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Alum an Efficient Catalyst for Erlenmeyer Synthesis

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ABSTRACT

A new and efficient method to synthesize azlactone derivatives using alum as catalyst was performed in the absence of additional solvent. This method is environmentally friendly and affords the product azlactones in high yields after simple workup.

KEYWORDS

Alum, solvent free, azlactone, Erlenmeyer reaction, condensation reaction.

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1. Introduction

Heterocyclic compounds occur widely in nature and are essential to life. In particular, azlactones exhibit a variety of biological and pharmaceutical properties.[1] They have also been found to be useful precursors for the synthesis of amino acids,[2] peptides,[3] and synthetically they have been used in the preparation of heterocycles,[4] biosensors,[5] and antitumor or antimicrobial compounds.[6] Thus, the development of facile and environmentally friendly synthetic methods for azlactones is currently of great interest. The Erlenmeyer reaction, which is the most widely used method for the preparation of azlactones, 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.[7] Recently, some new reagents have been reported for the synthesis of azlactones, including Al_2O_3-H_3BO_3,[8] supported KF,[9] $Bi(OAc)_3$,[10] $Bi(OTf)_3$,[11] $ZnCl_2$,[12] $Ca(OAc)_2$,[13] $Yb(OTf)_3$,[14] $(NH_4)_2HPO_4$,[15] ZnO,[16] and Al_2O_3.[17] Some of these methods, however, suffer from drawbacks, which include the use of hazardous materials,[8] materials that are not available or costly,[10,11,14] long reaction times,[7] and low yields.[9] In this paper we describe the use of alum as a catalyst in the Erlenmeyer reaction, under solvent-free condition using ultrasonic irradiation.

The application of solvent-free reaction conditions in organic chemistry has been explored extensively within the last decade. It was shown to be an efficient technique for various organic reactions. Solvent-free conditions often lead to a remarkable decrease in reaction time, increased yields, easier workup, and in some cases enhancement of regio and stereo selectivity.[18]

Ultrasound has also increasingly been used in organic synthesis. Ultrasonic irradiation enhances the chemical reaction via the process of acoustic capitation.[19] Simple experimental procedures, very high yields, increased selectivities, and clean reactions of many ultrasound-induced organic transformations offer additional convenience in the field of synthetic organic chemistry.[20]

Alum $[KAl(SO_4)_2.12H_2O]$ has been found to be effective in the synthesis of *cis*-isoquinolic acids,[21a] mono- and disubstituted 2,3-dihydroquinazolin-4(1H)-ones,[21b] dihydropyrimidines via Biginelli reaction,[21c] coumarins,[21d] 1,3,4-oxadiazoles,[21e] dibenzoxanthenes,[21f] 1,5-benzodiazepines,[21g] and trisubstituted imidazoles,[21h] etc. However, there are no examples of the use of alum as a catalyst for the synthesis of azlactone derivatives.

2. Result and Discussion

In continuation of our interest toward the exploitation of alum as a cheap, easily available and ecofriendly catalyst for the development of new synthetic methodologies in organic synthesis,[22] we now report a simple and efficient alum-catalyzed synthesis of azlactone derivatives (Scheme 1). The transformation involves the reaction of an aldehyde with hippuric acid in the absence of additional solvent at room temperature under ultrasound irradiation.[23]

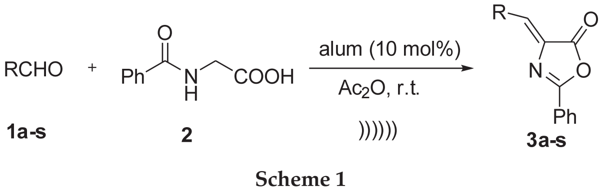
In the initial reaction, benzaldehyde, hippuric acid and acetic anhydride were combined in the presence of 10 mol % of alum without additional solvent by grinding the reagents together at ambient temperature. This gave only trace amounts of the desired product (Table 1: entry 1). Grinding the reagents, followed by heating at 50 °C, 80 °C and 100 °C, afforded the desired product in yields of 65–77 % after 60 min (Table 1: entries 2–4). However, the best result was obtained by ultrasound irradiation at ambient temperature, thus affording the product in 96 % yield and after only eight minutes (Table 1, entry 5).

Table 1 Effect of catalyst on the synthesis of azlactone **3a**.[a]

Entry	Reaction condition	Time/min	Yield [b]/%
1	Grinding/rt	60	Trace
2	50 °C	60	65
3	80 °C	60	75
4	100 °C	60	77
5	Ultrasound/rt	8	96

[a] Benzaldehyde (2 mmol), hippuric acid (2.2 mmol), acetic anhydride (6.6 mmol), and alum (10 mol %).
[b] Yields refer to pure isolated products.

