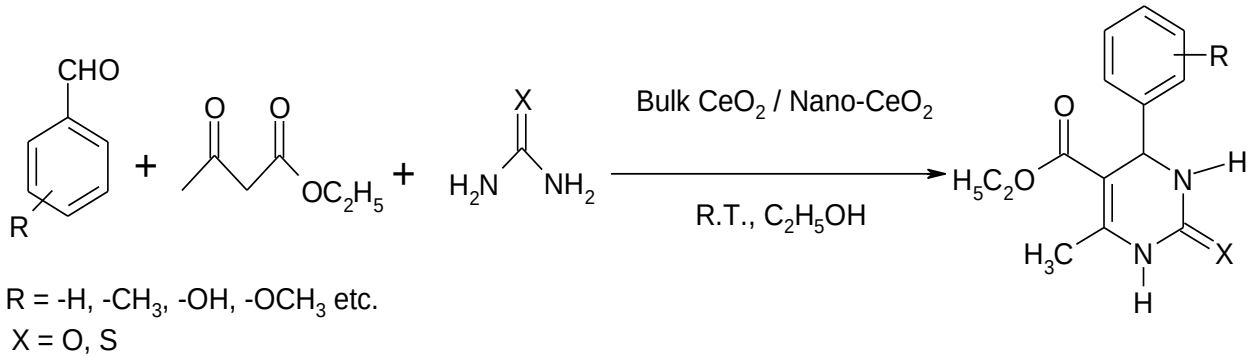
Multicomponent one pot synthesis of Substituted 3,4-Dihydropyrimidin-2-(1H)-ones by Nanocrystalline CeO_2

Patil Vishvanath D.*, Salve Amruta M., Gharat V.D. and Gawand N.
Organic Chemistry Research Laboratory, Department of Chemistry, C.K. Thakur A.C.S. College New Panvel, Raigad, Maharashtra, INDIA
*vishvanathpatil@gmail.com

Abstract
One of the most prominent multicomponent reactions (MCRs), Biginelli reaction has been utilized for the synthesis of 3,4-dihydropyrimidin-2-(1H)-ones catalyzed one-pot condensation of aldehyde, β-ketoester and urea in presence of ethanol. The present study deals with synthesis of biologically active 3, 4-dihydropyrimidin-2(1H)-ones using nano crystalline CeO_2.



R = -H, -CH_3, -OH, -OCH_3 etc.
X = O, S

Keywords: Multicomponent reaction, heterocycle, nanoparticle.

Introduction

As one of the most prominent multicomponent reactions (MCRs), Biginelli reaction has been utilized for the synthesis of 3,4-dihydropyrimidin-2-(1H)-ones catalyzed one-pot condensation of aldehyde, beta-ketoester and urea in presence of ethanol. 3, 4-dihydropyrimidin-2(1H)-ones constituting an important class of heterocyclic organic compounds which possess therapeutic and pharmacological properties such as anti-tumor agent, anti-inflammatory, anti-viral and anti-malarial activities.[4,8,18]

These compounds also serve as calcium channel blockers and neuropeptides Y (NPY) antagonists.[16] These compounds can be synthesized using the classical Biginelli reaction. Apart from original reaction condition, various new reaction conditions have been introduced for the classical Biginelli reaction which include use of Lewis acid catalysts such as $Al(NO_3)_3 \cdot 9H_2O$[10], Iron (III) tosylate[20], $SbCl_3$, Cr $III(NO_3)_3 \cdot 9H_2O$[11] and $LaCl_3/ClCH_2COOH$.[9] Calix arene sulfonic acid under ultrasonic irradiation was successfully investigated for the Biginelli reaction.[22]

The use of ionic liquid systems such as Brønsted acidic ionic liquid [Btto][*p*-TSA],[19]N-(4-sulfonic A), butyl triethyl ammonium hydrogen sulphate[2] and $[Et_3N–SO_3H]Cl$[7], nano-$BF_3.SiO_2$[13], nano alumina[21] found them to be efficient catalysts. The present study deals with synthesis of biologically active 3, 4-dihydropyrimidin-2(1H)-ones using bulk and nano crystalline CeO_2.

