Current Chemistry Letters 6 (2017) 77–90

Contents lists available at GrowingScience

Current Chemistry Letters

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One-pot solvent free synthesis of dihydropyrimidinones using calcined Mg/Fe hydrotalcite catalyst

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C H R O N I C L E

Article history:
Received August 21, 2016
Received in revised form
October 24, 2016
Accepted 17 November 2016
Available online
17 November 2016

Keywords:
Hydrotalcite
Dihydropyrimidinone
Aromatic aldehydes
Multicomponent reactions
Heterogeneous catalysis

A B S T R A C T

The Mg/Fe = 3 hydrotalcite as reusable solid catalyst was found to be an excellent heterogeneous base catalyst for the synthesis of 3,4-dihydropyrimidinones/thiones, a multicomponent reaction using substituted aromatic aldehyde, ethyl acetoacetate and urea/thiourea. The work has been carried out under thermal solvent free conditions. Mg/Fe = 3 hydrotalcite heterogeneous solid catalyst offers simple means of recovery and the isolated catalyst was reused for number of times without significant loss of catalytic activity.

1. Introduction

Dihydropyrimidinone and their derivatives are one of the prime interests because of their promising biological and pharmacological activities such as antihypertensive reagent,[1] antimicrobial,[2] anti-inflammatory,[3] antifungal,[4] and calcium channel blockers.[5] In addition, they also act as an anticancer agent,[6] and anti-HIV agent.[7] Therefore, synthesis of this type of heterocyclic compound is of much current importance.

MCR's is the efficient tools in the modern organic synthetic chemistry in view of their significant features such as atom economy, straightforward reaction designing. MCR drawn great interests in the synthesis of biological and pharmacological compound by introducing several steps in one pot reaction, as they lead to time, energy and environmental saving.[8,9,10] Green chemistry approach holds significant potential for energy efficiency, prevents solvent waste and toxicity but also in development of new methodologies towards previous not obtainable material, using existing technologies. The synthesis of organic compound without using organic solvent attributed to reduce the amount of residual solvent and environmental pollution. Solvent free reactions attract most of the researcher to develop new protocols in synthetic organic process.[11,12]

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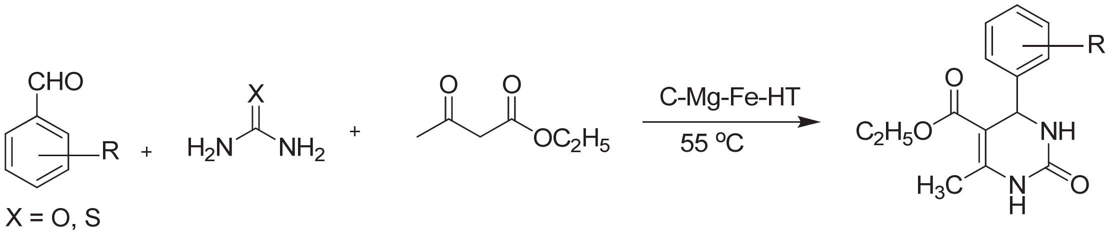
doi: 10.5267/j.ccl.2016.11.004

The first synthetic method for the synthesis of dihydropyrimidione-2(1H)ones was reported by Biginelli, that involves one-pot three component condensation of bezaldehyde, ethylacetoacetate and urea under strongly acidic condition.[13] However, this reaction usually required harsh reaction condition, long reaction time and afford low yield. To overcome those disadvantages, improved procedure with different type of catalytic system and conditions such as PPh_3,[14] Zeolite,[15] $Yb(OTf)_3$,[16] H_3BO_3,[17] Ziegler-Natta catalyst,[18] Indium(III) halides,[19] trypsin,[20] $Mn(OAc)_3.2H_2O$,[21] $FeCl_3$-Supported nanopore Silica,[22] Ceric ammonium nitrate under ultrasound irradiation,[23] P-sulphonic acid calixarenes[2],[4] Iron(III) tosylate,[25] montmorillonite KSF,[26] 1-n-butyl-3-methyl imidazolium tetrafluoroborate ($BMImBF_4$) or hexafluorophosphorate ($BMImPF_6$) in ionic liquids,[27] $LiClO_4$,[28] Lanthanum Chloride,[29] nonmagnetic supported sulphonic acid,[30] $KAl(SO_4)_2.12H_2O$ supported on silica,[31] graphite,[32] polyphosphate ester,[33] HCOOH,[34] and classical conditions including microwave irradiation,[35] and so on. However, above mention methods have potential utility, in spite of these many methods suffer from drawbacks such as use of expensive reagent, volatile strong acidic condition, high temperature, long reaction time, unsatisfactory yields and non-recyclable catalyst. Therefore, to avoid these limitations there is need for versatile, simple and environmentally efficient process for synthesis of dihydropyrimidione-2(1H) ones.

