

## Synthesis, Characterization and Catalytic Activity of $\text{Ce}_1\text{Mg}_x\text{Zr}_{1-x}\text{O}_2$ (CMZO) Solid Heterogeneous Catalyst for the Synthesis of 5-Arylidine Barbituric acid Derivatives

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A series of  $\text{Ce}_1\text{Mg}_x\text{Zr}_{1-x}\text{O}_2$  (CMZO) mixed metal oxide with different molar ratio were prepared by simple co-precipitation method. The prepared materials were tested for their catalytic activity performance using Knoevenagel condensation of various aromatic aldehydes with barbituric acid under solvent-free condition in microwave. The best catalytic activity was obtained with CMZO (1:0.6:0.4). The synthesized materials were characterized by using XRD, FT-IR, SEM-EDS techniques.

**Key Words:** Co-precipitation method, CMZO, Knoevenagel condensation, Solvent-free, Microwave

### Introduction

Barbituric acid and its derivatives are associated with a number of biological activities such as antibacterial, hypotensive and sedative.<sup>1</sup> They are also used as hypnotic and anesthetic agent.<sup>2</sup> As a result of their importance from a pharmacological, industrial and synthetic point of view, there has been increasing interest in the development of efficient methodologies for the synthesis of 5-arylidine barbituric acid *via* Knoevenagel condensation reaction. Generally they are synthesized by condensing the barbituric acid with aldehydes under conventional reflux conditions in aqueous medium.<sup>3</sup>

Many synthetic methods<sup>4,6</sup> for the preparation of these compounds have been reported and uses variety of catalysts such as aminosulphonic acid,<sup>7</sup>  $\text{NH}_4\text{OH}/\text{AcOH}$ , K-10 clay, silica gel, basic alumina, NaCl, KSF-Clay, KSF-NaCl,<sup>6</sup> triethylbenzylammonium chloride.<sup>8</sup> Many of these methods involved expensive reagents, higher temperature and lower yields. However, the research continues to develop efficient and versatile method for the synthesis of 5-arylidine barbituric acid.

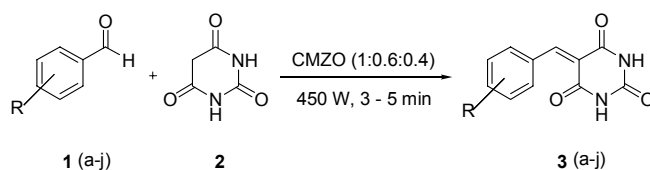
Organic synthesis in the absence of solvent is a powerful tool for the creation of structurally diverse molecules, due to their special selectivity, the easy set-up and work-up, is of great interest.<sup>9</sup> Moreover, solvent free reactions sometimes are faster, taking just a contact with each other. This aspect, coupled with the lower overall cost of running a reaction without solvent and no specially needed equipment, could become a decisive factor in industry. Recently, organic reactions under solvent free condition have attracted chemist's interests, particularly from the view point of green chemistry.

The application of microwave irradiation to the combinatorial chemistry becomes a powerful tool in accelerating the pace of library synthesis.<sup>10-14</sup> Domestic Microwave oven is most popularly used in the synthesis, because of its low cost and ready availability. However, specially fabricated mono-mode microwave reactors provide homogeneous heating, temperature control and more importantly improved safety features. Major aim of this integrated technology is to exploit high degree of molecular diversity and high throughput organic synthesis to rapid

access greatly expanded drug-like compound collection without tedious or time-consuming processes.<sup>15,16</sup>

In recent years, the use of heterogeneous catalysts has received considerable interest in various disciplines including organic synthesis. Synthetic organic routes followed by using heterogeneous catalysts have advantages over their counterparts in which, used catalyst can be easily recycled. Recently, mixed metal oxide as a solid heterogeneous catalyst would be an encouraging alternative owing to its ecofriendlyness and easy synthesis. The use of mixed metal oxide based catalyst offers several advantages, such as active over a wide range of temperature and more resistant to thermal excursions. A mixed metal oxide represents one of the most important and widely employed categories of solid catalyst, either as active phase or supports. A metal oxide and mixed metal oxides utilizes both acid-base and redox properties and constitutes the largest family of catalyst in heterogeneous catalysis.<sup>17-20</sup> In the field of catalysis metal oxide and mixed metal oxide have been extensively used as a catalyst for various organic transformations reactions such as, oxidation reactions,<sup>21-23</sup> dehydrogenation and condensation reaction,<sup>24,25</sup> epoxidation reactions,<sup>26</sup> photocatalytic reaction<sup>27,28</sup> *etc.* Among the various metal oxide and bimetallic mixed metal oxides of  $\text{CeO}_2$ ,  $\text{ZrO}_2$  and  $\text{MgO}$  are widely used as catalyst and catalyst supports in some organic transformation reactions.<sup>29,30</sup>