Material and Methods

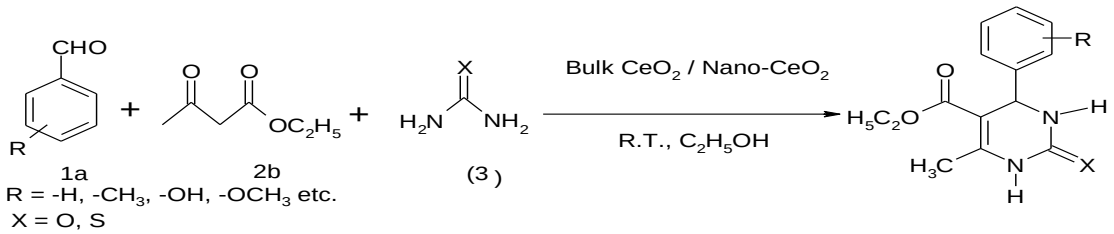
All chemicals were of AR grade and used without further purification. The reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm E-Merck Silica Gel 60F254 precoated plates and were observed with U.V. light. ^{1}HNMR spectra of synthesized compounds were recorded on Varian Mercury plus 300 MHz NMR spectrometer.

The values of all the chemical shifts were expressed in terms of δ with reference to tetramethylsilane (TMS, δ=0) as an internal standard and expressed as ppm. All IR spectra were recorded on Perkin Elmer FT-IR spectrometer as KBr pellets. Melting points were determined by open capillary method and used without correction.

General procedure for synthesis of 3, 4-dihydropyrimidin-2(1H)-ones: A reaction mixture was prepared by dissolving aromatic aldehyde (1a) (1.0 mmol), ethyl acetoacetate (2b) (1.0 mmol) and urea or thiourea (3) (1.0 mmol) in C_2H_5OH (1.5 ml) followed by addition of nano catalyst (0.1mmol).

The reaction mixture was stirred magnetically at room temperature and progress of reaction mixture was studied by using TLC.

The reaction mixture was filtered and catalyst was separated and washed thoroughly with ethyl acetate and reused for the next round of same set of reaction. The catalyst was found to be active to form corresponding product with considerable yield for at least three rounds. The purification of product was done using hot ethyl alcohol.



R = -H, -CH_3, -OH, -OCH_3 etc.
X = O, S

Table 1
Investigation of solvent effects for the synthesis of 5-Ethoxycarbonyl -6-methyl-4-phenyl-3, 4-dihydropyrimidin-2(1H)-one (2a) at room temperature

Entry	Solvent	Bulk CeO_2		Nano-CeO_2	
		Time (min.)	Yield[c] (%)	Time (min.)	Yield[c] (%)
1	CH_2Cl_2	75	35	75	50
2	$CHCl_3$	75	36	75	55
3	CH_3CN	60	40	60	60
4	C_2H_5OH	60	50	10	94

[a]Aldehyde (1.0 mmol) was reacted with ethylacetoacetate(1.0 mmol) & urea(1.0 mmol) in presence of bulk and Nano CeO_2- in solvent C_2H_5OH at room temperature
[cc']Isolated Yields

Table 2
Investigation of catalytic effect of bulk and Nano CeO_2 on synthesis of 5- Ethoxycarbonyl-6-methyl-4-phenyl-3, 4-dihydropyrimidin-2(1H)-one (2a)

Entry	Amount of Catalyst (mmol)	[a]Bulk CeO_2		[a]Nano CeO_2	
		Time (min.)	Yield[b](%)	Time (min.)	Yield[b] (%)
1	0.02	75	30	40	52
2	0.04	75	32	45	58
3	0.06	60	35	47	65
4	0.08	60	40	52	66
5	**0.1**	**60**	**50**	**10**	**94**
6	0.2	20	50	20	94

[a]Aldehyde(1.0 mmol) was reacted with ethylaceto acetate (1.0 mmol) & urea(1.0 mmol) in presence of bulk and Nano-CeO_2 in C_2H_5OH as catalyst at room temperature.
[b]Isolated Yields