Hydrotalcite and hydrotalcites like compounds are natural layer materials with anionic species such as hydroxide and carbonates located in the interlayer, which have been reported to be used as catalyst or catalyst supports,[36,37] ion – exchanger,[38] and drug delivery reagent.[39] As far as green chemistry concern hydrotalcite attention as heterogeneous catalysts, due to their stability and the scope for modification of their surface properties by intercalation of various metal ions in its structure. These materials has been developed and applied as heterogeneous catalyst and metal support for organic transformation including condensation, isomerisation and cycloadditions.[40,41,42] In view of the advantage associated with the use of hydrotalcite as catalyst in performing synthetic organic chemistry, we report multicomponent and simple approach using Mg/Fe=3 hydrotalcite as a catalyst to produce dihydropyrimidione-2(1H)one under solvent free condition.

2. Results and discussion

A systematic study was carried out to optimize the reaction conditions including the quantity of catalyst, reaction medium and nature of catalyst. To find the optimal reaction conditions, we carried out reaction of benzaldehyde, ethylacetoacetate and urea/thiourea as a model reaction (**Scheme1**).



Scheme 1. Synthesis of dihydropyrimidinones/thiones

To illustrate the efficiency of catalyst, this reaction was run with Mg/Fe hydrotalcite of molar ratio = 2:1,3:1,4:1,5:1 (**Table 1**). Basicity of HT's mainly depends on calcinations temperature and Mg/Fe molar ratio. On calcinations, at a high temperature, the Lewis basicity of hydrotalcites increases, while the bronsted basicity of hydrotalcite decreases. Total basicity of hydrotalcite increases gradually with Mg/Fe molar ratio and comes to maximum value at the Mg/Fe = 3. Hence calcined Mg/Fe = 3 hydroalcite was found to be best catalyst for this reaction. When reaction carried out without catalyst, no product was observed for long time in absence of catalyst.

Table 1. Evaluation of catalysts activity in reaction of benzaldehyde with urea, and ethyl acetoacetate

Entry	Hydrotalcite	Yield of product (%)
1	C-Mg-Fe HT-2	45
2	C-Mg-Fe HT-3	90
3	C-Mg-Fe HT-4	21
4	C-Mg- Fe HT-5	62
5	Without HT	No reaction
6	Without HT	80 (at 105 °C)

Reaction conditions: benzaldehydes (3 mmol), urea (4 mmol), ethyl acetoacetate (3 mmol), catalyst (0.02 g), temperature (55 °C)

In next step, the amount of the catalyst was optimized for the synthesis. According to data represented in (**Table 2**) the best yield was obtained by using 0.02 g of calcined Mg/Fe = 3 hydrotalcite. Further increasing in quantity of catalyst, did not increase the yield. Hydrotalcite acts as heterogeneous solid catalyst.

Table 2. Evaluation of C-Mg-Fe-HT-3 catalyst loading in reaction of benzaldehyde with urea and ethyl acetoacetate

Entry	Catalyst quantity (g)	Yield of product (%)
1	0.01	65
2	0.02	90
3	0.03	90
4	0.04	90
5	0.05	90

Reaction conditions: benzaldehydes (3 mmol), urea (4 mmol), ethyl acetoacetate (3 mmol), temperature (55 °C)

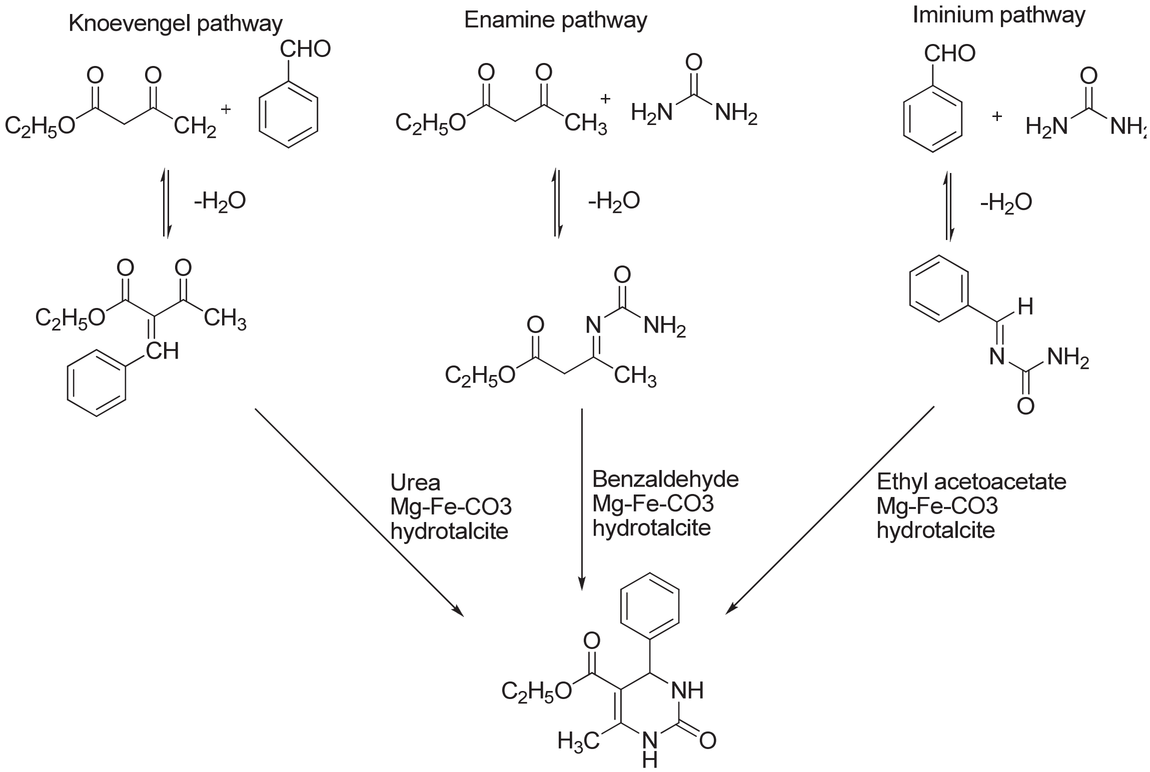
After the reaction, the catalyst can be reused for model reaction number of times without significant decrease in product yield and which is essential for designing truly green synthesis protocol (**Table 3**).

