An efficient synthesis of azlactone derivatives catalyzed by cellulose sulphuric acid

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Abstract
A simple and efficient route has been developed for the synthesis of 4-Arylidene-2-phenyl-5(4)-oxazolones (Azlactone) derivatives through the condensation of aromatic aldehydes and hippuric acid in acetic unhydride medium in presence of catalytic amount of cellulose sulphuric acid (CSA) at 60 °C is described. The reaction goes smoothly, simple experimental procedure, easy work- up and good to excellent yield of the products are the advantages of the present work. Moreover, the CSA was successfully reused for three cycles without significant loss of activity.

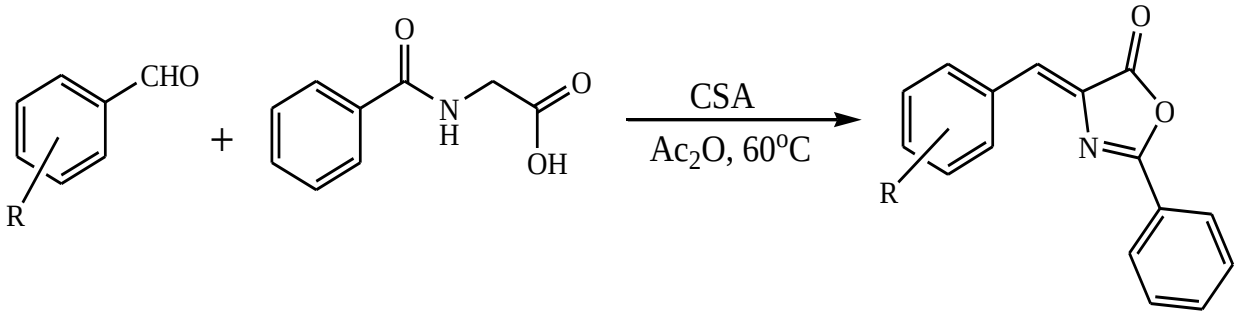
Keywords: Azlactone, CSA, aldehyde, hippuric acid

1. Introduction

4-Arylidene-2-phenyl-5(4)-oxazolones are important synthons for the synthesis of several biologically active molecules [1]. It is also used as precursors for the synthesis of aminoacid [2, 3], peptides [4], heterocycles [5, 6], biosensors [7, 8], and anti-tumor [9, 10] or anticancer [11, 12] compounds. Development of facile and environmentally friendly synthetic methods for azlactones constitutes an active area of investigation.

Due to their widespread applicability, research are continued to search new methods which is most suitable in terms of pollution abatement, yield and time. Generally azlactones are synthesized by Erlenmeyer method, which involve 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 [13]. Recently, some new reagents have become available for the synthesis of azlactones, such as Al_2O_3-H_3BO_3 [14], supported KF [15], $Bi(OAc)_3$ [16], $Bi(OTf)_3$ [17], $ZnCl_2$ [18], and $Ca(OAc)_2$ [19]. Each method has its own merits but some need high temperature and is difficult to handle. Also some catalysts are homogeneous, needs tedious work-up procedure. However, the search continues in search of simple, mild, environmentally friendly and easy method for azlactones synthesis.

Biopolymers, especially 'cellulose' and its derivatives[20] have some unique properties, which make them attractive alternatives for conventional organic or inorganic supports for catalytic applications. Among others, they are extremely inert, inexpensive, biodegradable and environmentally benign allowing various reaction conditions to be employed. Cellulose is the most abundant natural material in the world and it has been widely studied during the past decades because it is a biodegradable material and a renewable resource. Recently, several synthetically useful organic transformations using bio-supported, biodegradable and recyclable cellulose sulphuric acid (CSA) as a catalyst have been reported in the literature [21].



1(a-j) **2** **3(a-j)**

Scheme 1

1.1 Experimental procedure

Melting points were determined in an open capillary in a paraffin bath apparatus and are uncorrected. The reactions were monitored by TLC and visualized with UV light. IR spectra were recorded on a matrix of KBr with FTIR-4100 (Jasco, Japan) spectrometer. ^{1}H NMR spectra were recorded on Varian NMR spectrometer, Model Mercury Plus (400 MHz) and the chemical shifts are given in ppm relative to TMS as an internal standard.