Synthesis and characterization of nanocrystalline CeO_2: CAN (3.65 gm.) as source of metal ion and 0.5 gm. of glycine along with L-Ascorbic Acid (1.117 gm.) are taken in given amount in de- ionized water. Mixture is heated on hot plate at 80°C in order to get homogenized and gel is formed after removal of excess of amount of the water. After removal of the water, gel get swallowed and then big bloom of gases comes out for 2-3 seconds. Finally, yellowish powder get formed this powder is further heated at 600°C in the Muffle furnace for 30 minutes to get fine CeO_2 nanoparticles having size (70.5-82.3) nm

Results and Discussion

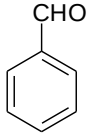
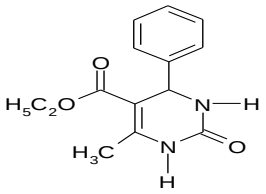
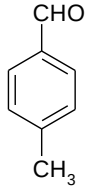
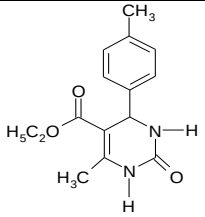
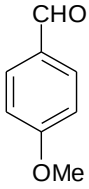
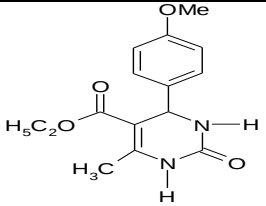
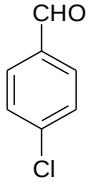
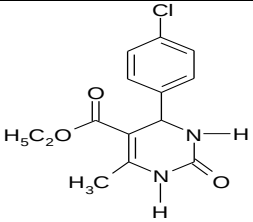
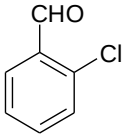
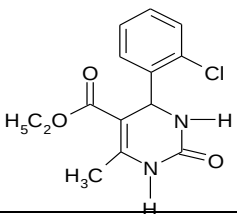
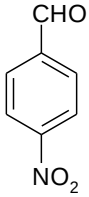
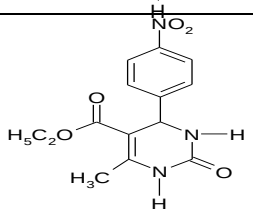
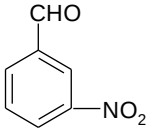
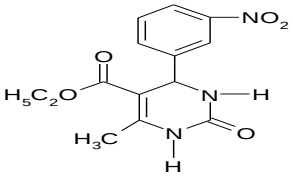
Study of synthesis of 3, 4-dihydropyrimidin-2(1H)-ones: The suitable reaction conditions were established by selecting condensation between benzaldehyde (0.101 ml, 1 mmol), ethylaceto acetate (0.127 ml, 1 mmol) and urea (0.065 gm., 1 mmol) as model reaction.

Selection of Solvent: The model reaction was performed in presence of bulk and nano crystalized CeO_2. When model reaction was performed in polar and non-polar solvents, it was observed that maximum yield of corresponding product was obtained in short reaction time when reaction was performed in C_2H_5OH, a polar solvent (Table 1, Entry 4).

Selection of Catalyst Loading: The catalytic activity of both bulk and nano CeO_2 was studied with respect to loading amount in reaction mixture (Table 2). Thus nano CeO_2 were effective in small amount that is 0.1mmol (Table 2, Entry 5). Even if the amount of catalyst was increased to 0.2 mmol, hardly any improvement in terms of yield and reaction time was observed.

Study of the scope of reaction: The use of 0.1 mmol of bulk and nano CeO_2 in C_2H_5OH was found to an optimum condition for the scheme 1. The scope and general nature of the scheme 1 thus established are studied by using various aromatic aldehydes. Further, the effectiveness of both catalysts was studied by performing scheme 1 in presence of nano CeO_2 separately and the results were compared (Table 3).

Table 3
Synthesis of 3, 4-dihydropyrimidin-2(1H)-ones derivatives with urea and thiourea using bulk CeO_2 and nano CeO_2 separately in C_2H_5OH at room temperature.

