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Research Article

The Zwitterionic Imidazolium Salt: First Used for Synthesis of 4-Arylidene-2-phenyl-5(4H)-oxazolones under Solvent-Free Conditions

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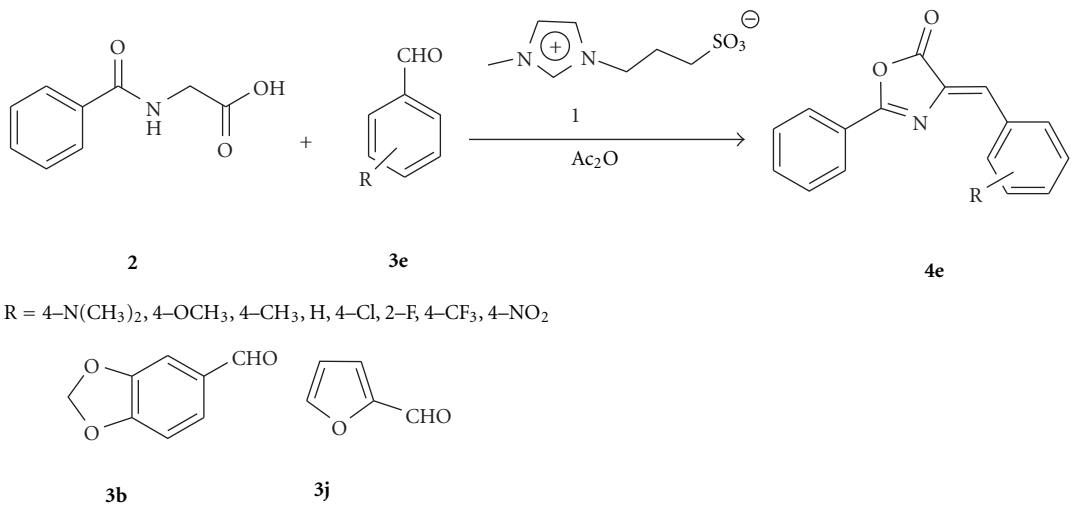
The zwitterionic imidazolium salt was prepared and characterized by ^{1}H NMR. It was first used for synthesis of azlactones via Erlenmeyer synthesis from aromatic aldehydes and hippuric acid under solvent-free conditions. It was found that aldehyde substituents play an important role in these reactions. Better conversions and therefore higher isolated yields were observed when electron-withdrawing groups (EWG-) were present in the aromatic aldehyde. Opposite results were shown when electron-donating groups (EDG-) were present in the aromatic aldehyde. However, azlactones were obtained in moderate to high yields.

1. Introduction

4-Arylidene-2-phenyl-5(4H)-oxazolones are very important intermediates for the synthesis of a variety of bioactive molecules, fine chemicals, and precursors of several biologically active molecules such as amino acids and peptides [1]. These compounds are especially active as anticancer [2], antitumor [3], and inhibitors of central nervous system. Besides, these compounds are unique precursors for the synthesis of amino acids, peptides [4], heterocyclic compounds [5], and biosensor [6, 7]. In fact, these precursors could be synthesized by Horner-Emmons, Heck, or Erlenmeyer-PlÖchl [8] reactions followed by a complementary asymmetric hydrogenation reaction. The most common route to oxazolones involves the condensation of aromatic aldehydes and hippuric acid with a stoichiometric amount of fused sodium acetate in the presence of acetic anhydride as the dehydrating agent [9], such methodology is known as the Erlenmeyer-Plöchl reaction [1].

Since the first report on the synthesis of azlactones published in 1883, a number of catalysts have been developed in recent years. For example, lead acetate [10], SO_3 in dimethylformamide [11], perchloric acid [12], polyphosphoric acid [13], carbodiimides [14], anhydrous zinc chloride [15], $Bi(OAc)_3$ [16], $Bi(OTf)_3$ [17], $Ca(OAc)_2$ [18], KF-alumina [19], $Yb(OTf)_3$ [20], $POCl_3$ [21], $H_3PW_{12}O_{40}$ [22], Sm [22], $RuCl_3$ [22], Al_2O_3 [23], organic bases [1, 24], K_3PO_4 [25], and organic-inorganic hybrid polyoxometalates [26] have been used to perform this condensation. However, some of these procedures have important drawbacks, such as the use of water-sensitive catalyst [11, 15, 19], the use of noble metal/or salts as catalysts [16, 20, 22], rigorous conditions [12, 21, 25], and the use of toxic reagents [1, 10, 12, 21, 25]. Additionally, many literatures [15–23, 26] show that the aldehydes bearing electron-donating groups (EDGs, such as $-NR_2$, $-NHR$, $-NH_2$, $-OH$, $-OR$, $-OCOR$, and $-CH_3$) were more reactive than electron-withdrawing groups (EDGs, such as $-NO_2$, $-CF_3$, $-CCl_3$, $-CN$, $-COOH$, $-CO_2R$, and $-F$). Only few reports [1, 24, 25] show opposite results. Then, there is a need for the development of environmentally benign methods, for example solvent-free condition, nontoxic reagents, mild reaction, simpler workup, and EDGs-active.



