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A Green Protocol for Erlenmeyer Plöchl Reaction by Using [bmIm]OH

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ABSTRACT

An evaluation of task specific basic ionic liquid [bmIm]OH in the Erlenmeyer Plöchl reaction was performed. [bmIm]OH affords fast reactions, in the absence of solvent with good yields. Green reaction conditions and reusability of catalyst are the most remarkable features of this synthetic method.

Keywords: Erlenmeyer Plöchl reaction, basic ionic liquid, [bmIm]OH.

INTRODUCTION

Erlenmeyer azlactones have been used in a wide variety of reactions as precursors for biologically active molecules [1], herbicides and fungicides [2], pesticides and agrochemical intermediates [3], anti-hypertensives [4] and in the asymmetric synthesis of amino acids [5]. Synthesis of oxazolone involves the condensation of aromatic aldehydes and hippuric acid with a stoichiometric amount of fused sodium acetate in the presence of acetic anhydrides as the dehydrating agent this reaction is known as the Erlenmeyer Plöchl reaction [6]. In literature numbers of methods are reported for the synthesis of azalactones [6-18] involving the use of sodium acetate [13], anhydrous zinc chloride [14], alumina [15], KPO_4 [16], calcium acetate [17] are the recent examples. Microwave assisted synthesis of azalactone by Erlenmeyer Plöchl reaction is also reported [18].

Green organic synthesis has attracted many researchers and thus has considerable awareness of applications of environmentally benign reaction media such as of ionic liquids as solvent [19], catalysts [20], and reagents [21]. Recently, basic functionalized and task specific ionic liquids such as- [bmIm]OH (Figure1) have been extensively applied in different organic reactions such

as Heck reaction [22], Henry reaction [23], Aldol condensation [24], Knoevenagel condensation [25], Diels-Alder reaction [26], heterocyclic synthesis [27].

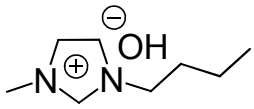


Figure 1. Structure of 1-n-butyl-3-methylimidazolium hydroxide ([bmIm]OH).

EXPERIMENTAL SECTION

Progress of reaction was monitored by silica gel-G coated TLC plates in Ethyl acetate: Hexane system (5:5). The spot was visualized by exposing dry plate in iodine vapours. Melting points were determined by the melting point determination apparatus (TEMPO) in open capillary tubes and are uncorrected. Proton NMR spectra were recorded on Bruker Advance II 400 & 200 NMR Ultra Shield Spectrometer using $CDCl_3$ as a solvent and tetramethyl silane as internal standard. Chemical shift value is expressed in delta parts per million (ppm).

General Procedure for preparation 4-(4-Benzylidene)-2-phenyl-5(4*H*) oxazolone (**3a**)

A mixture of hippuric acid **1** (100 mg, 0.558 mmol),benzaldehyde **2a** (71 mg, 0.669 mmol), acetic anhydride(68mg, 0.669 mmol) in [bmIm]OH (266 mg,1.67 mmol) was stirred at RT for 90min. After completion of reaction (indicated by TLC), 5 ml of water was added and the product was extracted with ethyl acetate (3 × 10 ml). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude product, it was recrystallized from ethanol to afford pure product **3a** 29 (68mg) with 71% yield. After isolation of the product, the remaining aqueous layer containing the ionic liquid was washed with ether (10 ml) to remove any organic impurity, dried under vacuum at 90 ^oC to afford [bmIm]OH, which was used in subsequent reactions. All other oxazolones **3b**-**3m**29 were prepared using above experimental procedure.

Spectroscopic data of representative compounds

4-(4-Benzylidene)-2-phenyl-5(4H)-oxazolone (**3a**).mp. 165-167 ^oC (lit.[15] mp 167–168 ^oC); 1H NMR (400MHz, CDCl3): 8.22-8.18 (m, 4H), 7.65-7.55 (m, 3H) 7.52-7.45 (m, 3H), 7.26 (s, 1H).

4-(4-Methylbenzylidene)-2-phenyl-5(4H) oxazolone **(3b)**. mp. 143-145 ^oC (lit.[15] mp 143–144 ^oC); 1H NMR (400 MHz, CDCl3): 8.19 (dd, *J*= 8.3, 1.2 Hz, 2H), 8.12 (d, *J*= 8.1 Hz, 2H), 7.62 (dd, *J*= 10.5, 4.3 Hz, 1H), 7.52-7.58 (m, 2H), 7.28 (d, *J*= 8.0 Hz, 2H), 7.23 (s,1H), 2.43 (s, 3H).

4-(4-Fluorobenzylidene)-2-phenyl-5(4H) oxazolone (3c). mp. 181-183 ^oC (lit.[15] mp 183–185 ^oC); 1H NMR (400 MHz, CDCl3): 8.18-8.25 (m, 2H), 8.14 (dd, *J*=8.3, 1.1 Hz, 2H), 7.59 (t, *J*= 7.4 Hz, 1H), 7.50 (t, *J*= 7.6Hz, 2H), 7.17 (s, 1H), 7.13 (t, *J*= 8.7 Hz, 2H).