Table 3. Reusability of C-Mg-Fe-HT-3 catalyst

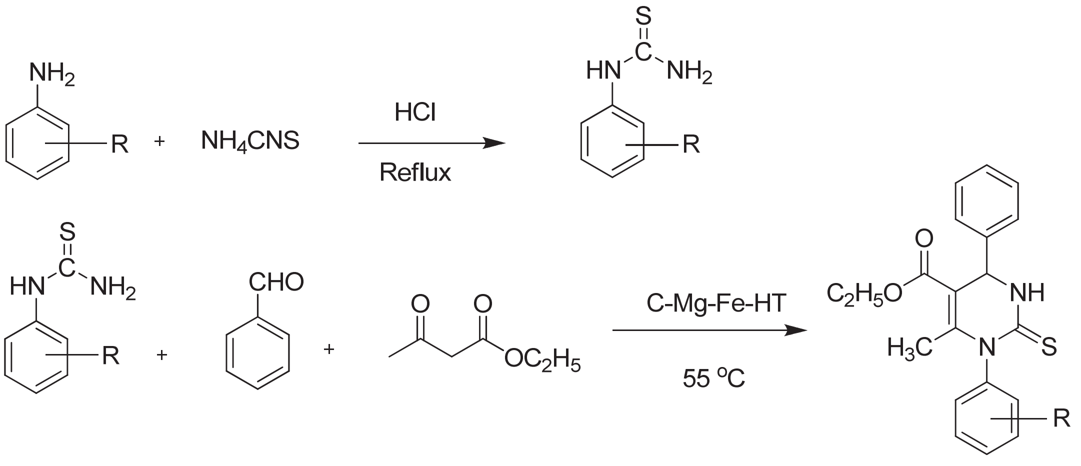
Run	Yield of product (%)
1	90
2	90
3	90
4	89
5	89

Reaction conditions: benzaldehyde (3 mmol), urea (4 mmol), ethyl acetoacetate (3 mmol), C-Mg-Fe-HT- 3 catalyst (0.02 g), temperature (55 °C).

The plausible mechanism for the formation of pyrimidine derivative has shown in (**Scheme 2**). To understand the mechanistic study of the pyrimidine we carried out three sets of reactions. Theoretically, there are at least three routes, which make possible this transformation: the enamine, Knoevenagel condensation, and iminium pathways. Firstly, ethyl acetoacetate was reacted with urea, enamine product was formed, which was then reacted with benzaldehyde under solvent free condition in presence of calcined Mg/Fe = 3 hydrotalcite required product was not formed. Secondly, ethyl acetoacetate was treated with benzaldehyde as a result of which knoevengel condensate was obtained which was treated with urea under solvent free condition in presence of calcined Mg/Fe = 3 hydrotalcite desired product was not formed. Finally, benzaldehyde was treated with urea yielded Schiff base or iminium ion which was then treated with ethyl acetoacetate under solvent free condition in presence of calcined Mg/Fe = 3 hydrotalcite to give 3,4-dihydropyrimidinione. We were also extending our study towards the synthesis of 6-Methyl-1,4,-diphenyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester, in which we first prepared different 1-(p-substituted/o-substituted Phenyl)thiourea precursors from different substituted aniline is reflux with ammonium thiocyanate in the presence of hydrochloric acid. The different 1-(p-substituted/o-substituted Phenyl) thiourea was treated with benzaldehyde, which yielded intermediate reacted with ethyl acetoacetate in presence of calcined Mg-Fe = 3 hydrotalcite under solvent free condition afford product 3,4-dihydropyrimidin-2-thiones (**Scheme 3**).