In the present work, we have prepared a series of mixed metal oxides containing Cerium (IV), Mg (II), Zr (IV) metals with different molar ratio by simple co-precipitation method (Table 1) and decided to investigate, their catalytic activity in the synthesis of 5-arylidine barbituric acid derivatives.



**Scheme 1.** Synthesis of 5-arylidine barbituric acid catalyzed by CMZO solid heterogeneous catalyst

**Table 1.** Series of Ce<sub>1</sub>Mg<sub>x</sub>Zr<sub>1-x</sub>O<sub>2</sub> mixed metal oxide prepared by co-precipitation method

Entry	Mixed metal oxide	Molar ratio
1	ZrO <sub>2</sub>	1:0
2	CeO <sub>2</sub> :ZrO <sub>2</sub>	1:1
3	CeO <sub>2</sub> :MgO:ZrO <sub>2</sub>	1:0.2:0.8
4	CeO <sub>2</sub> :MgO:ZrO <sub>2</sub>	1:0.4:0.6
5	CeO <sub>2</sub> :MgO:ZrO <sub>2</sub>	1:0.6:0.4
6	CeO <sub>2</sub> :MgO:ZrO <sub>2</sub>	1:0.8:0.2
7	CeO <sub>2</sub> :MgO	1:1
8	MgO	1:0

### Experimental Section

**Chemicals.** All the chemicals used were of synthesis grade reagents (Merck) and obtained from commercial suppliers and used as such. All products are known compounds and their physical data; <sup>1</sup>H NMR spectra were essentially identical with those of authentic samples.

**Catalyst preparation.** A series of Ce<sub>1</sub>Mg<sub>x</sub>Zr<sub>1-x</sub>O<sub>2</sub> mixed oxide were prepared by simple co-precipitation method. An aqueous solution containing the requisite quantities of ammonium ceric nitrate, magnesium nitrate and zirconyl nitrate, were prepared separately by using deionized water and mixed together with constant stirring followed by the addition of 20 mL 5% polyethylene glycol (PEG-400) as structure directing agent. This solution was hydrolyzed with 1:1 aqueous ammonia with vigorous stirring until the solution reached to (pH = 9). A yellowish precipitate was formed and the precipitate was allowed to settle down in an electric oven at 60 °C for 24 h. The resulting precipitate was filtered and washed with deionized water and dried at 120 °C for 12 h. Finally the dried powders were calcined at 500 °C for 1 h in air atmosphere. All pure single and mixed oxides were prepared by following same procedure.

**Catalyst characterization.** The prepared mixed metal oxides were characterized by XRD, FT-IR, SEM-EDS techniques. The X-ray powder diffraction patterns of catalyst were recorded on Bruker 8D advance X-ray diffractometer using CuKα radiation of wavelength = 1.54056 Å. The IR spectra were recorded on FT-IR spectrometer (JASCO-FT-IR/4100) Japan, using dry KBr as standard reference in the range of 4000 - 500 cm<sup>-1</sup>. To study the morphology of CMZO (1:0.6:0.4) the SEM analyses were carried out with JEOL; JSM-6330 LA operated at 20.0 kV and 1.0000 nA. The elemental compositions of metal in CMZO (1:0.6:0.4) catalyst were examined using energy dispersive spectrophotometer (EDS).

**Microwave method: General procedure for the synthesis of 5-arylidine barbituric acid derivative.** All chemicals used in this study were commercially available and used without further purification. In a typical reaction procedure an aromatic aldehyde (1 mmol) and barbituric acid (1 mmol) and 0.2 gm of CMZO (1:0.6:0.4) catalyst were taken in a 50 mL of beaker and well mixed with the help of glass rod and irradiated at 450 wt in the domestic microwave oven for 3 - 5 min. The progress of reaction was monitored by TLC [*n*-hexane:ethylacetate (7:3)], after com-

**Table 2.** Knoevenagel condensation of 4-Cl-benzaldehyde and barbituric acid catalyzed by Ce<sub>1</sub>Mg<sub>x</sub>Zr<sub>1-x</sub>O<sub>2</sub> at 450 W in microwave.

