, 2H), 7.62 – 7.58 (m, 1H), 7.52 (dd, *J* = 10.5, 4.6, 2H), 7.28 (d, *J* = 8.0, 2H), 7.23 (s, 1H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.3, 125.6, 128.0, 128.6, 128.9, 129.6, 132.1, 132.3, 133.1, 133.3, 133.4, 133.6, 139.0, 163.5, 167.7; IR (KBr) 1792.52, 1645.95, 1605.45, 1554.86, 1489.75, 1327.75, 1925.45, 1161.42, 1107.42, 983.52, 858.65, 815.74 cm^{-1}.

4-(4-Methoxybenzylidene)-2-phenyloxazol-5-one (3)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.8, 2H), 8.16 (d, *J* = 7.4, 2H), 7.59 (t, *J* = 7.4, 1H), 7.52 (t, *J* = 7.5, 2H), 7.21 (s, 1H), 7.00 (d, *J* = 8.9, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 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; IR (KBr) 1789.14, 1770.82, 1654.15, 1596.78, 1512.40, 1448.76, 1309.91, 1266.52, 1162.39, 1031.25, 831.65 cm^{-1}.

4-(But-2-enylidene)-2-phenyloxazol-5-one (3j)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.06 (m, 2H), 7.61 – 7.55 (m, 1H), 7.49 (dd, *J* = 9.7, 5.3, 2H), 6.97 (d, 1H), 6.52 – 6.37 (m, 1H), 2.02 (d, *J* = 7.1, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 19.4, 127.3, 128.0, 128.8, 132.5, 132.9, 133.2, 144.2, 145.5, 161.9, 167.0; IR (KBr) 3034.94, 2962.14, 2938.03, 2913.44, 1789.14, 1762.14, 1654.63, 1556.76, 1449.73, 977.25, 882.27, 860.58, 780.37 cm^{-1};

Table 1. Effect of different acidic ionic liquids for the synthesis of 4-benzylidene-2-phenyloxazol-5-one (**3a**)[a]

Entry	Ionic liquid	Time (min)	Yield (%)[b]
1	[hdmim] H_2PO_4	90	82
2	[hmim] H_2PO_4	80	84
3	[bmim] H_2PO_4	70	89
4	[bnmim] H_2PO_4	40	92

[a] **1a** (5 mmol) treated **2** (5 mmol) with Ac_2O (15 mmol) in the presence of different acidic ionic liquids under ultrasound at room temperature.[b] Isolated yield

Table 2. Synthesis of azalactone derivatives catalysed by [bnmim]H_2PO_4.

Entry	Aldehyde	Time (min)	Yield (%)[a]	Melting Point (°C)	
				Found	Reported
3a	C_6H_4CHO	40	92	168-170	168-169[22]
3b	4-MeC_6H_4CHO	45	91	142-143	143-144[22]
3c	4-$MeOC_6H_4CHO$	50	84	158-160	155-157[22]
3d	2-ClC_6H_4CHO	50	90	159-160	159-16[22]
3e	4-ClC_6H_4CHO	50	92	185-186	186-187[22]
3f	3-ClC_6H_4CHO	45	92	152-154	155[22]
3g	3-$NO_2C_6H_4CHO$	40	86	166-168	166-167[22]
3h	4-$NO_2C_6H_4CHO$	40	90	238-240	240-241[22]
3i	Furfural	60	88	168-170	170[14]
3j	Crotonaldehyde	50	85	150-152	152[14]

[a]Yield refers to isolated product

Table 3. Recycling of [bnmim]H_2PO_4 for the synthesis of 4-benzylidene-2-phenyloxazol-5-one (**3a**)[a]

Entry	Cycle[b]	Yield (%)[c]
1	Fresh	92
2	1st	90
3	2nd	88
4	3rd	87
5	4th	87

[a] **1a** (5 mmol) treated **2** (5 mmol) with Ac_2O (15 mmol) in the presence of [bnmim]H_2PO_4 (15 mol%) under ultrasound at room temperature. [b]Reaction time-40 min. [c] Isolated yield

Results and Discussion:

In continuation of our development of novel synthetic methodologies, [23] herein, we would like to report a facile, efficient and green methodology for the synthesis of azalactone derivatives from various aryl aldehydes with hippuric acid in the presence of catalytic amount of [bnmim]H_2PO_4 (Figure **1**) under ultrasound at room temperature.

To investigate the optimum condition for reaction of benzaldehyde, hippuric acid and acetic anhydride in presence of catalytic amount of acidic ionic liquid under ultrasound at room temperature has been considered as the standard model reaction. We were screened different acidic ionic liquids such as, 1-hexyl-2,3-dimethylimidazolium dihydrogen phosphate([hdmim]H_2PO_4), 1-hexyl-3-methylimidazolium dihydrogen phosphate ([hmim]H_2PO_4), 1-butyl-3-methylimidazolium dihydrogen phosphate ([bmim]H_2PO_4) and 1-benzyl-3-methylimidazolium dihydrogen phosphate ([bnmim]H_2PO_4) for the model reaction. By using, [bmim]H_2PO_4 and [bnmim]H_2PO_4, the desired product was obtained in satisfactory yields (Table **1**, entry 3, 4). By considering the reaction time and yield of product, [bnmim]H_2PO_4 was selected as the optimum catalyst to promote the azalactone derivatives. To check the activity of catalyst, we have carried out same reaction without catalyst but product yield was very less (39%) and consume much time also. It means that the catalyst play important role in the reaction.

By encouraging this result, a wide variety of aromatic aldehydes condensed with hippuric acid in acetic anhydride medium. In a similar fashion, we have taken the different aryl aldehydes containing electron-withdrawing or electron-donating groups with various active methylene compounds. They all gave the expected results with good to excellent yields at mild reaction conditions and the results are summarized in Table **2.** Thus, this is an excellent method for the synthesis the azalactone derivatives.

Further investigation was the reusability of catalyst is important for the large-scale operation and industrial point of view. Therefore, the reusability of [bnmim]H_2PO_4 was examined in the model reaction under optimized reaction condition and it was observed that the [bnmim]H_2PO_4 was successfully reused for four cycles without significant loss of activity (Table **3**).

Conclusion:

In conclusion, we report here a [bnmim]H_2PO_4 is highly efficient catalyst for the synthesis of azalactone derivatives from various aldehydes, hippuric acid with acetic anhydried. Aromatic aldehyde bearing electron-donating and electron withdrawing groups did not affect on yield of products. The noteworthy merits offered by this methodology are cleaner reactions, mild reactions condition, simple work-up procedures and good to excellent yields. In addition, the

[bnmim]H_2PO_4 was successfully reused for four cycles without significant loss of activity, which makes the present protocol is more economic and environmentally benign.

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