4-(4-Bromobenzylidene)-2-phenyl-5(4H)-oxazolone (3d). mp 204-206 ^oC (lit.[16] mp 204 ^oC); 1H NMR (400MHz, CDCl3): 8.17 (d, *J*= 7.4 Hz, 2H), 8.06 (d, *J*= 8.5Hz, 2H), 7.62 (dd, *J*= 15.4, 8.1 Hz, 3H), 7.54 (t, *J*=7.8Hz, 2H), 7.15 (s, 1H).

4-(4-Chlorobenzylidene)-2-phenyl-5(4H) oxazolone (*3e*). mp. 193-195 ^{o}C (lit.[16] mp 196 ^{o}C); 1H NMR (400MHz, CDCl3): 8.19 (s, 1H), 8.18 (d, *J*= 1.4 Hz, 1H),8.16 (d, *J*= 1.8 Hz, 1H), 8.15 (s, 1H), 7.61-7.65 (m,1H), 7.55 (t, *J*= 7.6 Hz, 2H), 7.42-7.49 (m, 2H), 7.19 (s,1H).

***4-(4-Nitrobenzylidene)-2-phenyl-5(4H) oxazolone* (*3f*)**. mp 234-236 ^{o}C (lit.[16] mp 238 ^{o}C); 1H NMR (400MHz, CDCl3): 8.33-8.39 (m, 2H), 8.28-8.34 (m, 2H),8.20 (dd, *J*= 8.3, 1.1 Hz, 2H), 7.62-7.69 (m, *1H), 7.56(dd, J= 10.7, 4.8 Hz, 2H), 7.20 (s, 1H).*

***4-(4-Methoxybenzylidene)-2-phenyl-5(4H)-oxazolone*(3g)**. mp 155-157 oC (lit.[15] mp 157-158 oC); 1H NMR(400 MHz, CDCl3): 8.15-8.20 (m, 4H), 7.57-7.63 (m,1H), 7.51-7.58 (m, 2H), 7.23 (s, 1H), 6.98-7.06 (m,2H), 3.92 (s, 3H).

***4-(2-Pyridinecarboxylidene)-2-phenyl-5(4H)-oxazolone* (3h)**. mp 165-168 ^{o}C (lit.[15] mp 168-169 ^{o}C);1H NMR (400 MHz, CDCl3) 8.78 (d, *J*=5.5 Hz, 2H),8.23 (d, *J*= 7.3 Hz, 2H), 8.03 (d, *J*= 5.8 Hz, 2H), 7.70 (t,*J*= 7.4 Hz, 1H), 7.60 (t, *J*= 7.6 Hz, 2H), 7.15 (s, 1H).

***4-(2-Thiophenecarboxylidene)-2-phenyl-5(4H)-oxazolone* (3i)**. mp 170–173 ^{o}C (lit.[15] mp 174-175 ^{o}C);1H NMR (400 MHz, CDCl3) 8.14-8.19 (m, 2H), 7.70(d, *J*=5.1 Hz, 1H), 7.63 (d, J *J*= 3.7 Hz, 1H), 7.62–7.58(m, 1H), 7.52 (t, *J*=7.6, 2H), 7.48 (s, 1H), 7.10-7.15 (m,1H).

4-(2-Furanylidene)-2-phenyl-5(4*H*)-oxazolone (3j).mp 174–176 oC (lit.[15] mp 175-176 oC); 1H NMR (400MHz, CDCl3) 8.13-8.22 (m, 1H), 7.72 (d, *J*=1.2, 1H),7.65 (dd, *J*=14.5, 5.5 Hz, 2H), 7.54 (dd, *J*=17.5, 11.5,2H), 7.30 (s, 1H), 7.21(s, 1H), 6.65-6.70 (m, 1H).

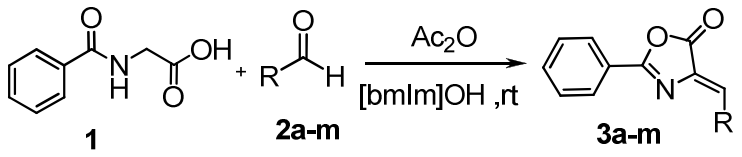
4-(2-Naphthylidene)-2-phenyl-5(4*H*) oxazolone (**3k**) .mp. 166-168^{o}C (lit.[13] mp 167 ^{o}C); 1H NMR (400 MHz,CDCl3): 9.10 (d, *J*=7.4 Hz, 1H), 8.38 (d, *J*=8.5 Hz,1H), 8.29 (dd, *J*= 8.3, 1.2 Hz, 2H), 8.20 (s, 1H), 8.03 (d,*J*= 8.2 Hz, 1H), 7.97 (d, *J*= 7.9 Hz, 1H), 7.68-7.72 (m,3H), 7.59-7.62 (m, 3H).

