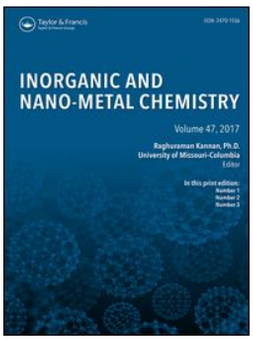

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Inorganic and Nano-Metal Chemistry

ISSN: 2470-1556 (Print) 2470-1564 (Online) Journal homepage: http://www.tandfonline.com/loi/lsrt21

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To cite this article: S. Sumathi & G. Buvaneswari (2017): Room temperature synthesis of 3, 4 – Dihydropyrimidin-2(1H)-one using Apatite like oxyphosphate, Inorganic and Nano-Metal Chemistry, DOI: 10.1080/24701556.2017.1284088

To link to this article: http://dx.doi.org/10.1080/24701556.2017.1284088

Accepted author version posted online: 06 Feb 2017.

Room temperature synthesis of 3, 4 - Dihydropyrimidin-2(1H)-one using Apatite like oxyphosphate

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Abstract

An oxyphosphate of formula $BiCa_4(PO_4)_3O$ was prepared and characterized by powder XRD, FTIR, and SEM-EDAX techniques. The catalytic activity of the synthesized compound was explored in the preparation of 3,4-dihydropyrimidin-2(1*H*)-one using Biginelli reaction. Influence of parameters such as temperature and solvent on this reaction using this heterogeneous catalyst was studied. A higher yield of 98% of the 3,4-dihydropyrimidin-2(1*H*)-one was achieved within 120 min of duration at room temperature in the presence of acetic acid (AcOH).

Keywords: Biginelli reaction, Phosphates, 3,4 dihydropyrimidin-2(1H)-one, Acetic acid, oxyphosphate.

Introduction

Multicomponent reactions are important with respect to synthetic organic chemistry, because the desired product can be achieved in one pot using three or more components. Biginelli[1] reported a multicomponent reaction in the year 1893 for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-one (DHPM) via the cyclic condensation of benzaldehyde, ethyl acetoacetate, and urea under acidic conditions. 3,4- dihydropyrimidin-2(1*H*)-ones have attracted the attention of the researchers because of its pharmacological activities such as antiviral, antitumor, antibacterial, anti-inflammatory actions[2-5]. A bioactive alkaloid such as batzelladine B containing this DHPM moiety isolated from marine source is found to inhibit the binding of the HIV gp – 120 to CD4 cells, so it brings out a new field towards the development of AIDS therapy[6]. Therefore this heterocyclic moiety has attracted the attention of many organic chemists. It is observed that generally, the experimental procedure reported for the Biginelli reaction involves the use of mineral acids, organic solvents and high temperature.

From the viewpoint of the potential applications of 3, 4-dihydropyrimidine-2(1*H*)-ones it is necessary to find out a versatile, simple and eco-friendly process. In recent times, Biginelli reaction with modified experimental conditions has been reported. Modifications have been made with respect to catalysts, solvents and temperature. Several improved procedures have been reported using Lewis acids and other heteropolyacids[7-13] as well as protic acids as promoters. Many other methods including, microwave radiations, ultrasonic, clay, ionic liquids and catalyst free procedures also reported[14, 15]. Recently kaolin[16], bronsted acidic ionic liquid based magnetic nanoparticle[17] have been reported. However, some of the newer reported methods also

suffer from drawbacks such as low yield, high temperature, cumbersome product isolation procedures, expensive catalysts and environmental pollution. Among the phosphates, natural phosphates[18], diammonium hydrogen phosphate[19], ammonium dihydrogen phosphate[20], hydroxyapatite[21] and fluorapatite[22] alone or doped with metal halides reported as catalysts in the Biginelli reaction. Modified apatite are found to be a better catalyst in this condensation reaction than that of hydroxyapatite or fluorapatite.