To determine the optimal catalyst loading required, the ultrasound reaction was repeated with varying amounts of alum (Table 2). A maximum yield of 96 % was obtained with 10 mol % of alum under ultrasound irradiation. Increase in catalyst loading to 15 mol % and 20 mol % did not have any



Scheme 1

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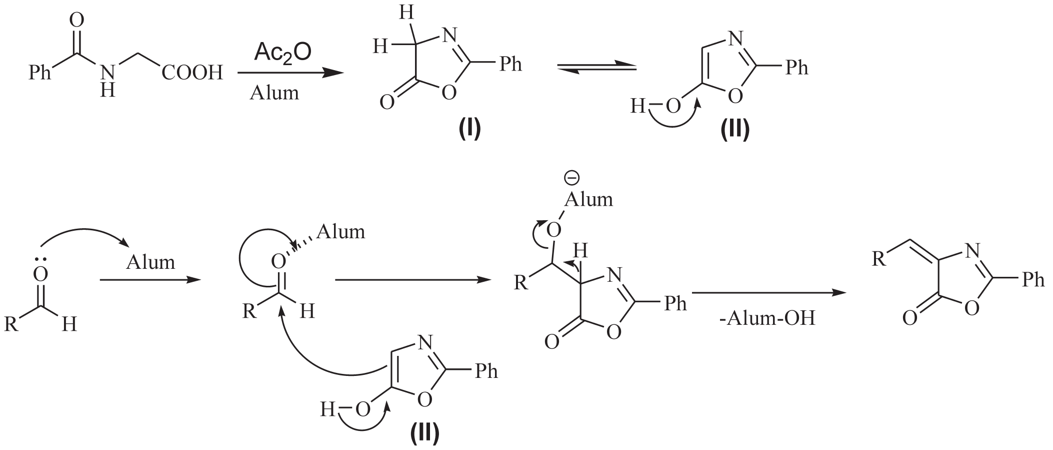

Scheme 2

significant effect on the yield of product.

The generality of this reaction was examined using a number of aromatic aldehydes, including those bearing electron-withdrawing groups (such as halides and nitro groups), and electron-donating groups (such as methyl or methoxy groups). In all cases, the reactions gave the corresponding products in good to excellent yields (Table 3). Unfortunately, when an aliphatic aldehyde was tested, none of the desired product was detected (Table 3, entry 3s). This methodology therefore offers improvements with regard to the simplicity in operation and green aspects of the reaction by avoiding expensive or corrosive catalysts.

Alum acts as an effective catalyst with respect to reaction times and yields, compared with other catalysts known to facilitate this transformation, as shown for the reaction of benzaldehyde with hippuric acid (Table 4). In this process, we propose that alum activates the aldehyde by binding to the oxygen atom of the aldehyde reactant,[21a] ultimately enhancing the electrophilicity of the aldehyde, leading to a decrease in reaction time.

Table 2 Optimization of catalyst loading for synthesis of azlactone **3a** under solvent free conditions.

Entry	Alum/mol %	Time/min	Yield[b]
1	0	8	–
2	5	8	78
3	10	8	96
4	15	8	96
5	20	8	95

[a] Benzaldehyde (2 mmol), hippuric acid (2.2 mmol), acetic anhydride (6.6 mmol), and alum (10 mol %).

[b] Yields refer to pure isolated products.

3. Conclusion

In conclusion, we have developed a convenient alum-catalyzed synthetic protocol for azlactones. The alum is commercially available and inexpensive. The time required for the completion of the reaction is markedly reduced and the yields of the products are increased. Hence, this route is rapid, economical and

Table 3 Erlenmeyer synthesis of azlactones. [a]