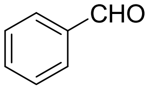
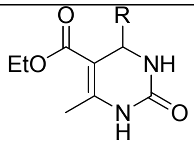
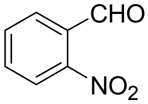
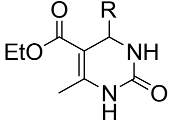
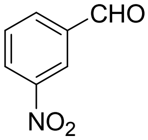
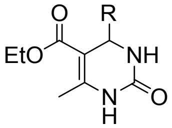
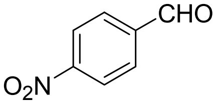
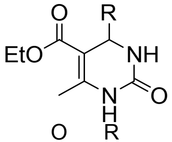
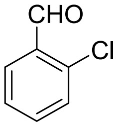
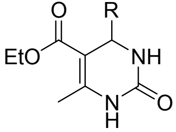
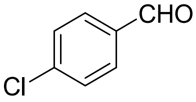
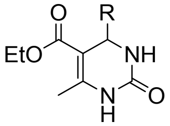
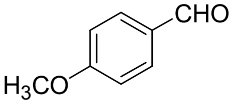
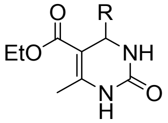
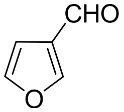
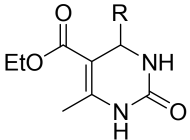
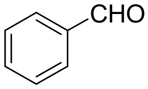
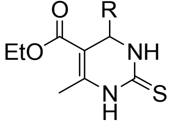
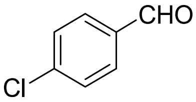
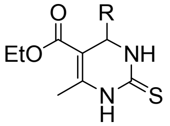
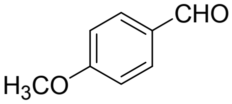
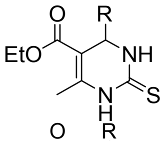
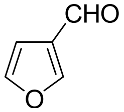
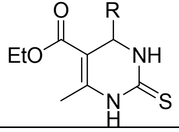
Scheme 2. Plausible routes to 3, 4,-dihydropyrimidine-2(1H)-ones



Scheme 3. Synthesis of 3,4-dihydropyrimidin-2-thiones

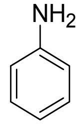
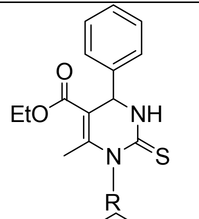
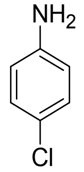
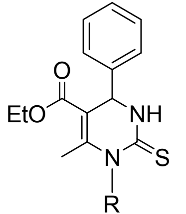
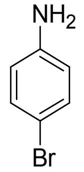
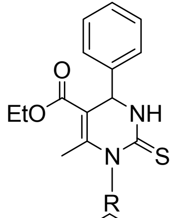
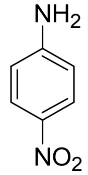
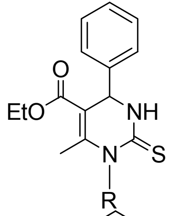
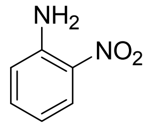
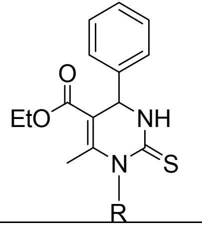
The above optimized reaction conditions were subsequently applied to the reaction between various aldehyde, ethyl acetoacetate and urea in solvent free condition at 55 ^{0}C. It is also clear that from the tabulated results (**Table 4**).

Table 4. Synthesis of a series of dihydropyrimidinone/thiones in the presence of C-Mg-Fe HT-3 at 55 °C

Entry	Benzaldehydes	Product	Time, min	Yield, %	Mp, ^{0}C	Mp, ^{0}C
					Found	Reported
1			30	90	204 - 206	202 - 204[43]
2			20	95	205 - 207	206 - 208[43]
3			25	92	225 - 227	226 - 227[43]
4			20	93	210 - 212	209 - 210[45]
5			25	90	216 - 218	217 - 218[45]
6			25	92	214 - 216	213 - 215[43]
7			25	88	201 - 203	201-203[43]
8			35	90	208 - 210	209 - 211[44]
9			35	92	208 - 209	208 - 210[43]
10			30	90	191 - 193	192 - 194[45]
11			35	87	151 - 153	150 - 152[43]
12			40	91	160 - 162	-

Aromatic aldehyde carrying either electron withdrawing or electron donating substituents also afford high yields of product with high purity and important feature of these process is that presence of functional group such as nitro, halides, hydroxyl, unsaturation etc. do not much affect the yield of the product. Acid sensitive group like furfuraldehyde also reacted very well under same conditions without formation of side products and *α,β*-unsaturated aldehyde also react very well with high yield. There is no polymerization and decomposition under this optimizes reaction condition. Similarly, thiourea and substituted thiourea have been reacted with similar success to afford the corresponding thio-derivative of 3,4-dihydropyrimidiniones. Also, different 1-(*p*-substituted/*o*-substituted phenyl) thioureas have been treated with benzaldehyde and ethyl acetoacetate under above optimized condition and it was observed that this reaction furnish good yield of desired products (**Table 5**).