Bismuth has an electronic configuration of $[Xe]4f^{14}5d^{10}6s^{2}6p^{3}$, and due to the weak shielding of the 4f electrons (Lanthanide contraction), bismuth(III) compounds exhibit Lewis acidity[23]. Recently, bismuth compounds have emerged as efficient Lewis acids due to their relatively low toxicity[24]. Some of the bismuth compounds such as bismuth triflate[25], bismuth chloride[26], bismuth subnitrate[27] and bismuth nitrate[28] were reported in the Biginelli reaction. Lewis acidic nature of the bismuth is utilized in many organic transformations. This kind of bismuth substituted oxyphosphate is not studied for any kind of organic transformations. Acidic nature of phosphate and bismuth drive us to for organic transformation. In view of the importance of Biginelli reaction products, current study is attempted to investigate the catalytic activity of hitherto unexplored apatite phosphates of the formula $BiCa_4(PO_4)_3O$ (BCPO) – an oxyphosphate for the first time in the Biginelli condensation reaction.

Experimental

Preparation of the catalyst

Oxyapatite of the formula - $BiCa_4(PO_4)_3O$, was prepared by high temperature solid state method[29] using stoichiometric quantities of Bi_2O_3 (CDH, 99 %), $CaCO_3$ (S.d fine. 99.9 %), $NH_4H_2PO_4$ (S.d. fine L.R). A thoroughly ground reactants were heated at 300^{o} C for 6 h, 700^{o} C

for 12 h, 950^{o} C for 24 h, 1050^{o} C for 24 h with intermittent grinding. The compound was characterized by powder X- ray diffraction (D8 Advance, Bruker) with CuK_{α} radiation in the 2θ range 10 -70^{o} at room temperature, Fourier Transform Infrared spectroscopy (FT-IR) (Thermonicolet Avator 330 USA model), Scanning Electron microscopy (F E I Quanta FEG 200).

General procedure for the preparation of 3,4-dihydropyrimidin-2(1H)-one

Biginelli reaction was carried out using a mixture of 10 mmol of ethyl acetoacetate, 10 mmol of benzaldehyde and 10 mmol of urea with 1.0 g of BCPO at room temperature (Acetic acid solvent). After the completion of the reaction (monitored by Thin layer chromatography), the catalyst was separated from the reaction mixture by filtration and the liquid part was poured into water. The solid product obtained was filtered and dried. The crude product was purified by recrystallization in ethanol. The products were characterized by melting point, FT-IR, Proton nuclear magnetic resonance (^{1}H NMR) and High resolution Mass spectroscopy (HR-Mass).

Results and Discussion

Catalyst Characterization

Powder X-ray diffraction analysis indicates the formation of highly crystalline and completely pure (Fig. 1) phase without any impurities. XRD pattern indexed based on JCPDS (52-1880). FT-IR confirms the formation of apatite phosphates[29, 31]. The peaks at 1042 and 971 cm^{-1} are attributed to the asymmetric stretching vibrations for PO_4^{3-}. The peaks ate 935 cm^{-1} and 559-602 cm^{-1} corresponds to the symmetric stretching and bending vibrations of PO_4^{3-} respectively (Fig. 2). SEM analysis exhibits the formation of homogeneous products. The

morphology displays the formation of diffused particles. EDAX analysis confirms the presence of bismuth, calcium, in the oxyapatite compound (Fig. 3).

Catalytic activity of $BiCa_4(PO_4)_3O$

Best results are achieved with 1 g of the catalyst at room temperature (Scheme 1) and 0.25 g of the catalyst under reflux condition (Table 1) without any solvent. Larger amount of the catalyst does not improve the yield. Effect of the solvents is studied both at room temperature and reflux condition. Among the solvents studied, acetic acid results in high % yield both at room temperature (98%) and under reflux condition (98%) (Table 2). The contribution of acetic acid is checked by carrying out the reaction in the absence of the catalyst. The yield of the product is found to be 69 % (at room temperature (2 h)). This confirms the catalytic efficiency of BCPO toward this reaction. Acetic acid- a Bronsted acid reflects its efficiency as an additive in the Biginelli reaction[32].