Entry	Mixed metal oxide	Molar ratio	At 450 W in Microwave	
			Yield (%) <sup>a</sup>	Time (min)
1	ZrO <sub>2</sub>	1:0	35	10
2	CeO <sub>2</sub> :ZrO <sub>2</sub>	1:1	40	15
3	CeO <sub>2</sub> :MgO:ZrO <sub>2</sub>	1:0.2:0.8	45	15
4	CeO <sub>2</sub> :MgO:ZrO <sub>2</sub>	1:0.4:0.6	55	10
5	CeO <sub>2</sub> :MgO:ZrO <sub>2</sub>	1:0.6:0.4	94	5
6	CeO <sub>2</sub> :MgO:ZrO <sub>2</sub>	1:0.8:0.2	62	10
7	CeO <sub>2</sub> :MgO	1:1	50	15
8	MgO	1:0	60	10

<sup>a</sup>Yield refer to isolated products.

**Table 3.** Knoevenagel condensation catalyzed by CMZO (1:0.6:0.4) solid heterogeneous catalyst at 450 W in microwave

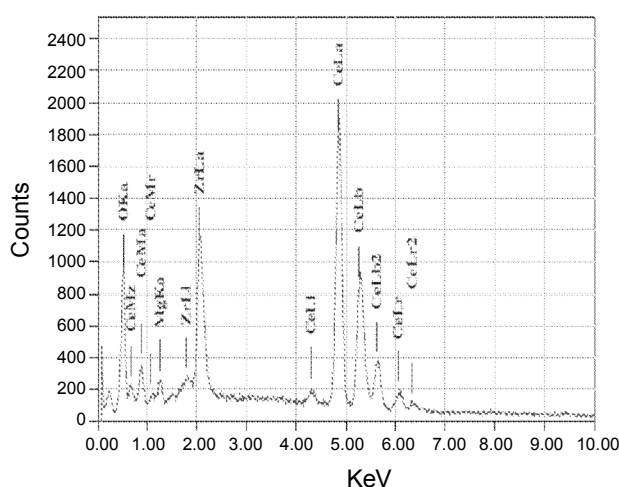
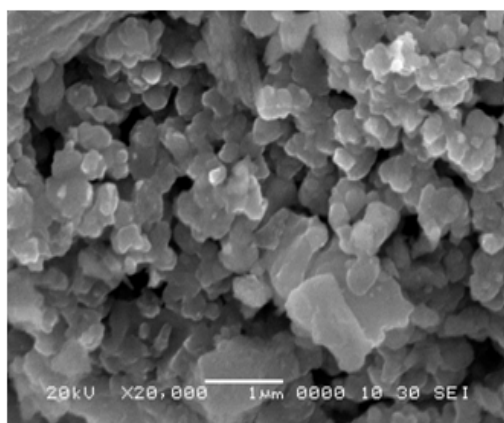
Entry	Ar	Time (min)	Yield <sup>a,b</sup> (%)	M.P. (°C)	
				Found	Lit.
3a	C <sub>6</sub> H <sub>5</sub>	3	90	264 - 266	263 - 265[6]
3b	3-ClC <sub>6</sub> H <sub>4</sub>	3	94	272 - 274	274 - 278[7]
3c	4-ClC <sub>6</sub> H <sub>4</sub>	3	94 (94,94) <sup>c</sup>	298 - 300	304 - 308[7]
3d	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	4	92	252 - 254	248 - 250[7]
3e	4-OHC <sub>6</sub> H <sub>4</sub>	3	94	> 320	> 350[7]
3f	4-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	5	90	281 - 282	282 - 284[7]
3g	4-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	3	92	306 - 308	307 - 309[7]
3h	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	3	90	281 - 283	282 - 284[7]
3i	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	4	92	268 - 269	269 - 271[7]
3j	4-FC <sub>6</sub> H <sub>4</sub>	3	94	295 - 296	-

<sup>a</sup>Yield refer to isolated products; <sup>b</sup>All compounds are known and their physical and spectroscopic data consistent with those of authentic samples; <sup>c</sup>Yield after consecutive cycles.

pletion of reaction, the reaction mixture washed with *n*-hexane followed by cold water to remove excess of aldehydes and any unreacted barbituric acid. The mixture was then placed in ethanol and heated to dissolve the product. After filtration of the catalyst, the solvent was evaporated. A solid was obtained which was recrystallized from ethanol to give the desired product in excellent yield. The authenticity of the products was established by comparing their melting points and <sup>1</sup>H NMR spectra with data in the literature.

