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Abstract: A series of 4-arylidene-2-phenyl-5(4)-oxazolones were synthesized from cyclodehydration-condensation of hippuric acid, aromatic aldehydes, and acetic anhydride catalyzed by ytterbium(III) triflate under mild conditions in excellent yields.

Keywords: Aromatic aldehyde, azlactone, hippuric acid, ytterbium triflate

4-Arylidene-2-phenyl-5(4)-oxazolones are important synthons for the synthesis of several biologically active molecules.^[1] They are also particularly useful precursors for the synthesis of aminoacids,^[2] peptides,^[3] hetero-cycles,^[4] biosensors,^[5] and antitumor^[6] or anticancer^[7] compounds. Development of facile and environmentally 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 Al₂O₃-H₃BO₃,^[9] supported KF,^[10] Bi(OAc)₃,^[11] Bi(OTf)₃,^[12] ZnCl₂,^[13] and Ca(OAc)₂.^[14] Most of methods are suitable, but some need high temperature (reflux

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temperature) and are difficult to handle. A simple, mild, environmentally friendly, and easy method for azlactones synthesis is highly desirable.

Recently, ytterbium triflate [Yb(OTf)₃] was used widely as a mild, recyclable, and environmentally friendly catalyst in organic reactions, such as the Aldol reaction,^[15] Mannich-type reaction,^[16] Diels–Alder reaction,^[17] Friedel–Crafts acylation, and alkylation.^[18] More recently, we have reported that metal triflate can efficiently catalyze many organic synthetic reactions.^[19]

Because of our continued interest in the use of $Yb(OTf)_3$ as an efficient and environmentally friendly catalyst, we report that $Yb(OTf)_3$ catalyzed the Erlenmeyer reaction for synthesis of azlactones under solvent-free conditions at 40°C.

Our 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).

Compared to anhydrous sodium acetate,^[8] Yb(OTf)₃ employed here shows high catalytic reactivity in terms of the amount of catalyst and yields of the product (Table 1, entry 1). Moreover, the catalytic efficiency of other metal triflates, such as Cu(OTf)₂, Mg(OTf)₂, Sr(OTf)₂, and Zn(OTf)₂were tested (Table 1, entries 2–9). Under the same conditions, Yb(OTf)₃ was found to be the best catalyst in azlactones synthesis, Zn(OTf)₂ was the second, and Cu(OTf)₂ was the worst.

Next, the amount of Yb(OTf)₃ and reaction temperature were investigated (Table 1, entries 10–15). Amounts of 5 mol%, 10 mol%, 20 mol% of Yb(OTf)₃ were used, and it was found that 10 mol% of Yb(OTf)₃ was enough to accomplish the reaction. Increasing the amount of catalyst did not obviously improve the yield (Table 1, entries 10–12). Similarly, reaction temperature was also studied. The yield was low (45%, Table 1, entry 13) at room temperature for 3 h, but 82% yield was obtained at 40°C, and increasing the temperature did not help to obviously improve the yield (Table 1, entries 12–15). The catalyst can be recovered easily,^[20] and the yields were not reduced drastically when the recycled catalyst was used (Table 1, entry 16). Moreover, the reaction could be performed on a largescale and gave satisfactory yield (Table 1, entry 17). Thus the following reactions were performed with 10 mol% of Yb(OTf)₃ at 40°C.

To explore the scope of our method, a wide variety of aromatic aldehydes smoothly gave the corresponding azlactones in good to excellent yields with



Scheme 1.

Entry	Metal triflate	Cat. amount equiv. ^a	Temperature (°C)	Reaction time (h)	Yield $(\%)^b$
1	Anhydrous sodium acetate	0.5	60	3	65 ^c
2	$Cu(OTf)_2$	0.1	40	3	ND^d
3	$Cu(OTf)_2$	0.1	100	3	ND^d
4	$Mg(OTf)_2$	0.1	40	3	60
5	$MgOTf)_2$	0.1	100	3	63
6	$Sr(OTf)_2$	0.1	40	3	50
7	$Sr(OTf)_2$	0.1	100	3	51
8	$Zn(OTf)_2$	0.1	40	3	70
9	$Zn(OTf)_2$	0.1	100	3	73
10	$Yb(OTf)_3$	0.05	40	3	73
11	$Yb(OTf)_3$	0.2	40	0.5	83
12	$Yb(OTf)_3$	0.1	40	0.5	82
13	$Yb(OTf)_3$	0.1	25	3	45
14	$Yb(OTf)_3$	0.1	60	0.5	85
15	$Yb(OTf)_3$	0.1	100	0.5	83
16	Yb(OTf) ₃	0.1	40	0.5	76, 73, 70, 66 ^e
17	Yb(OTf) ₃	0.1	40	1	80 ^{<i>f</i>}

Table 1. Preparation of azlactone (3a) under different conditions

^aBased on benzaldehyde.

