

ERLENMEYER SYNTHESIS OF AZLACTONES BY SONOCHEMICAL REACTION IN IONIC LIQUIDS

Mohammad Reza Poor Heravi

Department of Chemistry,
Pyame Noor University (PNU),
P. O. Box. 97, Abhar, Iran
E-mail: heravimr@yahoo.com

Received 15 December 2008
Accepted 12 February 2009

ABSTRACT

A series of 4-aryldiene-2-phenyl-5(4)-oxazolones were synthesized from cyclodehydration-condensation of hippuric acid, aromatic aldehydes, and acetic anhydride under sonochemical reaction in ionic liquids with easy work-up in excellent yields.

Keywords: azlactone, aromatic aldehyde, hippuric acid, ionic liquids, sonochemical reaction.

INTRODUCTION

Azlactones are important synthones for the synthesis of several biologically active compounds [1]. They are also particularly useful precursors for the synthesis of amino acids [2], peptides [3], heterocycles [4], biosensors [5], and antitumor [6] or anticancer [7] compounds. Development of facile and environmental friendly synthetic methods for azlactones constitutes an active area of investigation. The most well-known route to azlactones is the Erlenmeyer method, which involves 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 [8]. Recently, some new reagents have become available for the synthesis of azlactones, such as Al_2O_3 - H_3BPO_3 [9], supported KF [10], $Bi(OAc)_3$ [11], $Bi(OTf)_3$ [12], $ZnCl_2$ [13], $Ca(OAc)_2$ [14], $Yb(OTf)_3$ [15]. Most of methods are suitable, but some need high temperature (reflux temperature) and are difficult to handle. A simple, mild, environmentally friendly, and easy method for azlactones synthesis is highly desirable. Activation of organic reaction with ultrasound constitutes an important and far-reaching domain of modern

sonochemistry. This is largely due to the fact that sonochemistry and the recent upsurge of interest in a sustainable chemistry share similar aims, such as the use of less hazardous chemicals and environmentally benign solvents. Sonochemists have now turned their attention to ionic liquids (ILs), in fact an impressive research field in recent years [16]. These substances are non-flammable and have negligible vapour pressures. It is well established that the rates of sonochemical reactions can be increased, at least within some limits, by choosing a less volatile one [17]. Since ILs are usually more viscous and denser than other organic solvents, cavitations should be more difficult to produce under such conditions where cohesive forces are large. However, once cavitation is reached, solvents of low vapour pressure will be devoid of the common limitation of high volatile solvents, i.e. more vapour will enter the cavitation bubble during its formation and the collapse is cushioned and less violent [18]. Moreover, unlike most conventional solvents, ILs will hardly undergo reactions within the collapsing bubbles and, consequently represent a suitable medium to explore cavitation effects devoid of solvent interferences. Ionic liquids have been incorporated into green chemistry protocols. Re-

cently, the non-innocent character of these substances has been questioned [19, 20].

EXPERIMENTAL

Materials and methods

All organic solvents were purchased from commercial sources and used as received or dried using standard procedures, unless otherwise stated. All chemicals were purchased from Merck. The potential of ionic liquids (ILs) as environmentally benign media for many chemical and biochemical reactions has already been established [17]. They are non-volatile, have excellent chemical and thermal stabilities, and can dissolve a variety of substrates [18]. ILs 1-butyl-3-methylimidazolium tetrafluoroborate [bmim][BF₄] and 1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF₆] have been used as satisfactory media in some kinds of condensation reactions, such as Knoevenagel condensation and Mannich condensation [18]. Melting points were determined on Gallenkamp and/ or electro thermal apparatus. Analytical thin-layer chromatography (TLC) was performed on precoated Merck 60 GF₂₅₄ silica gel plates with a fluorescent indicator, and detection by means of UV light at 540 and 360 nm. Flash chromatography was conducted on Merck 60 silica gel (230-400 mesh). IR spectra were recorded in the range of 4000-600 cm⁻¹ on a FT-IR VARIAN spectrophotometer. Solid samples were recorded on KBr (Merck) pellets. ¹H NMR spectra were recorded on a Bruker DRX500 instrumental at 500 MHz, respectively in CDCl₃. Tetramethylsilane (TMS) was used as the internal standard (d=0.00 ppm).

