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MOLECULAR IODINE–CATALYZED, MILD, EFFECTIVE, ECOFRIENDLY, MICROWAVE-ASSISTED, ONE-POT SYNTHESIS OF 5-ARYLMETHYLIDENE-2-PHENYLOXAZOL-4-ONES (AZALACTONES) UNDER SOLVENT-FREE CONDITIONS

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Fourteen azalactones have been synthesized in excellent yields under solvent-free conditions by heating an aldehyde, hippuric acid, and acetic anhydride in the presence of molecular iodine as a catalyst in a microwave oven. The short reaction time, cleaner reaction, and easy workup make this protocol practical and economically attractive.

Keywords: Azalactones; microwave-assisted synthesis; molecular iodine; solvent-free condition

INTRODUCTION

Members of azalactone family are useful precursors in the synthesis of many organic compounds including amino acids, peptides, heterocycles, biosensors, antimicrobial agents, antitumor agents, and other bioactive molecules.^[1,2] Although there are several methods for the synthesis of azalactones, the classical and most widely used strategy for their synthesis is through the Erlenmeyer reaction. Erlenmeyer synthesis involves cyclodehydration of hippuric acid, followed by condensation with an aldehyde in the presence of acetic anhydride to give azalactones. Several catalysts and reagents have been used to bring about this reaction.^[3] Each of the reported protocols has its own merit, with at least one drawbacks: poor yields, expensive catalyst, long reaction times, harsh reaction conditions, or tedious workup procedures. Therefore, exploring new catalytic systems, preferably an environmentally benign method, to overcome these drawbacks is a challenging task for chemists.

From our laboratory, we have reported the successful use of molecular iodine as a catalyst for the synthesis of various biologically important organic molecules and in different organic transformations such as synthesis of dibenzo[*a,j*]xanthenes by a one-pot condensation of 2-naphthol with aldehydes,^[4a] syntheses of β -acetamido- β -aryl-propiophenones,^[4b] α,α' -bis(arylmethylidene) cycloalkanones,^[4c] and *N,N'*-disubstituted ureas/thioureas,^[4d] regioselective synthesis of β -iodoethers,^[4e] and rapid

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Scheme 1. Synthesis of 5-arylmethylidene-2-phenyloxazol-4-ones.

chemoselective synthesis of azines.^[4e] Recently, we have reported the formation azalactones from hippuric acid and araldehydes in the presence of zinc oxide as catalyst under ambient conditions.^[5] In continuation of our work on developing simple and environmentally benign synthesis of azalactones, herein we report a simple, efficient, and cost-effective one-pot synthetic method for the synthesis of these compounds from hippuric acid, acetic anhydride, and an aldehyde using molecular iodine as a catalyst in a microwave-assisted multicomponent reaction.

RESULTS AND DISCUSSION

Initially, we carried out the reaction of hippuric acid, acetic anhydride, and *p*-methoxybenzaldehyde in the presence of catalytic molecular iodine under different reaction conditions such as grinding, heating on a hot plate, refluxing with excess acetic anhydride, and microwave irradiation. Considering reaction time and yield, it is noted that the best results are obtained when the reaction is carried out under microwave irradiation using a domestic microwave oven [five cycles of 10 s each, with cooling periods of 10 s, at 320 W].

To examine the catalytic activity of iodine under solvent-free conditions, a mixture of *p*-methoxybenzaldehyde, hippuric acid, and acetic anhydride was irradiated

Table 1. Conversion of aryl aldehydes into their corresponding 5-arylmethylidene-2-phenyloxazol-4-ones in the presence of molecular iodine in a microwave oven at 320 W

Aldehyde	Product	Yield	Time (s)
<i>a</i> R = C ₆ H ₅	3a	91	50
<i>b</i> R = 4-MeOC ₆ H ₄	3b	96	60
<i>c</i> R = 3,4,5-(MeO) ₃ C ₆ H ₂	3c	96	60
<i>d</i> R = 4-NO ₂ C ₆ H ₄	3d	94	65
<i>e</i> R = 2-NO ₂ C ₆ H ₄	3e	91	70
<i>f</i> R = 3-NO ₂ C ₆ H ₄	3f	91	70
<i>g</i> R = 4-CH ₃ C ₆ H ₄	3g	95	60
<i>h</i> R = 4-ClC ₆ H ₄	3h	95	65
<i>i</i> R = 3-ClC ₆ H ₄	3i	94	65
<i>j</i> R = 2,4-Cl ₂ C ₆ H ₃	3j	92	60
<i>k</i> R = 2-furyl	3k	93	70
<i>l</i> R = (CH ₃) ₂ NC ₆ H ₄	3l	91	60
<i>m</i> R = C ₆ H ₅ (CH ₂)	3m	94	70
<i>n</i> R = 4-FC ₆ H ₄	3n	95	50

Notes. All the products are known and are characterized either by IR, ¹H NMR, ¹³C NMR, and LC-MS analysis or by comparison with the samples prepared by other reported methods. Isolated yields. Melting points of compounds are consisted with reported values.

with varying amount of iodine in a microwave oven for 50 s. It was found that the best results were obtained when 5 mol% of iodine was used. The excellent yield obtained led us to expand this system for the preparation of different azalactones as shown in Scheme 1. The generality of the system was confirmed by using various aromatic aldehydes (Table 1), having both electron-withdrawing and electron-donating substituents. In almost all the cases, the reaction was complete within 50–70 s, giving excellent yield of the desired product. The course of reaction was monitored by thin-layer chromatography (TLC). All the products obtained are characterized by comparison of their melting point with the reported melting points, comparison with authentic samples, and/or their ^1H NMR, ^{13}C NMR, and mass spectral analysis.

EXPERIMENTAL

All araldehydes, ketones, acetic anhydride, hippuric acid, and iodine were commercial products and were used without further purification. Yields refer to isolated products. Melting points were measured on a Büchi B-540 apparatus; IR and ^1H NMR spectra were recorded on Nicolet 400D Fourier transform–infrared (FT-IR) and Bruker AMX (200-MHz) spectrometers respectively. The IR spectra were taken using KBr pellets. Liquid chromatography–mass spectrometry (LC-MS) was performed on a Agilent Technologies 1200 series instrument. All reactions were conducted in a LG domestic microwave oven [model MS-1947C/01 (230 V/320 W/2450 MHz)].

General Procedure for the Synthesis of 5-Arylmethylidene-2-phenyloxazol-4-ones

A mixture of hippuric acid (5 mmol), aldehyde (5 mmol), and molecular iodine (5 mol%) in acetic anhydride (2 ml, 20 mmol) was irradiated in a microwave oven for an appropriate time (Table 1). The contents were cooled to room temperature, and ethanol (5 ml) was added. The mixture was kept aside for 30–45 min, and the crude azalactone thus separated was filtered, washed with hot water, and recrystallized from acetone/water (2:1) to get the pure product.

CONCLUSION

In conclusion, we have developed a mild and an efficient route for the synthesis of azalactones using molecular iodine as a catalyst under microwave irradiation. This method not only provides an excellent complement to azalactones synthesis *via* the Erlenmeyer method but also avoids the use of hazardous reagents and harsh reaction conditions. The advantages of this method include good substrate generality, use of inexpensive reagents and environmentally benign catalyst, and experimental simplicity.

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