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Microwave Assistedexpeditious Synthesis of Azlactone Derivatives

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Abstract

Synthesis of 4-arylidene-2-phenyl-5(4)-oxazolones (Azlactone) derivatives *via* thecondensation of aromatic aldehydes and hippuric acid in acetic anhydridewith excellent yield under microwave irradiation. The reaction is catalyzed by cadmium chloride, and is equally successful with both aliphatic and aromatic aldehydes. This method provide a simple and rapid protocol in terms of clean reaction profiles, short reaction times, and simple work-up procedure.

Keywords: Azlactone, aldehyde, hippuric acid, microwave

1. Introduction

Azlactone derivatives have been used in a wide range of biological and pharmaceutical properties are reported and they have attracted much chemical interest. They 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] compounds. Development of facile and environmentally friendly synthetic methods for azlactones constitutes an active area of investigation. After primary synthesis report in 1893 by Erlenmeyer [12],several other methods using difrrent catalysts such as $CaHPO_4$[13],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 procedures have some drawbacks, such as long reaction time, unsatisfactory yields, use of expensive, corrosive catalysts and rigorous work-up procedures. However, the search continues in search of simple, mild, environmentally friendly and easy method for azlactones synthesis.

The use of microwave for the synthesis of organic compounds under solvent-free conditions proved to be efficient, safe and environmentally benign technique, with shorter reaction time, high yields, and easier manipulation. Additionally, it can also avoid the use of hazardous and expensive solvents and can be environmentally benign to make manipulations much easier[20].

Cadmium chloride ($CdCl_2$) is an economically cheap Lewis acid catalyst used in several synthetically useful organic transformations have been reported in the literature[21].

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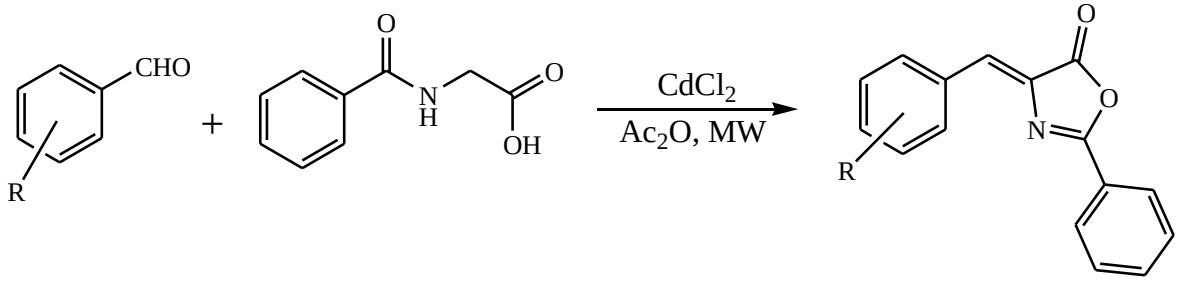

1(a-j) **2** **3(a-j)**

Scheme 1

2.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.

General Procedure

A dry 50 ml flask was charged with aromatic aldehyde (5 mmol), hippuric acid (5 mmol), acetic anhydride (15 mmol) and $CdCl_2$ as a catalyst (0.5g) was taken in a Borosil beaker (50 mL). The reaction mixture was mixed properly with the help of glass rod and exposed in a microwave oven at the power of 180W and irradiated for a period of 10 sec at a time. After each irradiation the reaction mixture was removed from the microwave oven for shaking. The completion of reaction monitored by TLC.The reaction mixture was cooled to room temperature and poured on ice-water (50 ml), a precipitated solid was filtered through Buckner funnel, washed with water, dried and recrystallized from ethanol to get the corresponding azlactone derivatives

3.Spectral data of representative compound:

4-benzylidene-2-phenyloxazol-5(4H)-one (3a): IR (KBr): νmax = 3072, 1789, 1651, 1552, 1450, 1315, 1158, 760, 658 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.27 (s, 1 H), 7.42–7.63 (m, 6 H), 8.18–8.21 (m, 4H) ppm.

4-(4-methylbenzylidene)-2-phenyloxazol-5(4H)-one (3b): IR (KBr): νmax = 3065, 1796, 1653, 1607, 1557, 1491, 1298, 1161, 1001, 889, 775 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.41 (s, 3 H), 7.21–7.34 (m, 3 H), 7.50–7.62 (m, 3H), 8.11–8.19 (m, 4H) ppm.

4-(4-nitrobenzylidene)-2-phenyloxazol-5(4H)-one (3h): IR (KBr): νmax = 3090, 1798, 1655, 1610, 1530, 1520, 1413, 1342, 1298, 1224, 1161, 1107, 981, 846, 775, 686,559 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.37 (ABq, 8.4 Hz, 4H), 8.23 (d, J= 8.4 Hz, 2H), 7.7 (t, J= 7.35 Hz, 1H), 7.59 (t, J= 7.35 Hz, 2H), 7.27 (s, 1H) ppm.

3. Results and Discussion

In order to find optimum reaction conditions, condensation of benzaldehyde, hippuric acid, acetic anhydridein the presence catalytic amount of $CdCl_2$under microwave irradiation. The optimum molar ratio of benzaldehyde : hippuric acid : acetic anhydride is 1:1:3 and $CdCl_2$(0.5g) under solvent-free conditions using microwave irradiation and under this conditions 4-benzyilidene-2-phenyl-5(4)-oxazolone (**3a**) was obtained in 92% yield after 5 min (entry **3a**).

By encouraging this result, a wide variety of aromatic aldehydes condensed with hippuric acid in acetic anhydride 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

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groups, as well as electron-donating groups, gave good to excellent yield of products (Table **1**).The procedure gives the products in high yields and avoids problems associated with solvent use such as cost, handling, specifically safety, because of fire hazard due to occurrence of sparks in microwave oven.

4. Conclusion:

In conclusion, we report here a $CdCl_2$works as an excellent catalyst for the synthesis of 4-arylidene-2-phenyl-5(4)-oxazolone derivatives under microwave irradiation. The noteworthy merits offered by this methodology are cleaner reactions, short reactions time, simple work-up procedures and good to excellent yields.

Table 1. Synthesis of 4-arylidene-2-phenyl-5(4)-oxazolone derivatives catalysed by $CdCl_2$.

Entry	Aldehyde	Time(min)	Yield (%)[a]	Melting Point (^oC)	
				Found	Reported
3a	C_6H_4CHO	5	92	167-169	168-169[22]
3b	4-MeC_6H_4CHO	5	93	142-144	143-144[22]
3c	4-$MeOC_6H_4CHO$	10	88	156-158	155-157[22]
3d	2-ClC_6H_4CHO	15	94	159-160	159-16[22]
3e	4-ClC_6H_4CHO	10	97	182-184	186-187[22]
3f	3-ClC_6H_4CHO	15	92	153-154	155[22]
3g	3-$NO_2C_6H_4CHO$	20	88	166-168	166-167[22]
3h	4-$NO_2C_6H_4CHO$	15	90	238-239	240-241[22]
3i	Furfural	10	89	169-171	170[14]
3j	Crotonaldehyde	15	87	150-152	152[14]

[a]Yield refers to isolated product

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