Scheme 1: The zwitterionic imidazolium salt (**1**) catalyzed the Erlenmeyer reaction.

Recently, Rostami has reported a new organic-inorganic hybrid polyoxometalates for the catalytic Erlenmeyer-Plöchl reaction involved using $[bmim]_3PW_{12}O_{40}$ and $[bmim]_4W_{10}O_{32}$ as catalysts [26]. They found that the ion identity has an important impact on its property, and the introduction of [bmin] ion resulting more efficient than that of the others (such as K^+). Furthermore, the using of $PW_{12}O_{40}{}^{3-}$ and $W_{10}O_{32}{}^{4-}$ will cause environmental problems. Besides, the aldehydes bearing electron-donating groups (EDGs) were given higher product yield and short time. Recently, zwitterionic salts have become research topic due to high ion density and high matrix mobility at ambient temperature [27]. Hajra has recently reported that zwitterionic-type molten salt may act as a bifunctional organocatalyst in the aza-Henry reaction [28] and for synthesis of 2-amidoalkyl and 2-carbamatoalkyl naphthols [29]. The imidazolium salt (**1**) contained [bmim] as cation and sulfonate as anion by covalent binding. According to [26], we want to know whether the introduction of sulfonate as anion instead of $PW_{12}O_{40}{}^{3-}$ and $W_{10}O_{32}{}^{4-}$ could impact on its catalytic property. Interested in this question and our continual research in the Erlenmeyer reaction [20], we report here the preparation, characterization, and catalytic activity of the imidazolium salt (**1**) in the catalyzed Erlenmeyer reaction for synthesis of azlactones under solvent-free conditions (Scheme 1).

2. Results and Discussion

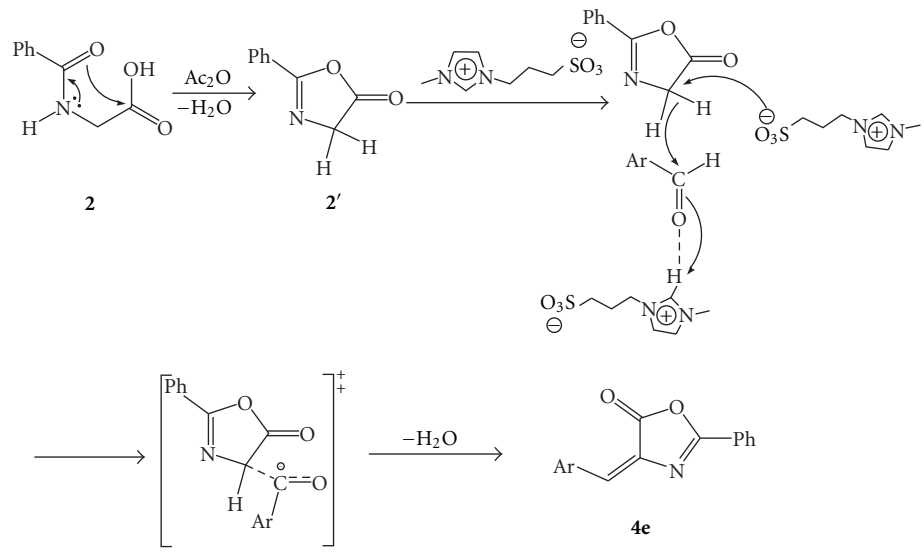
The imidazolium salt (**1**) was synthetized [27] and characterized by ^{1}H NMR. In order to evaluate the catalytic activity of sulfonate, several sulfonates such as imidazolium salt (**1**), methanesulfonic acid, and sulfamic acid were tested in the Erlenmeyer reaction. The results are reported in Table 1. It was found that imidazolium salt (**1**) (Table 1, entry 1) provided azlactone **4e** in the highest isolated yield in very simple procedure and was therefore selected for further study.