Oxyphosphate is noted to show a better activity. The derivatives of Biginelli products are synthesized by varying the aldehydic part in benzaldehyde using the optimized reaction condition (Catalyst –BCPO, amount - 1 g; Solvent – acetic acid; room temperature reaction). Even though, the same percentage of yield is observed with acetic acid as solvent both at room temperature and at reflux condition, room temperature condition is chosen for the derivatives because of its operational simplicity and low energy consumption. Irrespective of the substituent in aromatic aldehydes moderate to good yields are obtained (Table 3). The products are

confirmed by FTIR, 1H NMR and HR mass spectroscopy and the spectral data of the derivatives are given in Table 5.

The recovered catalyst was washed with ethanol and dried at 80^{o}C. The reusability of the recovered catalyst was checked for the model reaction with acetic acid at room temperature (upto 3 cycles) (Table 3). The yields of the product are comparable with the first cycle. It shows the efficiency of the oxyapatite catalyst towards this reaction.

The activity of the current catalyst is compared with other catalysts where acetic acid and toluene is used as solvent. The details are summarized in the table mentioned below (Table 4). Considering the similar size of the ions Ca^{2+} and Bi^{3+} [39], replacement of Ca^{2+} by Bi^{3+} introduces a highly charged ion into the lattice thus enhancing the acidic character [40]. The activity of this catalyst could be due to the enhanced acidic nature of the compound by bismuth substitution because the surface area of the synthesized compound is found to be meager (SA = 0.2381 $m^2 g^{-1}$). Most of the heterogeneously catalyzed Biginelli condensation reactions are reported at higher temperature [41, 42]. But the current system (BCPO) gives 98 % of the product within 120 min of duration at room temperature

Ramalinga et al [43] proposed the mechanism for the bismuth type of compounds where the formation of acyl imine intermediate is stabilized by bismuth. Acyl imine intermediate is the rate determining step for the biginelli condensation. But still the mechanism for this type of bismuth compound is underway. In the case of oxyapatite, an enhanced activity is observed towards both the electron withdrawing and electron releasing substituents (Table 3). From the results it is concluded that the substituted apatite like oxyphosphate compound is suitable

catalyst for the preparation of 3, 4-dihydropyrimidin-2(1*H*)-one and its derivatives at room temperature.

Conclusions

In conclusion, it is noted that Bi^{3+} ions substitution in hydroxyapatite and O in OH site modifies the surface chemistry and thus enhances the catalytic activity. Bismuth substituted oxyapatite $BiCa_4(PO_4)_3O$ has proved to be an effective catalyst. An excellent yield of 98 % is obtained at room temperature within 120 min of duration with simple experimental procedure compared with other phosphate catalysts.

Acknowledgement

The authors thank SAIF, Department of chemistry, IITM for SEM-EDAX, ^{1}H NMR and HR-Mass spectroscopy. We also thank TBI and Powder XRD lab VIT University, Vellore.

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Table 1 Optimization of experimental condition with respect to catalyst amount

Amount of the catalyst (g)	Catalyst	
	Room temperature %Yield (Time/min)	Reflux condition %Yield (Time/min)
2.0 (3 mmol)	25(85)	81(40)
1.0 (1.5 mmol)	47(55)	78(45)
0.5 (0.75 mmol)	34(60)	62(30)
0.25 (0.37 mmol)	35(70)	83(75)

Table 2 Optimization of experimental condition with respect to solvent

Solvent	Catalyst	
	Room temperature % Yield (Time/h)	Reflux condition % Yield (Time/h)
Acetic acid	98(2)	98(0.45)
Acetonitrile	42(2)	20(2)
Ethanol	4(3)	81(6.5)
n-hexane	11(2)	14(2.45)
Chloroform	11(14)	22(12)
Toluene	7(11)	40(3)

