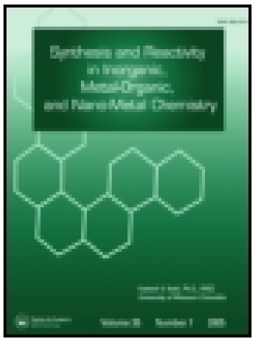

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Microwave-Assisted Erlenmeyer Synthesis of Azlactones Catalyzed by MgO/Al_2O_3 under Solvent-Free Conditions

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Abstract:

MgO/Al_2O_3 catalyzes the synthesis of azlactone derivatives from condensation reaction of aldehydes (or ketones) with hippuric acid and acetic anhydride as a dehydrating agent under microwave irradiation. The low toxicity, low cost, ease of handling and high activity of MgO/Al_2O_3 make this procedure particularly attractive. Also, this catalyst can be easily recovered by decant and can be reused for this condensation five times in succession without considerable loss of its catalytic activity.

Keywords: Azlactone, Hippuric acid, MgO/Al_2O_3, Microwave irradiation, Solvent-Free

INTRODUCTION

Azlactones or 2,4-substituted oxazolin-5-ones and their derivatives have been used in a wide variety of reactions as precursors for the synthesis of various bioactive molecules and show a wide range of pharmaceutical properties.[1] They are particularly useful precursors for the synthesis of aminoacids,[2] peptides,[3] heterocycles,[4] *N*-substituted pyrroles,[5] biosensors[6] and antitumor[7] or anticancer[8] compounds. Hence, synthesis of this heterocyclic nucleus is of continuing interest.

They are usually obtained by condensation reactions of different arylaldehydes with hippuric acid in acetic anhydride, in the presence of anhydrous sodium acetate as a basic catalyst, according to the Erlenmeyer method.[9] A literature search revealed that different reagents have been used to constraction of azlactones involving the perchloric acid,[10] polyphosphoric acid,[11] carbodiimides,[12] $POCl_3$,[13] Al_2O_3,[14] $Bi(OAc)_3$,[15] $Bi(OTf)_3$,[16] silica-supported heteropolyacids,[17] $Yb(OTf)_3$,[18] $Ca(OAc)_2$,[19] supported KF[20] and anhydrous zinc chloride.[21] Although several methods for the synthesis of azlactones have been reported, there is still a demand for simple and facile methodologies for the preparation of azlactones using a cheap and readily available catalyst.

The first study of heterogeneous basic catalysts, which was pointed out by Hattori,[22] was that pines et al.[23] studied sodium metal dispersed on alumina acted as an effective catalyst for double bond migration of alkenes in the 1950s. In the following 50 years, until now, the studies of solid base catalysts have been continuous and progressed steadily. From a single metal oxide, such as MgO, to functionalized mesoporous materials, a variety of solid base catalysts have been developed and studied.

In recent years, the application of microwave-assisted reactions in organic synthesis have attracted a great deal of interest due to the use of microwave irradiation (MWI) develops a facile procedure associated with advantages of short reaction times, uniform heating, higher yields, enhanced selectivity, and associated ease of manipulation.[24, 25]

EXPERIMENTAL

General experimental section

All chemicals including Benzoylaminoethanoic acid (known as hippuric acid) and aldehydes were purchased from Merck or Fluka. Melting points were determined using an electro thermal digital apparatus and are uncorrected. IR spectra were prepared on a galaxy series FT-IR 5000 spectrophotometer using KBr discs. ^{1}H-NMR (300 MHz), ^{13}C-NMR (75 MHz) spectra were recorded on Bruker spectrophotometer in $CDCl_3$ using TMS as an internal standard. Elemental analyses (C, H and N) were conducted using the Elemental Analyser Vario EL III. Microwave irradiation was carried out in a National Microwave Oven, Model No. NN-K571MF. (2450 MHz)

Synthesis of catalyst

A series of Metal Oxides (Metal = Mg, Ni, Pb, Bi and Ce)/Al_2O_3 catalysts were prepared by an incipient wetness method.[26] The gamma Al_2O_3 was first crushed and sieved to 70–100 mesh, then calcined at 5 ^{o}C/min to 500 ^{o}C, followed by holding isothermally at 500 ^{o}C for 2 h. Following the calcinations, an aqueous solution of metal nitrate hexahydrate (10 wt%) was impregnated onto the calcined alumina then dried under vacuum at 110 ^{o}C for 8 h and calcined at 900 ^{o}C for 2h. All calcinations mentioned above were conducted in a muffler furnace under atmospheric conditions. The synthesized catalysts were used in all powder catalyst activity testings.