General procedure for silent Erlenmeyer synthesis of azlactones

For comparative purpose, all studies in this work were carried out without sonication under stirring (silent conditions) maintaining the rest of experimental parameters unaffected. A typical experimental procedure is as follows: In a flat-bottomed vial of 25 mL, of aromatic aldehyde (2 mmol), hippuric acid (2.2 mmol), acetic anhydride (6.6 mmol) were added to 2 mL of [bmim][PF₆] or [bmim][BF₄], with and without 1 mL of methanol as co solvent, and stirred for a given reaction time at room temperature (25°C). All processes were

monitored by TLC. After completion, the crude was extracted with diethyl ether (5x4 ml). The ethereal solution was reduced to half volume in a rotary evaporator and then filtered through a 3 cm-silica gel bed, to avoid contamination of the ionic liquid. The final adducts were isolated by evaporation of the crude mixture and, if necessary, purified by chromatography or recrystallization from acetone/water.

Typical procedure for sonicated Erlenmeyer synthesis of azlactones

These processes were performed on the same scale described above for the silent reactions. Vials were sonicated in a P-Selecta ultrasonic cleaning bath operating at 40 KHz. All reactions started at room temperature (25°C) and the maximum temperature reached in the longest runs was 30°C. The tank dimension capacity of 4 l. Vials were immersed into the bath by positioning them in the regions of high intensity from the base, approximately 3 cm below the surface of the liquid. The sonochemical reaction in ionic liquids, were equally monitored by TLC and worked up as described.

(E)-4-Benzylidene-2-phenyloxazol-5(4H)-one (3a): Mp 168-169 °C (mp 168-169°C [21]); ¹H NMR (CDCl₃, ppm): δ 2.42, (s, 3H, CH₃), 7.22-7.41 (m, 3H, Ar-H and -CH=), 7.55-7.60 (m, 3H, ArH), 8.15-8.25 (m, 4H, ArH). IR (KBr) ν_{max} 3435, 2986, 1795, 1656, 1546, 1165 cm⁻¹. HRMS (EI) Found: M+, 249.0864. C₁₆H₁₁NO₂ requires M+, 249.0658. LRMS m/z (EI): 249 (60 % M+). ES+: MNa+, 272, MH+, 250. Elemental analysis: Found (%): C, 77.23; H, 4.54; N, 5.56. Calcd. for C₁₆H₁₁NO₂: C, 77.10; H, 4.45; N, 5.62.

(E)-4-(4-Methylbenzylidene)-2-phenyloxazol-5(4H)-one (3b): Mp 143-144 °C (mp 141-143°C [21]); ¹H NMR (CDCl₃, ppm): δ 2.42, (s, 3H, CH₃), 7.22-7.41 (m, 3H, Ar-H and -CH=), 7.55-7.60 (m, 3H, ArH), 8.15-8.25 (m, 4H, ArH). IR (KBr) ν_{max} 3435, 2986, 1795, 1656, 1546, 1165 cm⁻¹. HRMS (EI) Found: M+, 263.0918. C₁₇H₁₃NO₂ requires M+, 263.0858. LRMS m/z (EI): 263 (100% M+). ES+: MNa+, 286, MH+, 264. Elemental analysis: Found (%): C, 77.64; H, 5.01; N, 5.54. Calcd. for C₁₇H₁₃NO₂: C, 77.55; H, 4.98; N, 5.32.

(E)-4-(4-Methoxybenzylidene)-2-phenyloxazol-5(4H)-one (3c): Mp 155-156 °C (mp 155-157°C [21]); ¹H NMR (CDCl₃, ppm): δ 3.87 (s, 3H, CH₃), 7.14 (d,

2H, $J=8.5$ Hz, ArH), 7.35 (s, 1H, $-\text{CH}=\text{}$), 7.62-7.74 (m, 3H, ArH), 8.16 (d, 2H, $J=8.4$ Hz, ArH), 8.32 (d, 2H, $J=8.5$ Hz, ArH). IR (KBr) ν_{max} 3432, 2938, 1785, 1655, 1546, 1164 cm^{-1} . HRMS (EI) Found: M^+ , 279.0891. $\text{C}_{17}\text{H}_{13}\text{NO}_3$ requires M^+ , 279.0956. LRMS m/z (EI): 279 (100% M^+). ES+: $M\text{Na}^+$, 302, $M\text{H}^+$, 280. Elemental analysis: Found (%): C, 73.17; H, 4.87; N, 5.07. Calcd. for $\text{C}_{17}\text{H}_{13}\text{NO}_3$: C, 73.11; H, 4.69; N, 5.02.

(E)-4-(4-Bromobenzylidene)-2-phenyloxazol-5(4H)-one (3d): Mp 195-196°C (mp 195-196°C [21]); ^1H NMR (CDCl_3 , ppm): δ 7.18 (s, 1H, $-\text{CH}=\text{}$), 7.62-7.74 (m, 5H, ArH), 8.16-8.21 (m, 4H, ArH). IR (KBr) ν_{max} 3436, 1795, 1655, 1546, 1160 cm^{-1} . HRMS (EI) Found: M^+ , 326.9991. $\text{C}_{16}\text{H}_{10}\text{BrNO}_2$ requires M^+ , 326.9876. LRMS m/z (EI): 328 (100% M^+). ES+: $M\text{Na}^+$, 361, $M\text{H}^+$, 329. Elemental analysis: Found (%): C, 58.52; H, 2.98; N, 4.17. Calcd. for $\text{C}_{16}\text{H}_{10}\text{BrNO}_2$: C, 58.56; H, 3.07; N, 4.27.