Table 1: Evaluation of several sulfonates in the Erlenmeyer reaction.

Entry	Catalyst	Reaction temperature (°C)	Reaction time (h)	Isolated yields (%)[a]
1	Imidazolium salt (**1**)	60	4	76
2	CH_3SO_3H	60	4	16
3	NH_2SO_3H	60	4	7

[a]Based on benzaldehyde; isolated yields based on benzaldehyde; 5 mmol benzaldehyde, 5.5 mmol hippuric acid, 10 mmol% catalyst, and 15 mmol acetic anhydride were used.

The overall process defined as the Erlenmeyer reaction was initially studied using benzaldehyde **3e** as the substrate (Table 2). As shown in Table 2, different conditions have been conducted such as the amount catalyst, temperature, and reaction time. The amounts of textbf1 were tested, and it was found that 5 mmol% of **1** was enough to accomplish the reaction (Table 2, entries 2–5) when 10 mmol% of stoichiometric amount were required as previously reported. Increasing the amount of catalyst did not obviously improve the yield. Besides, 2-phenyloxazol-5-one was found as by-product when used without catalyst in the reaction which was in accordance with [23]. 2-phenyloxazol-5-one was proved as important intermediate in the Erlenmeyer reaction. Similarly, reaction temperature and time were also investigated. The isolated yield was low (15%, Table 2, entry 6) as the condensation of hippuric acid to 2-phenyloxazol-5-one needs high temperature. However, some unknown by-products were formed when reaction temperature heated up to reflux temperature and caused lower yield than the yield in 60°C. In the reflux temperature, heavy slurry was found causing initial reactor agitation problems and an extended process reaction time [24]. It was found that four hours seem to be the optimum reaction time as shown in Table 2 (entries 10–13). Extended time was not available to higher yield (Table 2, entry 13).



Scheme 2: A plausible reaction mechanism.

Table 2: Reaction conditions in the Erlenmeyer reaction.

Entry	The amount of catalysts (mmol %)	Reaction temperature (°C)	Reaction time (h)	Isolated yields (%)[a]
1	0	60	4	41[b]
2	2.5	60	4	67
3	5	60	4	75
4	10	60	4	76
5	20	60	4	78
6	5	25	24	15
7	5	40	4	56
8	5	60	4	75
9	5	Reflux temperature	4	62
10	5	60	1.5	53
11	5	60	2.5	56
12	5	60	4	75
13	5	60	5	75

[a]Based on benzaldehyde; isolated yields based on benzaldehyde; 5 mmol benzaldehyde, 5.5 mmol hippuric acid and 15 mmol acetic anhydride were used.
[b]Not isolated yield, some by-products were found.

To explore the scope of our catalyst, a wide variety of aldehydes were investigated in this system including aromatic and aliphatic aldehdyes (Table 3, entries 1–12). Unfortunately, aliphatic aldehyde cannot be activated in this system (Table 3, entries 11-12). Interestingly, aromatic aldehyes with the electron-withdrawing groups (EWG) were present more active than that of opposite aldehydes (Table 3, entries 1–9). EDG aldehydes resulted in lower conversion and longer reaction time. Similar phenomenon was only mentioned by Thomas's research group [1, 24, 25]. Compared to the previous report [26], it was thought that the existence of [bmin] made high catalyst activity of $[bmim]_3PW_{12}O_{40}$ and $[bmim]_4W_{10}O_{32}$. According to this theory and our research, it can be deduced that the existence of sulfonate may cause the different electronic effect, and a supposed reaction mechanism was given [28, 29] in Scheme 2. 2-phenyloxazol-5-one (**2′**) was first generated in condensation reaction which happened in the presence of acetic anhydride as the dehydrating agent. The imidazolium salt could activate both aldehydic carbonyl oxygen and acidic hydrogen of 2-phenyloxazol-5-one (**2′**). The zwitterionic imidazolium salt (**1**) may act as a bifunctional organocatalyst in this reaction. The electrophilic activation of the aldehyde carbonyl is expected to take place through hydrogen bond formation with C-2 hydrogen atom of the imidazolium moiety. Similar mechanisms were indicated in the aza-Henry reaction [28] and aza-Michael addition [29].