General procedure for preparation of azlactone derivatives

To a mixture of hippuric acid (1.1 mmol) and the appropriate aldehyde or ketone (1 mmol) were added acetic anhydride (0.25 mL) and MgO/Al_2O_3 (10mol %). The reaction mixture was irradiated using the microwave oven for the appropriate time according to Table 2. The progress of the reaction was followed by thin layer chromatography (TLC). After completion of the reaction, the mixture was cooled to room temperature and then added hot ethanol (2:1) to it, the suspension stirred for 15 min and the catalyst separated by decant. Then solvent concentrated in vacuo to leave the product, a bright yellow solid, which was recrystallized from ethanol.

Selected spectral data

*(2-Bromobenzylidene)-2-phenyloxazol-5-one (**3k**)*

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35-7.65 (m, 6H), 7.77 (s, 1H), 8.21 (d, *J* = 7. 4 Hz, 2H), 8.95 (d, *J* = 7.7 Hz, 1H); IR (KBr, cm^{-1}) 3058, 1793, 1650, 1550, 1323, 1150, 860, 761; Elemental analysis calcd for $C_{16}H_{10}BrNO_2$: C, 58.56; H, 3.07; N, 4.27 found: C, 58.06; H, 3.25; N, 4.45.

4-cyclohexylidene-2-phenyloxazol-5(4H)-one (3n)

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.34-2.13 (m, 10H, cyclohexyl), 7.34-7.88 (m, 5H); IR (KBr, cm^{-1}) 3049, 1780, 1650, 1540, 1319, 1128, 857, 738; Elemental analysis calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81 found: C, 75.06; H, 6.19; N, 5.09.

RESULTS AND DISCUSSION

As a part of our continuous interest directed towards the development of practical safe and environmentally friendly procedures for some important transformations,[27–31] we wish to report a new and efficient method for the synthesis of azlactones from condensation reaction of aldehydes (or ketones) with hippuric acid and acetic anhydride as a dehydrating agent in the presence of MgO/Al_2O_3 catalyst under microwave irradiation (Scheme1).

To achieve suitable conditions for the synthesis of azlactone **3**, various reaction conditions have been investigated in the reaction of benzaldehyde **1** and hippuric acid **2** as a model reaction (Table 1). This reaction was carried out using benzaldehyde (1 mmol), hippuric acid (1.1 mmol) in the presence of acetic anhydride (0.25 mL) and MgO/Al_2O_3 catalyst (10mol %) for 6 min under microwave irradiation (Table 1, Entry 3).

Then, we attempted the reaction of other aldehydes or ketones with hippuric acid under optimized conditions (Table 2). In all cases, the corresponding products were obtained in good to high yields and in case of some aliphatic aldehydes such as propionaldehyde and isobutyraldehyde, under optimized conditions, the corresponding products coulde not be obtained. Also the reactivity of ketones was lower than aldehydes.

The possibility of recycling the catalyst was examined using the reaction of benzaldehyde, hippuric acid and acetic anhydride in the presence of catalyst under optimized conditions. After completion of the reaction as indicated by TLC, the solid product was dissolved in hot ethanol and then the catalyst was separated from the reaction mixture by decant and were washed with hot ethanol (2 × 5 mL), then reused for subsequent reactions for at least five times without any activation process (Table 3).

A possible mechanism for this transformation is proposed in Scheme 2. The reaction of hippuric acid and acetic anhydride produced intermediate (I). This intermediate upon an intermolecular cyclization, yielded the azlactone (II) that supported by good evidence in Erlenmeyer synthesis.[33] Then azlactone derivatives (III) can be obtained from aldol condensation of azlactone (II) and carbonyl compounds. In final step, Mgo/Al_2O_3 catalyst as Lewis acid activates the carbonyl group of aldehyde, and then nucleophilic attack of the intermediate II to the activated carbonyl group of aldehyde produced III.

CONCLUSION

In conclusion, we have developed preparation of a recyclable and highly efficient heterogeneous basic catalyst for the azlactone derivatives synthesis. This procedure offers several advantages such as: high yield of products, operational simplicity, clean reaction conditions, minimum pollution of the environment and environmental friendly character with recyclability of the catalyst without any noticeable loss of activity after at least 5 times.

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Table 1 Optimization of reaction conditions

Entry	Conditions	Metal Oxides/Al_2C	(mol %)	Time (min)	Yield/ %[a]
1	Room Temperature	MgO/Al_2O_3	10	120	26
2	Reflux	MgO/Al_2O_3	10	60	78
3	MW (300)	MgO/Al_2O_3	10	6	92
4	MW (300)	MgO/Al_2O_3	20	6	92
5	MW (300)	MgO/Al_2O_3	5	6	89
6	MW (450)	MgO/Al_2O_3	10	6	86
7	MW (300)	CeO/Al_2O_3	10	6	76
8	MW (300)	Bi_2O_3/Al_2O_3	10	6	70
9	MW (300)	NiO/Al_2O_3	10	6	66
10	MW (300)	PbO/Al_2O_3	10	6	61

[a] Isolated yields.