(E)-4-(2,4-Dibromobenzylidene)-2-phenyloxazol-5(4H)-one (3e): Mp 203-205°C (mp 204-205°C [21]); ^1H NMR (CDCl_3 , ppm): δ 7.38 (s, 1H, $-\text{CH}=\text{}$), 7.42-7.64 (m, 5H, ArH), 8.16-8.20 (m, 4H, ArH). IR (KBr) ν_{max} 3433, 1797, 1658, 1545, 1161 cm^{-1} . HRMS (EI) Found: M^+ , 294.0621. $\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}_4$ requires M^+ , 294.0643. LRMS m/z (EI): 294 (100% M^+). ES+: $M\text{Na}^+$, 317, $M\text{H}^+$, 295. Elemental analysis: Found (%): C, 58.52; H, 2.98; N, 4.17. Calcd. for $\text{C}_{16}\text{H}_{10}\text{BrNO}_2$: C, 58.56; H, 3.07; N, 4.27.

(E)-4-(3-Nitrobenzylidene)-2-phenyloxazol-5(4H)-one (3f): Mp 165-166°C (mp 166-167°C [21]); ^1H NMR (CDCl_3 , ppm): δ 7.55 (s, 1H, $-\text{CH}=\text{}$), 7.52-7.84 (m, 4H, ArH), 8.16 (d, 2H, $J=7.6$, ArH), 8.31 (d, 1H, $J=8.5$, ArH), 8.67 (d, 1H, $J=7.5$, ArH). IR (KBr) ν_{max} 3443, 3100, 1797, 1655, 1545, 1161 cm^{-1} . HRMS (EI) Found: M^+ , 404.9091. $\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}_4$ requires M^+ , 294.0666. LRMS m/z (EI): 294 (100% M^+). ES+: $M\text{Na}^+$, 307, $M\text{H}^+$, 295. Elemental analysis: Found (%):

C, 65.43; H, 3.39; N, 9.48. Calcd. for $\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}_4$: C, 65.31; H, 3.43; N, 9.52.

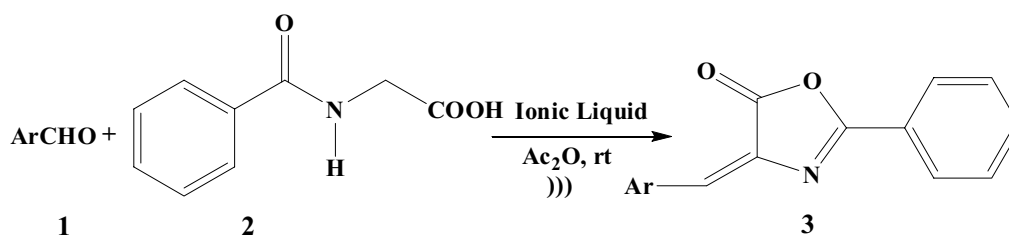
(E)-4-(4-Nitrobenzylidene)-2-phenyloxazol-5(4H)-one (3g): Mp 240-241 °C (mp 240-241°C [21]); ^1H NMR (CDCl_3 , ppm): δ 7.17 (t, 1H, $J=8.0$ Hz, ArH), 7.30-7.41 (m, 4H, ArH and $-\text{CH}=\text{}$), 7.49-7.63 (m, 3H, ArH), 8.12 (d, 2H, $J=7.8$, ArH). IR (KBr) ν_{max} 3440, 3093, 1790, 1658, 1545, 1169 cm^{-1} . HRMS (EI) Found: M^+ , 294.0665. $\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}_4$ requires M^+ , 294.0677. LRMS m/z (EI): 407 (100% M^+). ES+: $M\text{Na}^+$, 307, $M\text{H}^+$, 295. Elemental analysis: Found (%): C, 65.43; H, 3.38; N, 9.47. Calcd. for $\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}_4$: C, 65.31; H, 3.43; N, 9.52.