Table 5. Synthesis of a series of 3,4-dihydropyrimidin-2-thiones in the presence of C-Mg-FeHT-3 at 55 °C

Entry	Anilines	Product	Time, min	Yield, %	Mp, °C
1			40	82	205 - 206
2			45	84	198 - 200
3			45	83	202 - 203
4			36	86	212 - 214
5			40	84	208 - 209

2.1. Characterization of hydrotalcite

2.1.1. XRD (X-ray diffractogram)

Powder XRD of calcined Mg/Fe = 3 hydrotalcite catalyst is in agreement with the standard hydrotalcite peaks, which indexes are correlating with the reported hydrotalcites. After calcinations, due to removal carbonate and water from the hydrotalcite structure mixed oxides of hydrotalcite precursors are formed. The powder X-ray diffraction pattern of LDH with Mg/Fe = 3:1 molar ratio (**Fig. 1**) shows peaks at $2\theta = 43.14$,62.60 ° which are corresponding to MgO and at $2\theta = 30.14$, 35.52, 43.14 and 62.60 ° which can be attributed to $MgFe_2O_4$ spinel structure (JCPDS 17-0465) those peaks have been observed in literature.[46,47]

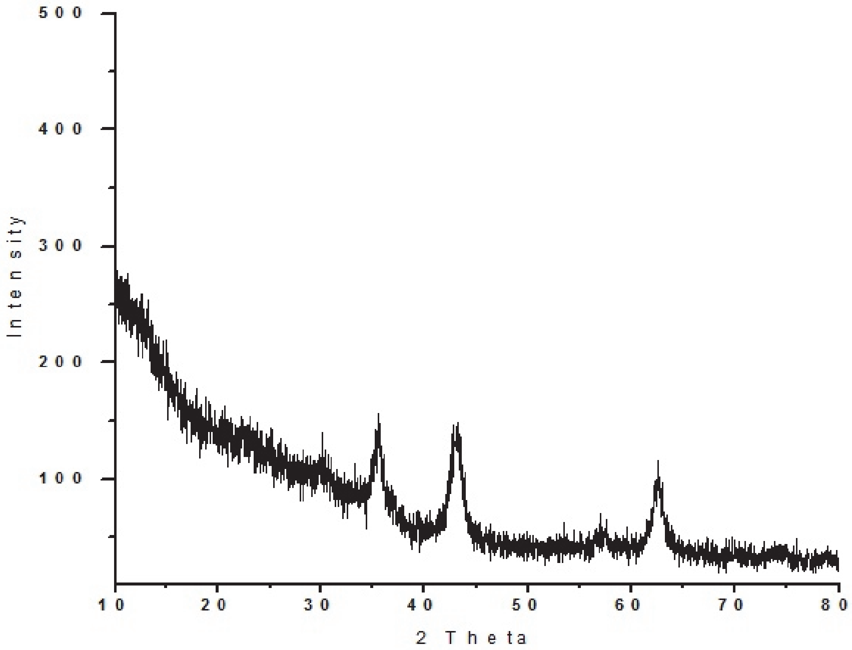


Fig. 1. XRD spectrum for hydrotalcite with Mg/Fe=3:1 calcinied at 500^0C.

2. 1. 2. *FTIR*

The FTIR spectra of LDH with Mg/Fe = 3:1 molar ratio as shown in (**Fig. 2 & Fig. 3**) are typical of LDH and which are in agreement well with the typical results previously report.[46-52]The broad band observed at 3442 cm^{-1} is attributed to interlayer water molecules, this band become weaker and is shifted to 3409 cm^{-1} when hydrotalcite calcined. The strong band at 1355 cm^{-1} is due to the mode ν_3 of the interlayer carbonate species as reported in the literature. The bands in the range of 500-750 cm^{-1} are attributed to metal-oxygen-metal bond stretching.