***4-(2-Propylidene)-2-phenyl-5(4H)-oxazolone* (3l)**. mp 84–86 ^{o}C (lit.[15] mp 86-87 ^{o}C); 1H NMR (400 MHz,CDCl3) 8.11 (d, *J*= 7.4 Hz, 2H), 7.59 (t, *J*=7.4 Hz,1H), 7.52 (t, *J*=7.6 Hz, 2H), 6.66 (t, *J*=8.0 Hz, 1H),2.72-2.79 (m, 2H), 1.23 (t, *J*=7.2 Hz, 3H).

4-(2-Ethylidene)-2-phenyl-5(4*H*)-oxazolone (3m). mp 69-71^{o}C (400 MHz, CDCl3) 8.05-8.10 (m, 2H), 7.56-7.61 (m, 3H), 6.79-6.82 (q, *J*= 6.6 Hz, 1H), 2.75–2.64(d, *J*= 6.6 Hz, 3H).

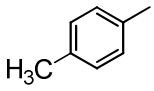
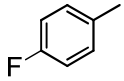
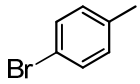
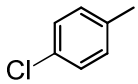
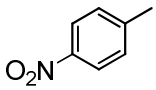
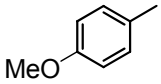
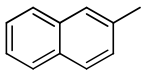
RESULTS AND DISCUSSION

Our new approach reported herein involved the use basic ionic liquid 1-*n*-butyl-3-methylimidazoliumhydroxide [28] [bmIm]OH as catalyst and reaction medium for the Erlenmeyer Plöchl reaction at room temperature under solvent-free conditions. We studied the reaction of hippuric acid **1,** benzaldehyde **2a** and acetic anhydride in ionic liquid [bmIm]OH, 4-(4- Benzylidene)-2-phenyl-5-(4*H*) oxazolone **3a** was isolated from the reaction mixture (Scheme 1).



Scheme 1 Condensation of hippuric acid with aldehyde.

Table 1 Erlenmeyer Plöchl reaction with different aldehydes

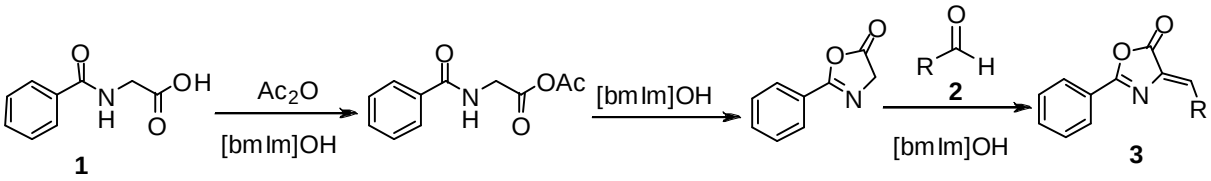
Entry	RCHO (**2**)	Product (**3**)	%Yield	Reaction Time (min)
1		**3a**	81	90
2		**3b**	84	100
3		**3c**	85	90
4		**3d**	91	90
5		**3e**	83	90
6		**3f**	87	90
7		**3g**	80	120
8		**3h**	60	150
9		**3i**	73	90
10		**3j**	74	90
11		**3k**	89	90
12	n-C_3H_7-	**3l**	65	60
13	C_2H_5-	**3m**	62	60

** Isolated yields.*

This clearly indicated that basic ionic liquid [bmIm]OH catalyzes the Erlenmeyer Plöchl reaction condition. Reactions of substituted aromatic and aliphatic aldehydes with hippuric acid, under above reaction conditions furnished, substituted oxazolones (Erlenmeyer azalactones) in good to moderate yields (Table 1).

Aromatic aldehydes with electron withdrawing group (entry **3-6**) gave good yields as compared to that of electron donating group on the aromatic ring (entry **2**, **7**, **11**). On the other hand when aromatic heterocyclic aldehydes were used moderate yields were obtained (entry **8-10**). Aliphatic aldehydes are also reacts under these conditions but gave lower yields as compare to aromatic aldehydes (entry **12, 13**), since unwanted aldol product forms on prolonged reaction time.

The ionic liquid used in the reaction was recovered from aqueous layer and washed with diethyl ether to remove any organic impurities and dried under vacuum to get the pure ionic liquid and is reuse for the above reactions. We have tested reusability of ionic liquid for compound **3f**, upon use of three times, showed no loss of its activity and does not vary yield of final product. The results were successfully reproduced on 0.1g, 5g and 25g scale for the compound **3f** with 87%, 90% and 90% yields respectively.



Scheme 2. The plausible reaction pathway for synthesis of oxazolone.

CONCLUSION

Conclusively, we have developed a mild, efficient and environmental friendly method for Erlenmeyer Plöchl reaction using reusable basic ionic liquid [bmIm]OH as a catalyst as well as reaction medium, in low reaction time and comparatively high yields.

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