^bIsolated yields based on benzaldehyde.

 $^c50\ {\rm mol}\%$ anhydrous sodium acetate was used, and the procedure was performed according to Ref. 8.

^dNo product was detected.

^eThe recovered catalyst was used.

^{*f*}100 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.

 $Yb(OTf)_3$ catalysis (Table 2). Moreover, all of benzaldehydes bearing electron-withdrawing groups, as well as electron-donating groups, gave good yields. Unfortunately, when aliphatic aldehyde was tested, no desired products were detected (Table 2, entry 10).

In conclusion, an efficient, rapid, and environmentally benign method for the preparation of azlactones has been developed in the presence of ytterbium(III) triflate under mild conditions. In addition, high yields and easy operation make this method advantageous in comparison to other methods.

EXPERIMENTAL

Melting points were recorded on a digital melting-point apparatus, WRS-1B, and are uncorrected. IR spectra were recorded using KBr pellets on an Avatar

Entry	ArCHO	Reaction time (h)	Azlactones	Yield $(\%)^a$	Mp (°C)
1	C ₆ H ₅ CHO	0.5	3a	82	168-169
2	4-MeC ₆ H ₄ CHO	0.5	3b	87	143-144
3	4-MeOC ₆ H ₄ CHO	0.5	3c	84	155-157
4	2-ClC ₆ H ₄ CHO	1	3d	91	159-161
5	4-ClC ₆ H ₄ CHO	1	3e	87	186-187
6	2,4-Cl ₂ C ₆ H ₃ CHO	1	3f	82	162-163
7	3-NO ₂ C ₆ H4CHO	1	3g	81	166-167
8	4-NO ₂ C ₆ H ₄ CHO	1	3h	83	240-241
9	Indole-3-carboxaldehyde	0.5	3i	78	207 - 208
10	CH ₃ CH ₂ CH ₂ CHO	5	—	ND^b	

Table 2. Preparation of azlactones from aldehydes catalyzed by Yb(OTf)₃

^aIsolated yields based on aldehydes.

^bNo product was detected.

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370 FI-infrared spectrophotometer. ¹H NMR spectra were recorded on a Varian Mercury Plus-400 instrument using CDCl₃ or DMSO as the solvent with TMS as an internal standard. Mass spectra were measured with Thermo Finnigan LCQ-Advantage (EI). Yb(OTf)₃ was prepared from ytterbium oxide and trifluoromethanesulfonic acid and recovered according to the literature.^[20]All reagents are commercially available and were used without further purification.

General Procedure for the Preparation of Azlactones

A dry 50-ml flask was charged with aromatic aldehyde (2 mmol), hippuric acid (2.2 mmol), acetic anhydride (6.6 mmol), and Yb(OTf)₃ (0.2 mmol). The mixture was stirred at 40°C for the time indicated in Table 2. After the reaction mixture was cooled to room temperature, 5 mL of 95% EtOH was added, and a yellow solid was precipitated. The yellow solid was filtered off and washed with hot water. The crude azlactone was purified by recrystallization from acetone/water. The aqueous layer was washed by CH₂Cl₂ and was concentrated in vacuo to give white crystals [Yb(H₂O)₉](OTf)₃, which were then heated at 190°C for 4 h in vacuo to give 113 mg of Yb(OTf)₃ (91.2%).

Data

3a: Mp 168–169°C (lit.^[21] mp 168°C); ¹H NMR (400 MHz, CDCl₃) δ = 7.27 (s, 1H, -CH=), 7.46–7.63 (m, 6H, ArH), 8.19–8.23 (m, 4H, ArH); MS: m/z 250 (M + H)⁺; IR (KBr) 3438, 1794, 1653 cm⁻¹.