Entry	R[a]	Product[b]	CeO_2 (bulk)		Nano CeO_2		M.P. (ºC) Observed (Literature)
			Time (min)	Yield[c] (%)	Time (min.)	Yield[c'] (%)	
1			60	50	10	94	207 (206-208)[22a]
2			60	35	15	92	170 (169-171)[24]
3			60	37	20	93	204 (202-204)[22d]
4			60	40	15	92	215 (213-215)[22d]
5			60	35	20	90	223 (222-224)[23]
6			40	38	10	94	211 (211-213)[22b]
7			50	42	10	91	230 (229-231)[22d]

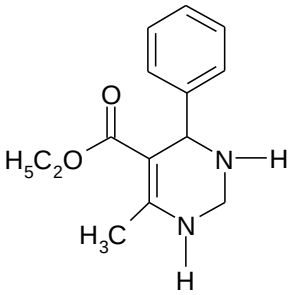
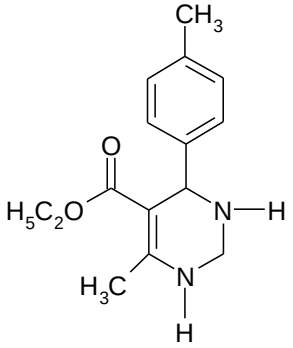
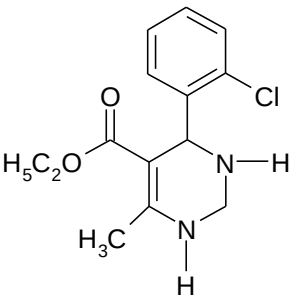
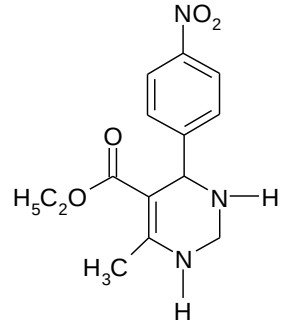
[a]Aldehydes(1.0 mmol) were reacted with ethylacetoacetate or methyl acetate (1.0 mmol) & urea or thiourea (1.0 mmol) in presence of bulk and Nano-CeO_2 in C_2H_5OH
[b]All products were identified by comparing their spectral data and melting points with data from literature
[cc']Isolated Yields.

Table 4
Study of reusability of heterogeneous bulk and nano crystalline CeO_2 (Entry 1, Table 4)

Run	Nano-CeO_2	
	Time (min.)	Yield [c] (%)
1	10	94
2	20	92
3	30	90

*Aldehyde (1.0 mmol) was reacted with ethylacetoacetate(1.0 mmol) & urea(1.0 mmol) in presence of Nano-CeO_2 in C_2H_5OH as catalyst at room temperature. [c]Isolated yields.

Spectral Data of the Products of Scheme 1 (Table 3)

Entry	Products	Spectral Data
1		5-Ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one M.P.- 207^0C I.R.(KBr) cm^{-1}:710, 1092, 1222, 1652, 1720, 2981, 3117, 3247 H^1NMR(300MHz,$CDCl_3$): δ=1.2(t,3H,J=6.8Hz), 2.17(s,3H), 4.5(m,2H,J=6.8Hz), 5.06(s,1H), 7.24(m,5H,Ar-H), 8.22(s,NH), 8.7(s,NH)
2		5-Ethoxycarbonyl-4-tolyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one M.P.- 170^0C I.R.(KBr) cm^{-1}:475, 480, 1087,1225,1649, 1707, 2981, 3115, 3245 H^1NMR(300MHz,$CDCl_3$): δ=1.2(t,3H,J=6.7Hz), 2.21(s,3H), 3.0(s,3H), 4.2(m,2H, J=6.7Hz), 5.3(s,1H), 7.3(m,4H), 8.05(s,NH), 8.46(s,NH)
3		5-Ethoxycarbonyl-4-(2-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one M.P.: 223^0C I.R.(KBr) cm^{-1}:760, 1082, 1223, 1445, 1641, 1702, 2982, 3097, 3237 H^1NMR(300MHz,$CDCl_3$): δ=1.2(t,3H,J=6.7Hz), 2.3(s,3H), 4.0(m, 2H, J=6.7Hz), 5.5(s,1H), 7.2-7.4(m,4H,Ar-H), 8.4(s,NH), 9.1(s,NH)
4		5-Ethoxycarbonyl-4-(4-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one M.P.: 211^0C I.R.(KBr) cm^{-1}: 452, 777, 1092, 1347, 1521, 1649, 1702, 1732, 2924, 3117,3235 H^1NMR(300MHz,$CDCl_3$): δ=1.25(t,3H,J=6.8Hz), 2.6(s,3H), 4.3(m,2H, J=6.8Hz), 5.02(s,1H),8.0-8.12(m,2H,Ar-H,J=7.3Hz), 8.21(d,2H,Ar-H, J=7.3Hz), 8.8(s,NH), 9.3(s,NH)