Compound[b]	Aldehydes	Time/min	Yield/% [c]	M.p./°	
				Found	Reported
3a	C_6H_5CHO	8	96	168–170	168–169[14]
3b	4-MeC_6H_4 CHO	10	92	142–144	143–144[14]
3c	4-MeOC_6H_4 CHO	8	90	154–156	155–157[14]
3d	2-ClC_6H_4 CHO	12	94	160–162	159–161[14]
3e	3-ClC_6H_4 CHO	12	94	152–154	155[16]
3f	4-ClC_6H_4 CHO	10	96	184–186	186–187[14]
3g	2-$NO_2C_6H_4$ CHO	10	95	164–166	165-166[16]
3h	3–$NO_2C_6H_4$ CHO	12	95	166-168	166–167[14]
3i	4–$NO_2C_6H_4$ CHO	8	96	240-242	240–241[14]
3j	$N(CH_3)_2C_6H_3$ CHO	8	92	210–212	210–212[16]
3k	2,6–$(Cl)_2C_6H_3$ CHO	10	94	162–164	162–163[14]
3l	2,4–$(OCH_3)_2C_6H_3CHO$	10	90	168–170	168–170[15]
3m	$C_6H_5CH{=}CH\text{-}CHO$	12	88	130–132	130–132[16]
3n	Indole 3-carbaldehyde	10	92	208–210	207–208[14]
3o	Furfural	8	92	168–170	170[8]
3p	Crotonaldehyde	8	85	152–153	I52[8]
3q	Cyclohexanone	12	85	138–140	I39[8]
3r	Acetophenone	14	88	104–106	105–106[16]
3s	Butyraldehyde	30	–	–	–

[a] Reaction conditions: aldehyde (2 mmol), hippuric acid (2.2 mmol), acetic anhydride (6.6 mmol), and alum (10 mol %), under ultrasound irradiation in solvent free condition.

[b] Compounds were characterized by IR, ^1H NMR, mass spectroscopy and compared with reported data.

[c] Isolated yield.

Table 4 Comparison of the results of alum in the reaction of benzaldehyde, hippuric acid and acetic anhydride with those of other catalysts reported in the literature.

Entry	Catalyst (loading)	Reaction conditions	Time	Yield/%
1	Alum (10 mol%)	Solvent free, r.t.	8 min	96[a]
2	Al_2O_3-H_3BO_3 (20 mol%)	$C_6H_6/C_6H_5.CH_3$, reflux	50 min	82[8]
3	$Bi(OAC)_2$ (11 mol %)	C_2H_5OH, Reflux	1 h	88[10]
4	$(NH_4)_2$ HPO_4 (10 mol %)	Solvent free, 80 °C	2.6 h	8115
5	Yb(OTf)3 (10 mol %)	Solvent free, 40 °C	0.5 h	82[14]
6	ZnO (60 mol %)	C_2H_5OH, r.t.	10 min	90[16]

[a] This work.

eco-friendly when compared to some of the other existing methods.

4. Experimental

All the reagents and aromatic aldehydes were obtained from commercial suppliers and were not purified. Melting points were determined in open capillaries and are uncorrected. The completion of reactions was monitored by TLC. IR spectra were recorded on KBr matrices with a Perkin-Elmer 1430 spectrophotometer (Manasquan, NJ, USA). ^1H NMR spectra were recorded on a Varian Model Mercury Plus 200 MHz NMR spectrometer (Lake Forest, CA, USA). Mass spectra [ES-MS] were recorded on a Water-Micro Mass Quattro-II spectrometer Welltech Enterprises, Inc., Capitol Heights, MD, USA). Bandelin Sonorex (35 KHz) ultrasonic bath was used for ultrasonic irradiation.

4.1. General Procedure for the Synthesis of Azlactone Derivatives (3a–s)

A dry 50-ml flask was charged with aldehyde (2 mmol), hippuric acid (2.2 mmol), acetic anhydride (6.6 mmol), and alum (10 mol %). The mixture was irradiated under ultrasound irradiation at ambient temperature for appropriate time (Table 3). Progress of the reaction was followed by TLC. After completion of the reaction, 5 mL of 95 % EtOH was added, and a yellow solid precipitated. The yellow solid was filtered off and washed with hot water. The crude azlactone was recrystallized from acetone/water to afford the pure products.

4.2. Spectral Data of Representative Compounds

4.2.1. *4(Z)-4-benzylidene-2-phenyloxazol-5(4H)-one* (3a)[14]

IR (KBr,ν_{max}): 3438, 1796, 1654 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) $\delta = 7.28$ (s, 1H, -CH=), 7.46–7.65 (m, 6H, ArH), 8.19–8.24 (m, 4H, ArH); MS: m/z 250 $(M+H)^+$

4.2.2. *4(Z)-4-4(1H-indol-3-yl) methylene)-2-phenyloxazol-5(4H)-one* (3n)[14]

IR (KBr,ν_{max}): 3442, 3230, 1729, 1642, 1170 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) $\delta = 7.27$–7.28 (t, 2H, $J = 8.0$ Hz, ArH), 7.54–7.72 (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 $(M+H)^+$.

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23 It should be noted that acetic anhydride is frequently utilized in the Erlenmeyer synthesis of azlactones to promote the condensation reactions – see for instance refs 14 and 15 for the use of *ca.* 3 mol equivalents of acetic anhydride.