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3b: Mp 143–144°C (lit.^[21] mp 141–143°C); ¹H NMR (400 MHz, CDCl₃) $\delta = 2.42$ (s, 3H, CH₃), 7.21–7.40 (m, 3H, ArH and -CH=), 7.52–7.61 (m, 3H, ArH), 8.11–8.20 (m, 4H, ArH); MS: m/z 264 (M + H)⁺; IR (KBr) 3433, 2917, 1794, 1654, 1160 cm⁻¹.

3c: Mp 155–157°C (lit.^[21] mp 156°C); ¹H NMR (400 MHz, DMSO) δ = 3.87 (s, 3H, CH₃), 7.12 (d, 2H, *J* = 8.4 Hz, ArH), 7.35 (s, 1H, -CH=), 7.62–7.74 (m, 3H, ArH), 8.12 (d, 2H, *J* = 8.4 Hz, ArH), 8.32 (d, 2H, *J* = 8.4 Hz, ArH); MS: m/z 280 (M + H)⁺; IR (KBr) 3432, 2938, 1789, 1654, 1162 cm⁻¹.

3d: Mp 159–161°C (lit.^[21] mp 159°C); ¹H NMR (400 MHz, CDCl₃) $\delta = 7.35-7.65$ (m, 7H, ArH and -CH=), 8.19 (d, 2H, J = 8.0 Hz, ArH), 8.92 (d, 1H, J = 8.0 Hz, ArH); MS: m/z 285 (M + H)⁺; IR (KBr) 3441, 1793, 1652, 1170 cm⁻¹.

3e: Mp 186–187°C (lit.^[9] mp 184°C); ¹H NMR (400 MHz, CDCl₃) δ = 7.19 (s, 1H, -CH=), 7.45–7.66 (m, 5H, ArH), 8.15–8.20 (m, 4H, ArH); MS: m/z 285 (M + H)⁺; IR (KBr) 3433, 1796, 1655, 1160 cm⁻¹.

3f: Mp 162–163°C (lit.^[21] mp 161°C); ¹H NMR (400 MHz, CDCl₃) δ = 7.39 (d, 1H, *J* = 7.6 Hz, ArH), 7.48 (s, 1H, -CH=), 7.53–7.66 (m, 4H, ArH), 8.17 (d, 2H, *J* = 7.6 Hz, ArH), 8.90 (d, 1H, *J* = 8.4 Hz, ArH); MS: m/z 319 (M + H)⁺; IR (KBr) 3444, 3091, 1798, 1656, 1170 cm⁻¹.

3 g: Mp 166–167°C (lit.^[12] mp 164°C); ¹H NMR (400 MHz, DMSO) $\delta = 7.54$ (s, 1H, -CH=), 7.67–7.85 (m, 4H, ArH), 8.15 (d, 2H, J = 7.6 Hz, ArH), 8.31 (d, 1H, J = 8.4 Hz, ArH), 8.68 (d, 1H, J = 7.6 Hz, ArH), 9.22 (s, 1H, ArH); MS: m/z 295 (M + H)⁺; IR (KBr) 3443, 3104, 1797, 1655, 1163 cm⁻¹.

3 h: Mp 240–241°C (lit.^[22] mp 241°C); ¹H NMR (400 MHz, CDCl₃) $\delta = 7.16$ (t, 1H, J = 8.0 Hz, ArH), 7.31–7.40 (m, 4H, ArH and -CH=), 7.49–7.63 (m, 3H, ArH), 8.12 (d, 2H, J = 7.8 Hz, ArH); MS: m/z 295 (M + H)⁺; IR (KBr) 3440, 3093, 1790, 1658, 1169 cm⁻¹.

3i: Mp 207–208°C (lit.^[23]mp 206°C); ¹H NMR (400 MHz, CDCl₃) $\delta = 7.27-7.28$ (t, 2H, J = 8.0 Hz, ArH), 7.53–7.72 (m, 5H, ArH and -CH=), 8.14 (d, 2H, J = 8.0 Hz, ArH), 8.40 (d, 1H, J = 8.0 Hz, ArH), 8.64 (s, 1H, CH), 12.35 (s, 1H, NH); MS: m/z 289 (M + H)⁺; IR (KBr) 3440, 3229, 1729, 1642, 1169 cm⁻¹.

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