As summarized in table 3, aromatic aldehydes having electron withdrawing group in presence of ethylacetoacetate or methylacetoacetate and urea or thiourea using catalyst bulk and nanocrystaline CeO_2 get reacted and resulted into 3,4-dihydropyrimidin-2(1H)-ones with excellent yields. A broad range of structurally diverse aromatic compound have shown selective reactivity to give 3, 4-dihydropyrimidinones with high yields.

During synthesis of 3, 4-dihydropyrimidinones nano CeO_2 was found to be more effective than bulk in carrying out conversions in terms of reaction time and yields (Table 3, Entries 1-6).

Study of recyclability of nano CeO_2: Nano CeO_2 catalysts were found to be heterogeneous in reaction mixtures during synthesis. Moreover, it was easy to recover catalysts from reaction mixtures which encouraged checking their reusability. It was observed that catalysts could afford corresponding products for at least three times without much loss in catalytic activity as shown in table 4.

The Proposed Mechanism: We propose the possible mechanism supported by data from literature involving the nano crystalline CeO_2 given in fig. 3.

Conclusion

Recent work help to pramote the high yield, optimum use of catalyst, recycling of catalyst, use of green solvent, minimum work, time saving which all promote the principle of green chemistry for sustainability.

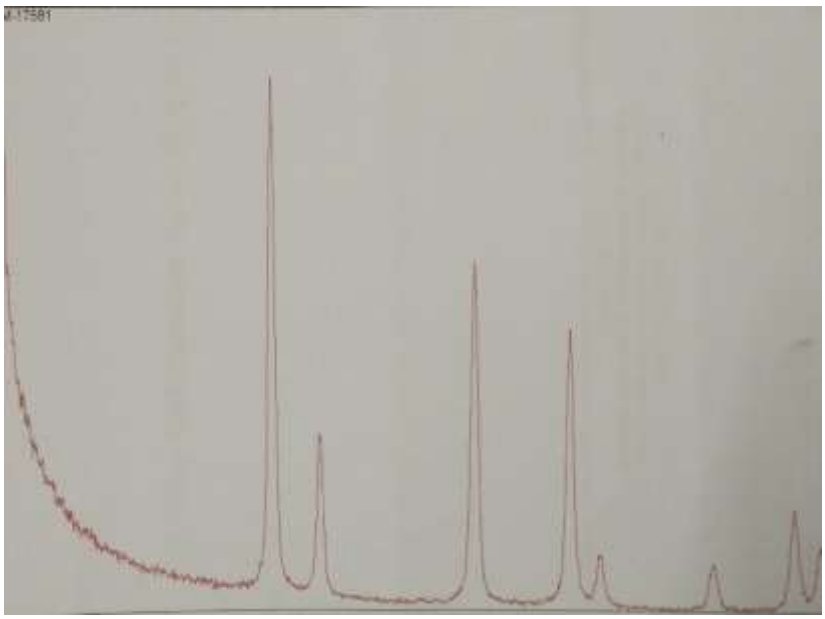


Figure 1: XRD of Ceria Nanoparticle

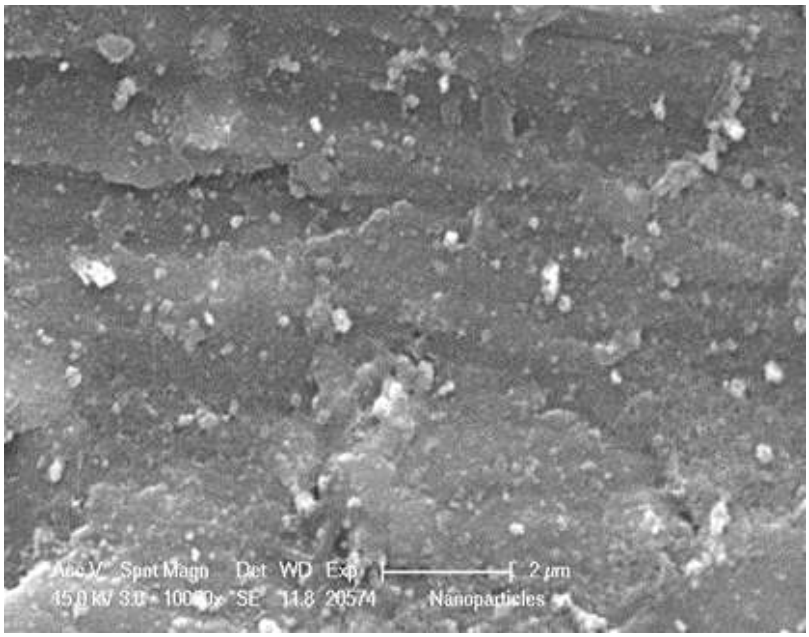
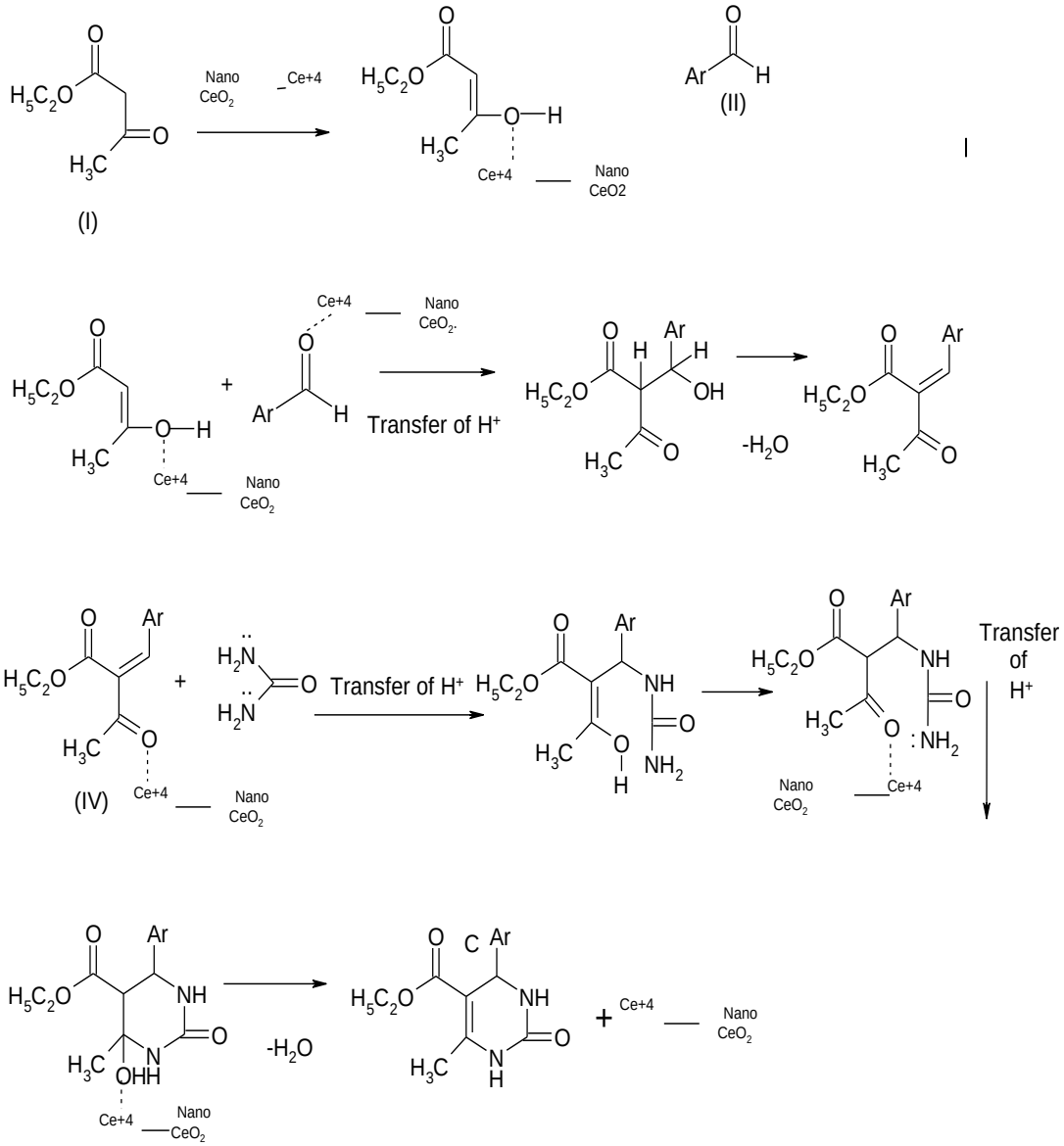