**Conventional method: General procedure for the synthesis of 5-arylidine barbituric acid derivative.** In a typical reaction procedure and aromatic aldehyde (1 mmol) and barbituric acid (1 mmol) and 0.2 gm of CMZO (1:0.6:0.4) and 10 mL ethanol were taken in 100 mL round bottom flask. The reaction mixture was reflux at 60 - 70 °C for appropriate time mentioned in Table 3. The progress of reaction was monitored by TLC [*n*-hexane:ethylacetate (7:3)]. At the end of reaction the reaction mixture was cooled at room temperature and filtered to recover the catalyst. Filtrate was poured on ice-cold water; the solid product was obtained, filtered the product and recrystallized from ethanol. The authenticity of the products was established

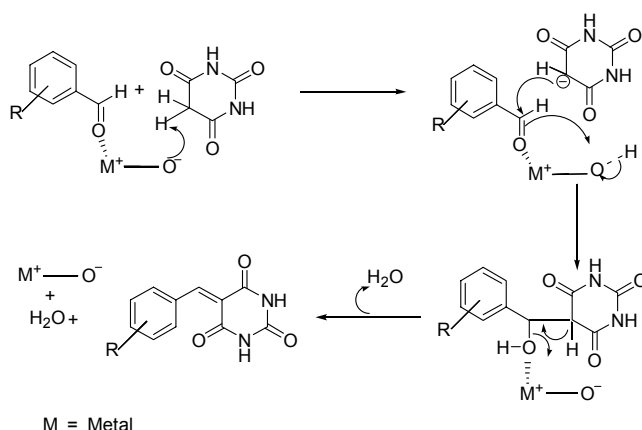




**Figure 3.** SEM and EDS patterns of CMZO (1:0.6:0.4) calcined at 500 °C.

Mg, Zr, O as 60.10 wt % (22.53 a%), 1.27 wt % (2.75 a%), 19.25 wt % (11.09 a%), and 19.38 wt % (63.63 a%).

After understanding the suitability and formation of prepared mixed metal oxides, their catalytic activity studies were undertaken. The catalytic performance was examined using Knoevenagel condensation reaction. Initially we performed a reaction of benzaldehyde and barbituric acid using pure and mixed metal oxides under solvent-free conditions using microwave (450 W) with respect to the time and yield of the products. The obtained results were summarized in Table 2. Catalytic activity result reveals that, the pure  $ZrO_2$  and  $CeO_2$ - $ZrO_2$  mixed oxides exhibited negligible activity for the synthesis of 5-arylidene barbituric acid derivatives. The pure MgO was also employed for the same reaction, but obtained results were not found satisfactory. Insertion of MgO additive in the mixed oxides increases the catalytic activity of catalyst to result in excellent yield of the products, probably due to involvement of strong acidic and basic sites.<sup>34</sup> Interestingly, among these different molar ratio of mixed oxide of  $Ce_1Mg_xZr_{1-x}O_2$  (1:0.6:0.4), catalytic material shows very good catalytic activity for the synthesis of various 5-arylidene barbituric acids (Scheme 1). Therefore it was further used as a catalyst to prepare the various derivatives of 5-arylidene barbituric acids (Table 3). A variety of different substituted aro-



**Scheme 2.** Plausible/probable mechanism catalyzed by CMZO solid heterogeneous catalyst

matic aldehydes possessing an electron donating ( $-CH_3$ ,  $-OCH_3$ ,  $-OH$ ) and electron withdrawing groups ( $NO_2$ ) offered good yield (90 - 94%) and reactions were completed within 3 - 5 min. (Table 3). Mechanically, we believe that the CMZO facilitates both acidic and basic sites ( $M^+—O^-$ ), ( $M$  = Metal cation), due to this reason the rate of reaction may enhance and giving rise to excellent yields. The plausible/probable mechanism is explained in Scheme 2.