3. Conclusions

In summary, imidazole-based zwitterionic-type molten salts are a new class of catalyst for the synthesis of 4-arylidene-2-phenyl-5(4H)-oxazolones through the Erlenmeyer reaction under solvent-free conditions. This present procedure is equally effective in aryl aldehydes with electron-withdrawing groups. The nonhazardous experimental conditions, ease of reaction, short reaction times, high yields, and metal-free catalyst are the notable advantages of this procedure. To the best of our knowledge, this is the first report of the Erlenmeyer reaction, promoted by a zwitterionic imidazolium salt under solvent-free conditions. The investigation of the mechanism of this reaction and the use of chiral zwitterions are underway and will be reported in due course. Thus, it provides a better and more practical alternative to the existing methodologies.

Table 3: Preparation of azlactones from different aldehydes.

Entry	R (aldehyde)	Reaction time (h)	Azlactones	Isolate yields (%)[a]	Mp found (°C)	Mp lit. (°C)
1	4-$N(CH_3)_2$	5.5	**4a**	70	211–213	214 [25]
2	Heliotropin	5	**4b**	67	197–199	199 [30]
3	4-OCH_3	5	**4c**	62	155-156	159 [25]
4	4-CH_3	6	**4d**	40	143-144	144 [25]
5	H	4	**4e**	75	168-169	166 [25]
6	4-Cl	5.5	**4f**	82	196-197	196 [25]
7	2-F	4	**4g**	55	166-167	168 [31]
8	4-CF_3	3	**4h**	85	173-174	174 [32]
9	4-NO_2	3	**4i**	89	240-241	239 [25]
10	2-Furaldehyde	5	**4j**	35	170–172	169 [25]
11	Isobutyraldehyde	5	—	ND[b]	—	—
12	3-Phenylpropionaldehyde	5	—	ND[b]	—	—

[a]Based on aldehyde; isolated yields based on aldehyde; 5 mmol aldehyde, 5.5 mmol hippuric acid, 5 mmol% imidazolium salt (**1**), and 15 mmol acetic anhydride were used; the reaction was carried out at 60°C.
[b]No product was detected.

4. Experimental

4.1. Materials. All chemicals and solvents were obtained from commercial sources and used without further purification. Melting points were recorded on X_4 micro- melting apparatus and uncorrected. FT-IR spectra were recorded using KBr pellets on a Nicolet Avatar Spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker Avance DMX 400 instrument using $CDCl_3$ and DMSO-d_6 as the solvents with TMS as an internal standard. Mass spectra were measured with an HP 5903 mass spectrometer with 70 eV energy.

*4.2. Synthesis of Imidazolium Salt **(1)** [27].* 1-methyimidazole (3.28 g, 40 mmol) was dissolved in acetone (80 mL), and 40 mL of 1,3-propanesultone (4.88 g, 40 mmol) in acetone were added slowly at 0°C. Mixtures were stirred at room temperature for 5 days in a dry N_2 atmosphere. The precipitate was recovered and washed by filtration and dried *in vacuo* at 60°C. White solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.09 (t, 2H, J = 7.0 Hz, CH_2), 2.45 (t, 2H, J = 11.3 Hz, CH_2), 3.85 (s, 3H, CH_3), 4.31 (d, 2H, J = 6.8 Hz, CH_2), 7.69 (s, 1H), 7.78 (s, 1H), 9.11 (s, 1H).

*4.3. Synthesis of 4-Phenyl-4-(phenylmethylene)-5(4H)-oxazolone **(4e)**.* A mixture of benzaldehyde (505 μL, 5 mmol), hippuric acid (0.98 g, 5.5 mmol), acetic anhydride (1.6 mL, 15 mmol), and imidazolium salt (0.051 g, 0.25 mmol) was taken in a dry 50 mL flask with constant stirring. The whole mixture was stirred at 60°C in oil bath for appropriate time (by TLC). The filtrate was cooled to room temperature, 5 mL 95% EtOH were added, and yellow solid was precipitated. The yellow solid was filtered off and washed with hot water. The crude azlactone was purified by recrystallisation from acetone/water (0.934 g, 75% as yellow solid). M.p. 168-169°C (Lit. [25] M.p. 168°C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.27 (s, 1H, –CH=), 7.48–7.63 (m, 6H, ArH), 8.19–8.23 (m, 4H, ArH). IR (KBr) 3420, 1793 (–C=O), 1653, 1384, 1167 cm^{-1}. Mass (m/z): 249, 116, 105, 89. See Supplementry Material available at http://dx.doi.org/10.1155/2013/ 280585.

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