(E)-4-(4-Chlorobenzylidene)-2-phenyloxazol-5(4H)-one (3h): Mp 187-188°C (mp 186-187°C [21]); ^1H NMR (CDCl_3 , ppm): δ 7.55 (s, 1H, $-\text{CH}=\text{}$), 7.52-7.84 (m, 4H, ArH), 8.16 (d, 2H, $J=7.6$, ArH), 8.31 (d, 1H, $J=8.5$, ArH), 8.67 (d, 1H, $J=7.5$, ArH). IR (KBr) ν_{max} 3443, 3100, 1797, 1655, 1545, 1161 cm^{-1} . HRMS (EI) Found: M^+ , 404.9091. $\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}_4$ requires M^+ , 404.9056. LRMS m/z (EI): 407 (100% M^+). ES+: $M\text{Na}^+$, 361, $M\text{H}^+$, 329. Elemental analysis: Found (%): C, 65.33; H, 3.48; N, 9.57. Calcd. for $\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}_4$: C, 65.31; H, 3.43; N, 9.52.

RESULTS AND DISCUSSION

In continuation of our previous research works on sonochemical reaction in [bmim][PF₆] ILs [20]. A series of (*E*)-4-aryldiene-2-phenyl-5(4H)-oxazolones **3a-k** were synthesized by reaction of benzaldehydes (**1a-k**) with hippuric acid (**2**) by sonochemical reaction in ionic liquids (Scheme 1), where the meanings of **a-k** are presented in Table 2.

My first attempt was performed with the benzaldehyde (**1a**) as substrate. To investigate optimal conditions for the Erlenmeyer reaction (Scheme 1), a series of experiments were tested (Table 1).



Scheme 1. Preparation of azlactones **3a-k** from reaction of benzaldehydes (**1a-k**) with hippuric acid (**2**).


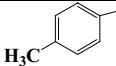
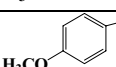
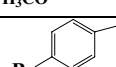
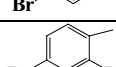

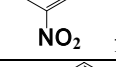
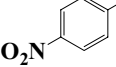

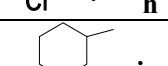
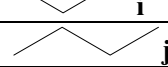
Table 1. Preparation of **3a** with comparison of Solvent free, use of ILs and sonochemical reaction.

Solvent (IL)	Co solvent(1/1)	T (°C)	Time (Min)	3a (%) ^a
Solvent free	-	40	30	82 ^{a, b}
[bmim][PF ₆]	MeOH	20	10	56
[bmim][BF ₄]	MeOH	20	10	61
[bmim][PF ₆]	MeOH,)))	20	3	98
[bmim][PF ₆]	EtOH	20	15	55
[bmim][BF ₄]	EtOH	20	20	53
[bmim][BF ₄]	EtOH,)))	20	3	94

^aIsolated yields

^b100 mmol benzaldehyde, 110 mmol hippuric acid, 10 mmol Yb(OTf)₃ and 32 ml acetic anhydride were used, and the reaction was carried out at 40°C [15].

Table 2. Reaction benzaldehydes (**1a-k**) and hippuric acid (**2**) in by sonochemical reaction in [bmim][PF₆] ILs, and methanol as co solvent.

Entry	Ar	Time (min)	Azlactone	Yield(%) ^a	MP (°C)	MP(°C), Ref.
1	 a	3	3a	98	168-169	168-169, [21]
2	 b	5	3b	97	143-144	141-143, [21]
3	 c	4	3c	96	155-156	155-157, [21]
4	 d	5	3d	97	195-196	195-196, [21]
5	 e	6	3e	96	203-205	204-205, [21]
6	 f	1	3f	99	165-166	166-167, [21]
7	 g	1	3g	99	240-241	240-241, [21]
8	 h	3	3h	97	187-188	186-187, [21]
9	 i	120	3i	-	-	-
10	 j	120	3j	-	-	-
11	 k	120	3k	-	-	-

^aIsolated yields

Table 1 shows that the use of [bmim][PF₆] as ionic liquid with methanol as co solvent at room temperature and 3 min (yield 98%) is optimize condition times and yields of the reactions for compounds **3a-h** are summarized in (Table 2). No azlactone products **3i-k** were isolated from reaction of the aliphatic aldehydes **i-k** with hippuric acid, because aryl aldehydes **a-h** (entries 1-8) are more reactive than aliphatic aldehydes **i-k** (entries 9-11).

CONCLUSIONS

The present work evidences that Erlenmeyer synthesis of azlactones, conducted at relatively low temperature, can efficiently be activated by ultrasound using an ionic liquid as reaction medium. The particular properties of these solvents, especially their extremely low vapour pressure combined with their greater viscosity and heat capacity, constitute emerging media when cavitation effects should be tested. It is expected that the combined use of ultrasound and ionic liquids will allow us to obtain major improvements in organic synthesis and materials chemistry.

Acknowledgements

I wish to thank my parents, wife (Dr. A. Hashemi) and daughters (Niloofar and Niki). Also, I am grateful from Payame Noor University (PNU).

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