Inspiring from these results as MgO is the best additive in the mixed metal oxide and shows excellent catalytic activity. Therefore, we have introduced CaO, SrO and BaO as another additives in the mixed metal oxide and investigated their catalytic potency for the synthesis of 5-arylidene barbituric acid. Surprisingly, we have got excellent results in terms of product yield and slight reduction in reaction time (Table 4). From the observed results, it was proved that, the catalytic activity follows the order  $CaO < SrO < BaO$ , that might be due to increase in the basic strength of alkaline earth metal oxides.<sup>35</sup> From this investigation we conclude that, not only MgO is the best additive but other II-A group metal oxides also serves as a best additives in the mixed metal oxides and shows good catalytic activity for the synthesis of 5-arylidene barbituric acid within a very short reaction times under solvent-free condition in microwave.

For the comparison purpose the same reaction were performed by conventional method (Table 5) under reflux conditions at 50 - 60 °C in ethanol medium. It was observed that, longer reaction time and poor yields were found for conventional methods. It consumes more energy in comparison with microwave method. In addition to that, microwave method consumes less energy provided high to excellent yields (90 - 94%) within extremely short reaction time. Therefore the microwave method is the best methods for the preparation of 5-arylidene barbituric acids derivatives using CMZO solid heterogeneous catalyst. The reusability of the catalyst is important for industrial point of view. Therefore, recovery and reusability of the catalyst was examined. The catalyst was separated, washed it with *n*-hexane, dried at 60 °C and activated at 120 °C for 1 h before catalytic run. The reusability of catalyst was investigated in the

**Table 4.** Knoevenagel condensation of 4-Cl-benzaldehyde and barbituric acid catalyzed by  $Ce_1M_xZr_{1-x}O_2$  at 450W in microwave (M =  $Ca^{2+}$ ,  $Sr^{2+}$  and  $Ba^{2+}$ )

Entry	Mixed metal oxide	Molar ratio	At 450 W in microwave	
			Yield (%) <sup>a</sup>	Time (min)
1	CeO <sub>2</sub> :CaO:ZrO <sub>2</sub>	1:0.6:0.4	94	2.5
2	CeO <sub>2</sub> :SrO:ZrO <sub>2</sub>	1:0.6:0.4	95	2
3	CeO <sub>2</sub> :BaO:ZrO <sub>2</sub>	1:0.6:0.4	95	1.5

<sup>a</sup>Yield refer to isolated products.**Table 5.** The comparative study for the Knoevenagel condensation of **3a**, **3c**, **3d**, **3h** by conventional and microwave methods

Entry	Conventional method		Microwave method	
	Time (min)	Yield <sup>a,b</sup> (%)	Time (min)	Yield <sup>a,b</sup> (%)
<b>3a</b>	55	84	3	90
<b>3c</b>	60	85	3	94
<b>3d</b>	60	84	4	92
<b>3h</b>	60	83	3	92

<sup>a</sup>Yield refer to isolated products; <sup>b</sup>All compounds are known and their physical and Spectroscopic data consistent with those of authentic samples.

reaction of 4-chlorobenzaldehyde with barbituric acid for three cycles with almost consistent activity (Table 3, entry 3c).

### Conclusion

We have prepared for the first time a series of mixed metal oxides  $Ce_1Mg_xZr_{1-x}O_2$  catalytic material by simple co-precipitation method and explore its potential uses in the synthesis of 5-arylidine barbituric acid derivatives as a heterogeneous catalyst. Catalytic activity results revealed that, the  $Ce_1Mg_xZr_{1-x}O_2$  (1:0.6:0.4) catalyst exhibits excellent catalytic activity for the condensation of various aromatic aldehydes and barbituric acid. Most importantly this catalyst facilitates the reaction under solvent-free conditions providing solid supports, with enhancing reaction rate and thereby the excellent yields of the products. We have also compared the yield obtained using microwave and conventional methods using CMZO solid heterogeneous catalyst. A conventional method gives poor yield in comparison with microwave methods. Therefore, the microwave method is the best method for the preparation of 5-arylidene barbiturates. Also, not only MgO is the best additive but also other alkaline earth metal oxides are acts as best additive in the mixed metal oxide and exhibits excellent catalytic activity in the order of  $CaO < SrO < BaO$ . A simple procedure combined with low toxicity and reusability of the catalysts, makes this method an economic and waste-free chemical process for the synthesis of 5-arylidine barbituric acid derivatives.

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