Figure 2: SEM of Ceria Nanoparticle.



Acknowledgement

Authors are thankful to Department of Chemistry of C.K. Thakur A.C.S. College, Panvel and Principal Prof. (Dr.) Vasant Barhate and authors are also thankful to RUSA for promoting research.

References

1. An L., Han Li-li, Wang Zu-jian, Huang Tong-hui and Zhu Hui-dong, Calix[8]arene Sulfonic Acid Catalyzed Three-Component Reaction for Convenient Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones/thiones under Ultrasonic Irradiation, *Biol. Pharm. Bull.*, **39**, 267–271 **(2016)**

2. Azimi S. and Hariri M., One-pot synthesis of fused 3,4-dihydropyrimidin- 2(1H)- thiones by three component condensation method by using recyclable ionic liquid under mild conditions, *Iran Chem. Commun.*, **3,** 13-20 **(2016)**

3. Bamoniri A., Mirjalili B.F. and Karbasizadeh H., Nano SbCl5.SiO2: An efficient and heterogeneous catalyst for the synthesis of 3,4-dihydropyrimidin-2(1H)-one (thione) derivatives under solvent-free conditions, *Scientia Iranica C*, **22(6)**, 2332-2340 **(2015)**

4. Focher F., Ubiali D., Pregnolato M., Zhi C., Gambino J., Wright G.E. and Spadari S., Novel Nonsubstrate Inhibitors of Human Thymidine Phosphorylase, a Potential Target for Tumor - Dependent Angiogenesis, *J. Med. Chem.*, **42**, 2601 **(2000)**

5. Hassanpour A., Abolhasani J. and Khanmiri R.H., One-Pot and Green Procedure for the Synthesis of 3,4-Dihydropyrimidin-2(1H)-(thio)ones Using ZnO Nanoparticles as a Solid Acid Catalyst, *Journal of the Korean Chemical Society*, **58(5)**, 445-449 **(2014)**

6. Hazarika P., Gogoi P., Hatibaruah S. and Konwar D., Water mediated efficient one-pot synthesis of bis-(4-hydroxycoumarin) methanes, *Green Chemistry Letters and Reviews*, **4(4)**, 327-339 **(2011)**

7. Joshi V.M., Vyawahare S.K., Tekale S.U., Shinde S.B., Fareesuddin M., Dake S.A., Shisodia S.U. and Pawar R.P., Microwave assisted expeditious synthesis of bioactive

polyhydroquinoline derivatives, *Eur. Chem. Bull.*, **2(7)**, 481-484 **(2013)**

8. Kappe C.O., 4-Aryldihydropyrimidines via the Biginelli Condensation:Aza-Analogs of Nifedipine-Type Calcium Channel Modulators, *Molecules*, **3(1)**, 1-9 **(1998)**

9. Khajesamani H., Pouramiri B., Kermany E.T. and Khabazzadeh H., An Efficient, Three-Component Synthesis of 3,4-Di Hydropyrimidin-2(1H)-Ones Using LaCl3/ClCH2COOH as Environmentally Benign and Green Catalytic System, *Journal of Sciences, Islamic Republic of Iran*, **25(4)**, 323- 327 **(2014)**