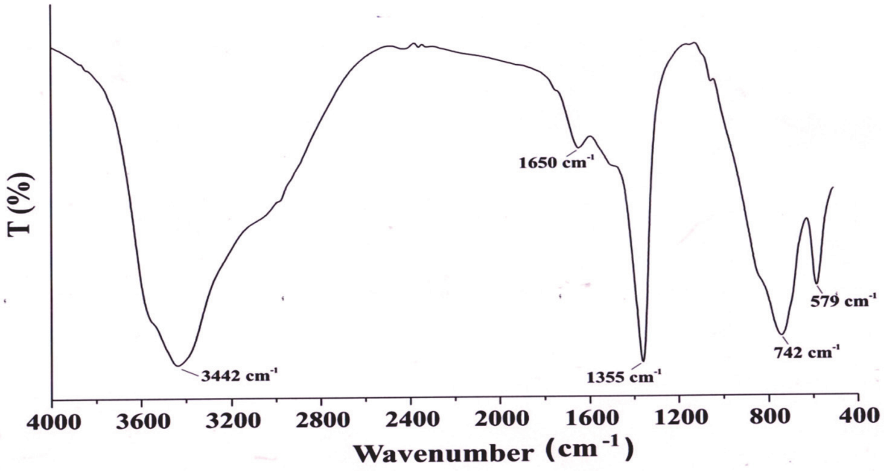


Fig. 2. FTIR spectra of LDH with uncalcined Mg/Fe = 3:1

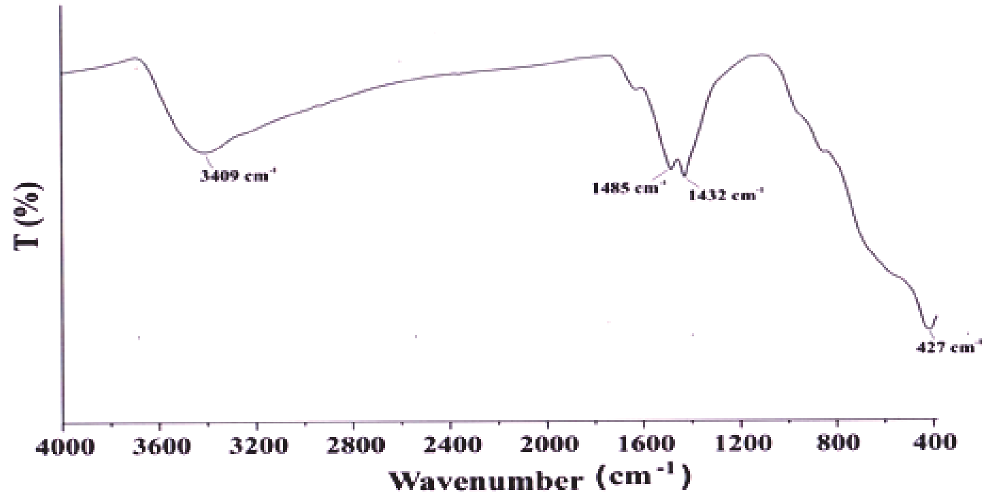


Fig. 3. FTIR spectra of LDH with Mg/Fe = 3:1 calcined at 500 °C

2.1.3. Thermogravimetric analysis and Scanning electron microscopy

The Thermogravimetric analysis (TGA) Plot of LDH having Mg/Fe molar ratio 3:1 shows three distinct phase loss in the range 50-200, 200-400 and 460-750 °C (**Fig. 4**). The first weight loss in the temperature range of 50-200 °C which was about 13%. This weight loss of hydrotalcite mainly due to interlayer and physisorbed water. Further weight loss of 21% which occurs between 200-460 °C which is related to removal of carbonate ions from the interlayer of hydrotalcite and first step dehydroxylation. Final the third mass loss, that occurs further than 460 °C can due to continuous dehydroxylation and decarbonization and formation of oxide metals as MgO which are detected in X-ray differ action of calcined LDH and possibly $MgFe_2O_4$ as reported in the literature.[47,50] Beyond 600 °C temperature, there was no significant mass loss was observed.