Table 3 $BiCa_4(PO_4)_3O$ catalyzed synthesis of different dihydropyrimidinones

Substituents attached to benzaldehyde	Yield (%)	Time (h)	Melting point (Mp) (°C)	
			Found	Reported
Nil (benzaldehyde) (4a)	98, 93[a], 90[b]	2	202-204	198-200 [33]
3,4-dimethoxy (4b)	87	7	176-178	175-177 [34]
4- methoxy (4c)	80	7	202-204	201-202 [33]
4-methyl (4d)	86	6	216-218	213-216 [33]
4-chloro (4e)	69	18	212-214	209-212 [34]
4-fluoro (4g)	52	6	182-184	182-184 [34]
4-ethyl (4h)	56	9	172-174	174-176 [35]

Note: [a, b] – second and third runs

Table 4 Comparison with other reported catalysts

Catalyst	Time	Temperature	Solvent	% yield	Ref
NaH_2PO_4	20-40 min	45-50^oC	Acetic acid	66	[32]
KH_2PO_4	20-40 min	45-50^oC	Acetic acid	89	[32]
K_2HPO_4	20-40 min	45-50^oC	Acetic acid	50	[32]
H_3BO_3	0.5 – 2 h	100^oC	Acetic acid	97	[36]
Heulandite	4 – 5 h	100^oC	Acetic acid	75	[37]
Natural phosphate doped with zinc chloride	48 h	Reflux	Toluene	95	[18]
$ZrH_2(PO_4)_2$	1 h	Reflux	Toluene	88	[38]
Hydroxyapatite	72 h	Reflux	Toluene	20	[21]
Fluorapatite	72 h	Reflux	Toluene	18	[22]
$BiCa_4(PO_4)_3O$	2 h	Room temperature	Acetic acid	98	Present work

Table 5 Spectral data for the derivatives (^{1}H NMR, FT-IR and HR-Mass)

4a	^{1}H NMR (500 MHz, DMSO-d_6): 9.153 (s,1H, NH), 7.713 (s,1H, NH), 7.233 (m,5H, Ar-H), 5.126 (s,1H, CH), 3.959 (q, 2H, CH_2,) 2.229 (s,3H, CH_3) 1.053 (t,3H,CH_3) IR (KBr): 3245, 3114, 1725, 1700, 1648 MS (m/z): 260.98
4b	^{1}H NMR: 9.130 (s, 1H, NH), 7.598 (s,1H,NH), 6.903-6.719 (m,3H,Ar-H), 5.1 (d,1H,CH), 4.012 (q, 2H, OCH_2CH_3), 3.712 (s,6H,OCH_3), 2.239 (s,3H,CH_3), 1.124 (t,3H, CH_3) IR (KBr): 3242, 3112, 1720, 1706, 1651 MS (m/z): 320.86 (M+)
4c	^{1}H NMR: 9.129 (s,1H,NH), 7.650 (s,1H,NH), 7.169-6.869 (m,4H), 5.101 (d,1H,CH), 4.010 (q,2H,OCH_2CH3), 3.724 (s,3H,OCH_3), 2.238 (s,3H, CH_3),1.112 (t,3H, CH_3) IR (KBr): 3247, 3113, 1722, 1708, 1654 MS (m/z): 290.34 (M+)
4d	^{1}H NMR: 9.130 (s,1H,NH), 7.659 (s,1H,NH), 7.131 (s,4H), 5.102 (d,1H,CH), 4.008 (q,2H, OCH_2CH_3), 2.264 (s,6H,CH_3), 1.114 (t,3H,CH_3) IR (KBr): 3243, 3113, 1704, 1649 MS (m/z): 274.13 (M+)
4e	^{1}H NMR: 9.219 (s,1H,NH), 7.752 (s,1H,NH), 7.405-7.244 (m,4H), 5.150 (d,1H,CH), 3.998 (q,2H, OCH_2CH_3), 2.244 (s,3H, CH_3), 1.115 (t,3H,CH_3) IR (KBr): 3246, 3112, 1724, 1706, 1651 MS (m/z): 294.07 (M+)
4f	^{1}H NMR: 9.200 (s,1H,NH), 7.729 (s,1H,NH), 7.281-7.130 (m,4H), 5.154 (d,1H,CH), 3.999 (q,2H, OCH_2CH_3), 2.246 (s,3H, CH_3), 1.112 (t,3H,CH_3) IR (KBr): 3243, 3113, 1704, 1649 MS (m/z): 278.13 (M+)
4g	^{1}H NMR: 9.137 (s,1H,NH), 7.669 (s,1H,NH), 7.150 (s,4H), 5.112 (d,1H,CH), 4.014 (q,2H,OCH_2CH_3), 2.557 (q,2H,CH_2), 2.244 (s,3H,CH_3), 1.139 (t,6H,CH_3) IR (KBr): 3245, 3114, 1725, 1700, 1648 MS (m/z): 288.00 (M+)