10. Kolvari E. and Mirzaeeyan M., AL(NO3)3 · $9H_2O$: an efficient catalyst for the one-pot synthesis of 3,4-dihydropyrimidin-2(1h)-ones both under reflux or solvent-free conditions, *Journal of Chemistry*, http://dx.doi.org/10.1155/2013/325268 **(2013)**

11. Lashkari M., Heydari R. and Mohamadpour F., An Efficient Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-Ones and Thiones Catalyzed by a Novel Brønsted Acidic Ionic Liquid under Solvent-Free Conditions, *Acta Chemica Iasi*, **24(1)**, 29-42 **(2016)**

12. Mirjalili B.F., Bamonirib A. and Akbari A., One-pot synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones (thiones) promoted by nano-$BF_3.SiO_2$, *J. Iran Chem. Soc.*, **8**, S135-S140 **(2011)**

13. Mirjalili B.F. and Zamani L., Nano-$Ticl_4.SiO_2$: a Versatile and Efficient Catalyst for Synthesis of Dihydropyrimidones via Biginelli Condensation, *S. Afr. J. Chem.*, **67,** 21–26 **(2014)**

14. Mohamadpour F., Maghsoodloua M.T., Heydaria R. and Lashkari, One-step procedure for the preparation of tertiary.alpha.-ketols from the corresponding ketones, *Org. Chem. Res.*, **2(2)**, 127-133 **(2016)**

15. Nasr-Esfahani M., Jafarhoseini S. and Mohammadi F., Fe_3O_4 Nanoparticles as an Efficient and Magnetically Recoverable Catalyst for the Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones under Solvent-Free Conditions, *Chinese Journal of Catalysis*, **32(9)**, 1484–1489 **(2011)**

16. Pendergast W., Dickerson S.H., Johnson J.V., Dev I.K., Ferone R., Duch D.S. and Smith G.K., Benzoquinazoline Inhibitors of Thymidylate Synthase: Enzyme Inhibitory Activity and Cytotoxicity of Some Sulfonamidobenzoylglutamate and Related Derivatives, *J. Med. Chem*., **36**, 3464 **(1993)**

17. Pourshamsian Kh., A novel class of heterogeneous catalysts based on toluene diisocyanate: the first amine-functionalized nano-titanium dioxide as a mild and highly recyclable solid nano catalyst for the Biginelli reaction, *Int. J. Bio-Inorg. Hybr. Nanomater*, **4(4)**, 225-231 **(2015)**

18. Ravnyak G.C., Kimball S.D., Beyer B., Cucinatta G., Dimarco J.D., Gougoutas J., Hedberg A., Malley M., McCarthy J.P., Zhang R.A. and Morreland S., Calcium Entry Blockers and Activators: Conformational and Structural Determinants of Dihydropyrimidine Calcium Channel Modulators., *J. Med. Chem*, **38**, 119 **(1995)**

19. Shingare M. and Dhanmane S., Simple and Efficient One Pot Solvent Free Synthesis of 3,4- Dihydropyrimidin-2(1H)-Ones and Thiones by using Ionic Liquid at Reflux Condition, *Chemistry and Materials Research*, **7(3),** 27-31 **(2015)**

20. Starcevich J.T., Laughlin T.J. and Mohan R.S., An Efficient Synthesis of 3,4-Dihydropyrimidin-2(1***H***)-Ones and Thiones Catalyzed by a Novel Brønsted Acidic Ionic Liquid under Solvent-Free conditions, *Tetrahedron Letters*, **54**, 983–985 **(2013)**

21. Tanna J.A., Chaudhary R.G., Gandhare N.V. and Juneja H.D., Alumina nanoparticles: A new and reusable catalyst for synthesis of dihydropyrimidinones derivatives, *Adv. Mater. Lett.*, **7(11)**, 933-938 **(2016)**

22. Zhang Y., Wang B., Zhang X., Huang J. and Liu C., An Efficient Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-Ones and Thiones Catalyzed by a Novel Brønsted Acidic Ionic Liquid under Solvent-Free Conditions, *Molecules*, **20**, 3811-3820 **(2015)**.

(Received 25th October 2020, accepted 29th December 2020)