1.2 General Procedure

A dry 50 ml flask was charged with aromatic aldehyde (5 mmol), hippuric acid (5 mmol), acetic anhydride (15 mmol) and CSA as a catalyst (0.5g). The mixture was stirred at 70 °C for the time mentioned in Table 2. After completion of reaction (monitored by TLC) the hot solution of reaction mixture filtered to separate the catalyst then reaction mixture was cooled and 5 ml of 95% ethanol was added, and a yellow product was precipitated. The yellow solid was filtered off

and washed with hot water. The crude azlactone was purified by recrystallization from ethanol to afford pure products.

1.3 Spectral data of representative compound

4-(4-chlorobenzylidene)-2-phenyloxazol-5(4*H*)-one (3e)
^{1}H NMR (DMSO, δ in ppm): 7.39-7.54 (m, 6H), 7.82 (d, 2H, 7.97 (d, 2H).IR (KBr): 3342, 3079, 1751, 1606, 1562, 1484, 1418, 1309, 1178, 848, 721cm^{-1}.

Table 1: Optimization of reaction condition for entry 3e (Table 2)

Entry	Wt of catalyst (g)	Time (min)	Yield (%)[a]
1	No catalyst	160	39
2	0.1	80	60
3	0.2	60	72
4	0.4	40	85
5	0.5	40	96
6	0.6	40	96

[a]Yield refers to isolated product.

Table 2: Synthesis of 4-arylidene-2-phenyl-5(4)-oxazolone derivatives catalysed by CSA.

Entry	Aldehyde	Time (min)	Yield (%)[a]	Melting Point (ºC)	
				Found	Reported
3a	C_6H_4CHO	20	90	166-168	168-169 [22]
3b	4-MeC_6H_4CHO	20	93	142-144	143-144 [22]
3c	4-$MeOC_6H_4CHO$	30	86	156-158	155-157 [22]
3d	2-ClC_6H_4CHO	40	94	159-160	159-16 [22]
3e	4-ClC_6H_4CHO	40	96	182-184	186-187 [22]
3f	3-ClC_6H_4CHO	40	92	152-154	155 [22]
3g	3-$NO_2C_6H_4CHO$	45	88	166-168	166-167 [22]
3h	4-$NO_2C_6H_4CHO$	40	93	238-239	240-241[22]
3i	Furfural	40	90	168-170	170 [14]
3j	Crotonaldehyde	50	90	152-154	152 [14]

[a]Yield refers to isolated product

Table 3: Recyclability of CSA for 3e (Table 2)

Entry	Cycle	Yield (%)[a]
1	Fresh	96
2	First	96
3	Second	95
4	Third	94

[a]Yield refers to isolated product.

2. Results and Discussion

To investigate the optimum condition for reaction, we have carried out the condensation of 4-chlorobenzaldehyde with hippuric acid using acetic unhydride as a solvent in presence of different amounts of catalyst, such as 0.1, 0.2, 0.4, 0.5, 0.6 g of CSA, and it was found that 0.5 g of catalyst was enough to accomplish the reaction with good yields (96%). Obviously increasing the amount of catalyst did not improve the yield. To check the activity of catalyst, we have carried out same reaction without catalyst but product yield was very less (39%) and consume much time also. It means that the catalyst play important role in the reaction (Table 1).

By encouraging this result, a wide variety of aromatic aldehydes condensed with hippuric acid in acetic unhydride medium. It was found that the reaction goes smoothly and gave the corresponding azlactones in good to excellent yields with catalyst. Moreover, all of benzaldehydes bearing electron-withdrawing groups, as well as electron-donating groups, gave good to excellent yield of products (Table 2).

Further investigation was the reusability of catalyst is important for the large-scale operation and industrial point of view. Therefore, the recovery and reusability of CSA was examined. So we have separated our catalyst from reaction mixture by filtering the reaction mixture in hot condition. It was washed subsequently with acetone, dried and reused for successive cycle and it was found that the catalyst is useful for several successive reaction without much more loss in its activity (Table 3).

3. Conclusion

In conclusion, we report here a CSA is highly efficient for the synthesis of 4-arylidene-2-phenyl-5(4)-oxazolone derivatives. Aromatic aldehyde bearing electron-donating and electron withdrawing groups did not affect on yield of products. The noteworthy merits offered by this methodology are cleaner reactions, short reactions time, simple work-up procedures and excellent yields. Additionally, the CSA was successfully reused for three cycles without significant loss of activity which makes the reaction convenient and environmentally benign.

4. References

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