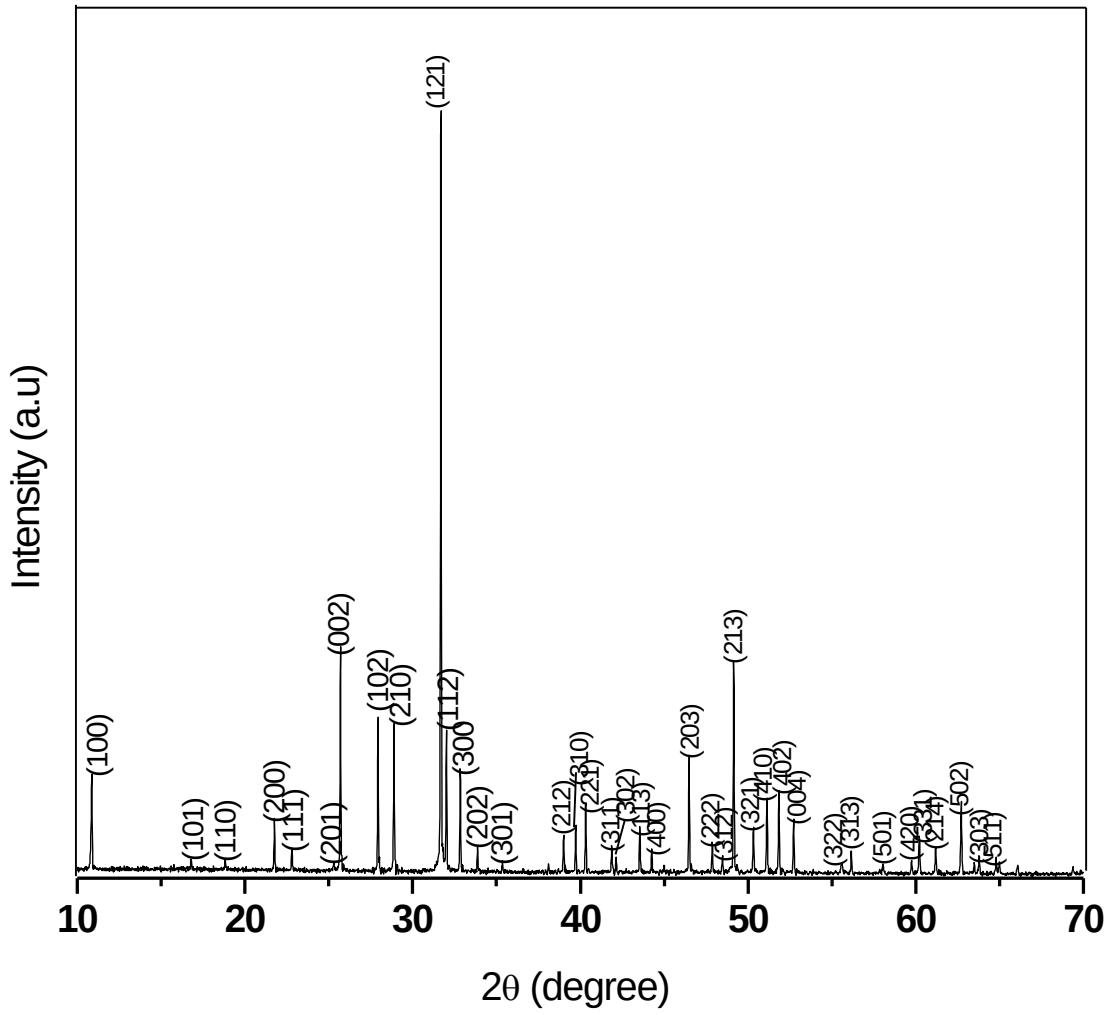


Fig.1 Powder XRD pattern of $BiCa_4(PO_4)_3O$