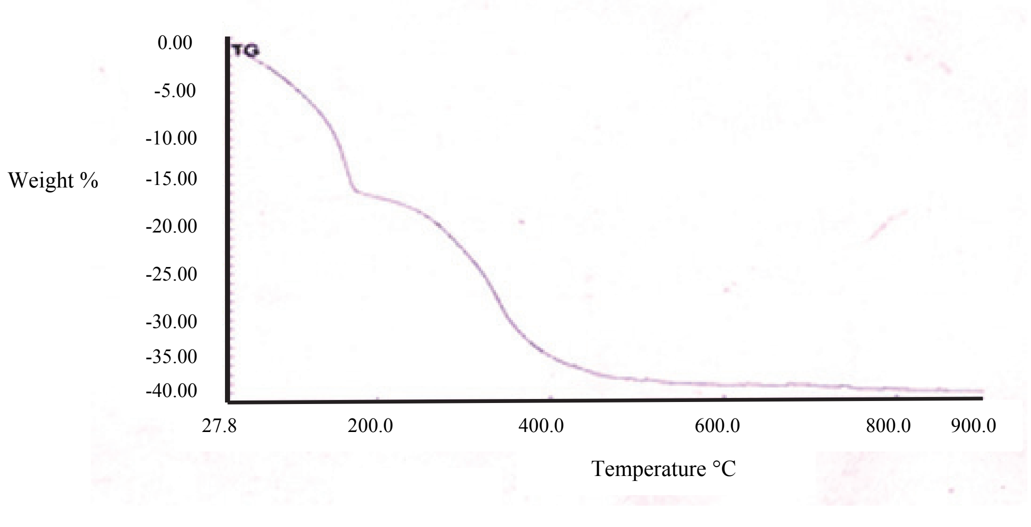


Fig. 4. TGA Plot of hydrotalcite with Mg/Fe = 3:1

Catalyst morphologies as indicated by the Scanning electron microscopy (SEM) image of C-Mg-Fe-HT-3 showed the materials to be clearly point out the homogeneity in shape for the sample and high crystallinity (**Fig. 5**).

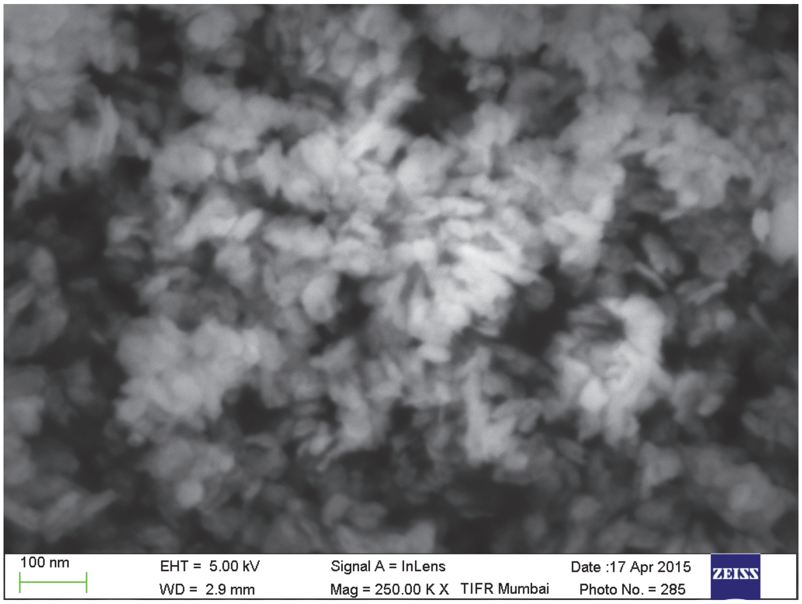


Fig. 5. SEM image of hydrotalcite with Mg/Fe = 3:1 calcinied at 500 °C

3. Conclusion

We have successfully described a new strategy that provides highly efficient and green one-pot synthesis of Dihydropyrimidione-2(1H)-one using Mg/Fe = 3 hydrotalcite as a heterogeneous base catalyst. Solvent free condition and non-toxic reusable hydrotalcite catalyst make this method simple, convenient, environmentally friendly and cost effective in character, which will have advantages over the reported methodologies.

Acknowledgement

The Authors are thankful to the principal and Management of G.N.C. College, G.T.B. Nagar, Mumbai for constant encouragement and providing necessary facilities. Authors are also thankful to TIFR, Mumbai for providing spectral data.

4. Experimental

4.1. Materials

All chemicals of AR grade were purchased from S. D. Fine Chemicals Ltd., Mumbai, India and were used without any further purification.

4.2. Method of characterization

Melting points of all synthesized compounds was measured on electro thermal apparatus using open capillary tubes and are uncorrected. TLC for purity of compounds was performed on silica gel coated aluminum plate as adsorbent and which was analyzed with UV light as visualizing agent. FT-IR Spectra were recorded on Bruker Spectrometer in the region of 400-4000 cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer using TMS as an internal standard and $CDCl_3$/DMSO-d_6 as solvent (chemical shifts in δ ppm). Powder X-ray diffraction pattern was collected with monochromatic CuKα radiation (λ = 1.54059 Å) at 40 kV and 15 mA using Shimadzu 7000S diffractometer. Thermo gravimetric analysis was performed with a RIGAKU Thermo Plus TG 8120 thermobalance with a heating rate of 10 °C/min from 25 to 900 °C. The morphological information gathered using scanning electron microscope ZEISS Ultra FESEM.

4.3. Catalyst preparation.

Mg-Fe-HTs with different Mg/Fe molar ratios (Mg/Fe = 2:1, 3:1, 4:1 and 5:1) were synthesized by co-precipitation method.[38,53] An aqueous solution of Mg $(NO_3)_2.6H_2O$ and Fe $(NO_3)_2.9H_2O$ were prepared and mixed aqueous solution of $Mg(NO_3)_2.6H_2O$ and $Fe(NO_3)_2.9H_2O$ was add drop wise using addition funnel to an aqueous solution containing NaOH and Na_2CO_3 under vigorous stirring. After complete addition, the solution was heated at 80 °C for 18 h and maintain pH of solution in range of 10-11 during stirring. After complete stirring, the solution was allowed to cool about room temps and filtered. The obtained residue was washed with hot deionized water several times till filtrate was neutral. The solid was dried in an oven at 60 °C in the air. Dry solid then calcined at 500 °C for 5 h.