Table 2 Synthesis of azlactones

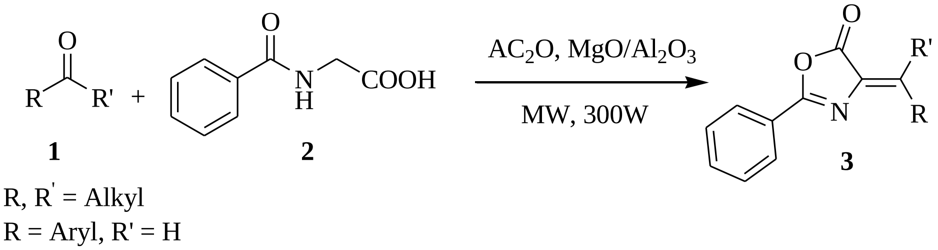
Entry	Carbonyl Compound (**1**)	Time (min)	Yeild (%) [a]	Azlactone	M.P (º C)	
					Found	Reported [lit.]
1	C_6H_5CHO	6	92	**3a**	168-169	167-168 [14.]
2	4-CH_3 C_6H_4CHO	6	89	**3b**	144-145	143-144 [14.]
3	4-CH_3O C_6H_4CHO	9	89	**3c**	156-157	155-157 [18.]
4	3-CH_3O C_6H_4CHO	7	86	**3d**	98-100	99-102 [14.]
5	2-CH_3O C_6H_4CHO	8	84	**3e**	157-158	156-157 [14.]
6	4-$(CH_3)_2N$ C_6H_4CHO	7	92	**3f**	213-214	212-214 [16.]
7	4-F C_6H_4CHO	6	91	**3g**	184-185	183-185 [14.]
8	2,4-Cl_2 C_6H_3CHO	9	88	**3h**	163-164	162-163 [18.]
9	4-NO_2 C_6H_4CHO	5	90	**3i**	238-240	237-239 [16.]
10	3-NO_2 C_6H_4CHO	6	90	**3j**	167-168	166-167 [18.]
11	2-Br C_6H_4CHO	7	87	**3k**	142-143	141-143 [16.]
12	2-Cl C_6H_4CHO	7	85	**3l**	163-164	162-163 [16.]
13	2-Thiophene CHO	5	52	**3m**	173-175	174-175 [14.]
14	Cyclohexanone	10	77	**3n**	136-138	137-138 [32.]

[a] Isolated yields.

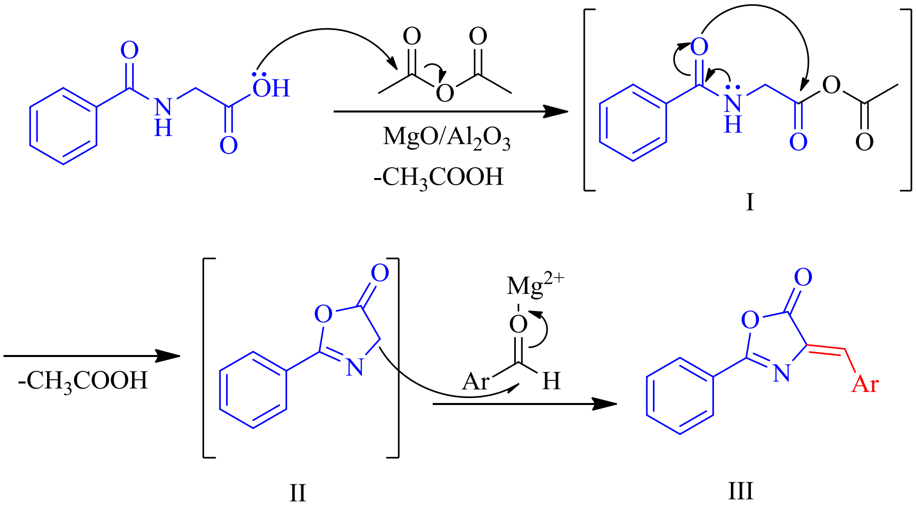
Table 3 Reusability of the catalyst

Recycle Number	Fresh	First	Second	Third	Fourth	Fifth
Yield (%)[a]	92	87	83	78	74	70

[a] Isolated yields.



Scheme 1. Condensation of hippuric acid and carbonyl compounds



Scheme 2. Plausible mechanistic pathway for the synthesis of azlactone derivatives