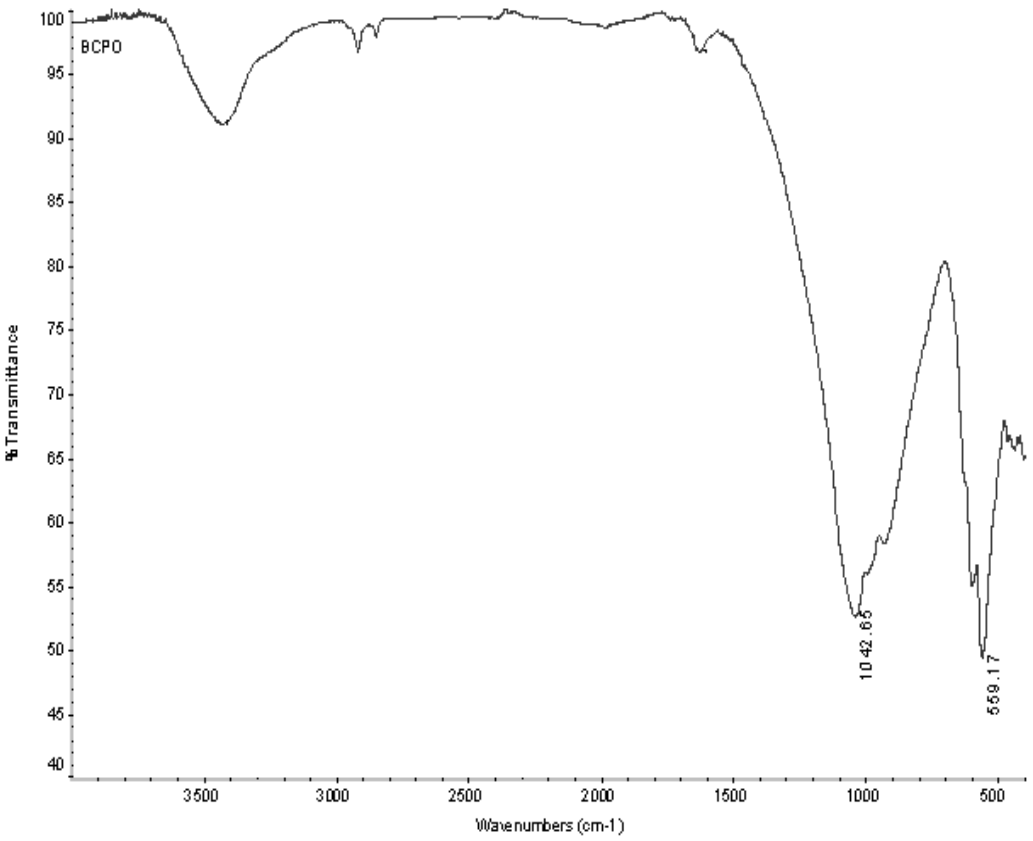
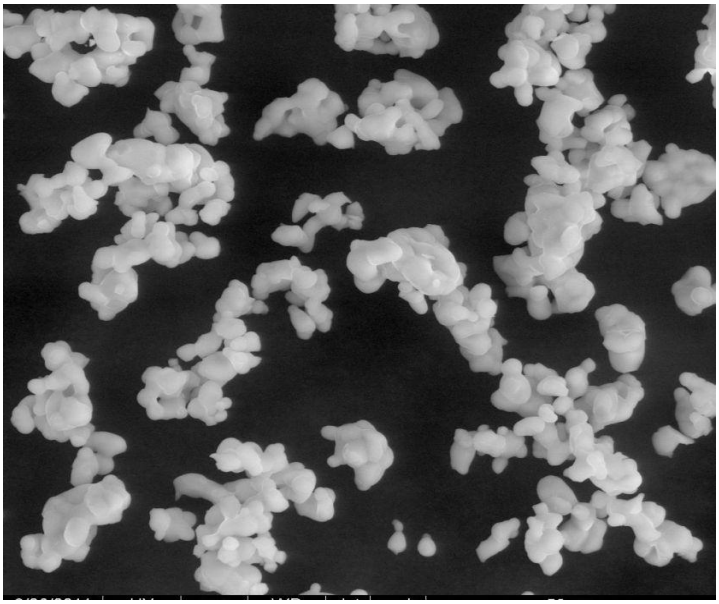