4.4.1. General procedure for synthesis of Dihydropyrimidinone/thione

Urea/thiourea (4 mmol), benzaldehyde (3 mmol), ethyl acetoacetate (3 mmol) and 0.02 g C-Mg-Fe hydrotalcite, as catalyst were taken in a round bottom flask and contents heated on oil bath at 55 °C for about 30 min. The reaction mixture was monitored by TLC using ethylacetate: hexane (2:8). After completion, reaction mixture was cooled to room temperature and the product formed was separated by filtration. The removal of solvent on water baths resulted in recovery of solid product. This product was recrystallised using ethanol. Purify product characterized by mp, NMR and IR.

4.4.2. General procedure for synthesis of 3,4-dihydropyrimidin-2-thiones

Ammonium thiocyanate (0.1 mol) was dissolved in 10 mL of H_2O, added with continuous stirring into a mixture of substituted aniline (0.1 mol) and 15 mL of concentrated HCl. The reaction mass was refluxed for few hours on water baths, then pour the reaction mass into cold water with continuous stirring. The product1-(p-substituted/o-substituted phenyl) thiourea obtained, which was crystallized from ethanol.1-(p-substituted/o-substituted phenyl) thiourea (4 mmol), benzaldehyde (3 mmol), Ethyl acetoacetate (3 mmol) and 0.02 g C-Mg-Fe hydrotalcite, as catalyst were taken in a round bottom flask and contents heated on oil bath at 55 °C for about 30 min. The reaction mixture was monitored by TLC using Ethyl acetate: Hexane (2:8). After completion, reaction mixture was cooled to room temperature and the product formed was separated by filtration. The removal of solvent on water baths resulted in recovery of solid product. This product was recrystallised using ethanol. Purify product characterized by mp, NMR and IR.

4.5. Physical and Spectral Data.

6-Methyl-4-(4-nitro-phenyl)-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester(Entry No:4) :White Solid, Yield = 93, mp = 210-212 °C, IR (KBr) [cm^{-1}]: 3455 cm^{-1} (NH), 1652 cm^{-1} (C=O ester); 1600 cm^{-1} (amide C=O); 1509 & 1347(NO_2). ^1H NMR (500 MHz, DMSO-d_6): δ ppm = 1.103 (t, 3H, CH_3), 2.273 (s, 3H,CH_3), 3.996 (q, 2H, CH_2), 5.280 (s, 1H, CH), 7.505-7.890 (m, 4H, ArH), 8.224 (s, 1H, NH), 9.351 (s, 1H, NH). ^{13}C NMR (500 MHz, DMSO-d_6): δ ppm= 14.505 (CH_3), 18.312 (CH_3), 54.225 (CH_2), 59.819 (CH), 98.717 - 152.520 (C=C, ArC), 165.512 (C=O).

4-(2-Chloro-phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (Entry No:6) :White Solid, Yield =92, mp = 214-216 °C IR (KBr) [cm^{-1}]: 3220 cm^{-1} (NH), 1689 cm^{-1} (C=O ester);1635 cm^{-1} (amide C=O); 617cm^{-1}(-Cl) . ^1H NMR (500 MHz, DMSO-d_6): δ ppm = 1.00 (t, 3H, CH_3), 2.305 (s, 3H, CH_3), 3.900 (q, 2H,CH_2), 5.636 (s, 1H, CH), 7.271 - 7.415 (m, 4H, ArH),7.697(s, 1H, NH), 9.266 (s, 1H, NH). ^{13}C NMR (500 MHz, DMSO- d_6): δ ppm = 14.305 (CH_3), 18.098 (CH_3), 51.955 (CH_2), 59.511 (CH), 98.362 - 151.882 (C=C, ArC), 165.381 (C=O).

6-Methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (Entry No:9):White Solid, Yield = 92, mp =208-209, IR (KBr) [cm^{-1}]: 3324 cm-1 (NH), 1665 cm^{-1} (C=O ester); 1571 cm^{-1} (amide C=S). ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm = 1.110 (t, 3H, CH_3), 2.510 (s, 3H, CH_3), 4.020 (q,2H,CH_2), 5.180 (s,1HCH), 7.221-7.369 (m,5H,ArH), 9.652 (s,1H,NH), 10.333 (s,1H,NH). ^{13}CNMR (500MHz, DMSOd$_6$): δ ppm = 14.431 (CH_3), 17.593 (CH_3), 54.484 (CH_2), 60.016 (CH), 101.176 - 145.465 (C=C, ArC), 165.570 (C=O). MS *m*/*e* = 276 (M+).

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