Fig. 2 FT-IR Spectrum of $BiCa_4(PO_4)_3O$



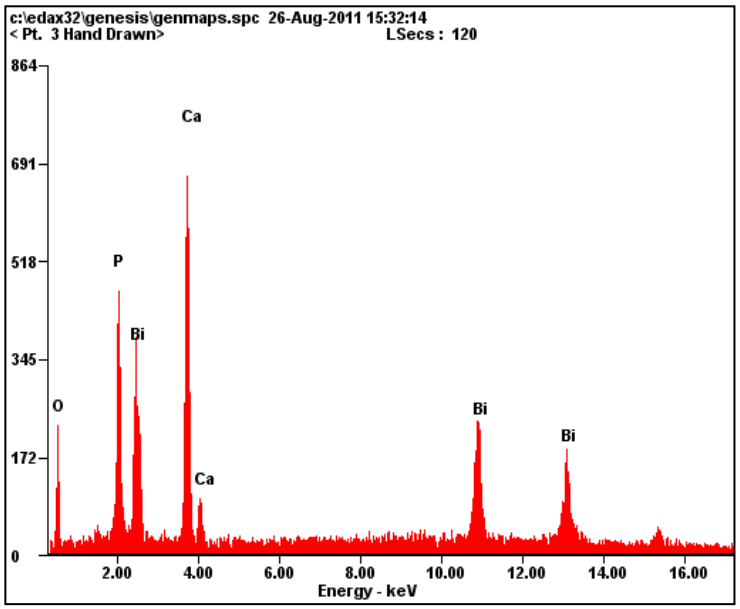
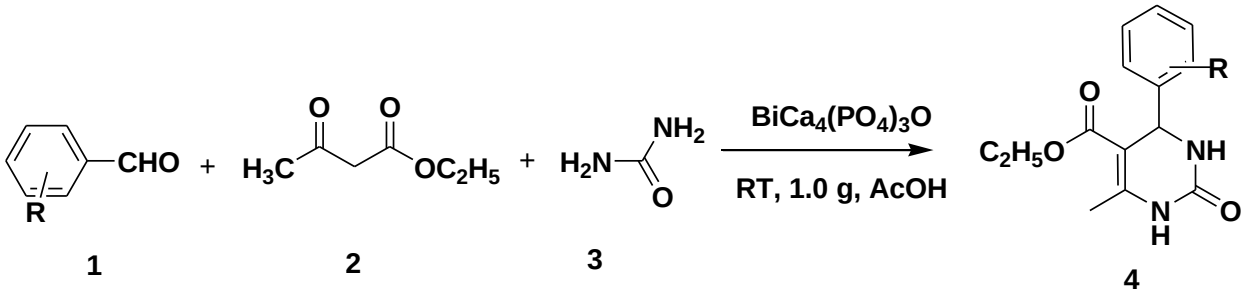


Fig. 3 SEM-EDAX of $BiCa_4(PO_4)_3O$



1 2 3 4

4a) R = H
4b) R= 3,4-OCH_3
4c) R= 4-OCH3
4d) R= 4-CH_3
4e) R= 4-Cl
4f) R= 4-F
4g) R= 4-C_2H_5

Scheme 1 Synthesis of 3, 4 – dihydropyrimidin-2(1H)-one catalyzed by oxyphosphate

