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Biginelli synthesis of 3,4-dihydropyrimidin-2(1H)-one using Layered Double Hydroxide (LDH) as a eco-friendly catalyst

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ABSTRACT

Three component condensation of B-keto ester, aldehyde and urea or thiourea catalyzed by layered double hydroxide (LDH) to give 3,4-dihydropyrimidin-2(1H)-one is described. Catalyst has high region specific and chemo selective activity as well as no toxicity. It is cheap eco-friendly and easily synthesized catalyst. The mild reaction conditions, easy isolation of the product and high yields are the important features of this protocol.

Keywords: Inorganic catalyst, Biginelli reaction, Layered Double Hydroxide (LDH), Multi-components reaction 3,4-dihydropyrimidin-2(1H)-one.

INTRODUCTION

Dihydropyrimidines were first synthesized by Pitro Bigibelli in 1893 using B-keto ester, aldehyde and urea. The original Biginelli reaction offers simple and reasonable access to these important compounds. Despite the usefulness of the Biginelli reaction, the efficiency of this method is considerably limited due to strong acidic and harsh reaction conditions. Recently, many synthetic methods for preparing these compounds have been developed to improve and modify this reaction by microwave (1,2), ultra- sound irradiation (3) and by using Lewis acid as well as Bronsted acids promoters. FeCl₃/ tetra acetyl ortho-silicate(4),triflates,(5), metal bromide,(6) poly-oxometalate(7), strontium(II) nitrate(8), cerium (III) chloride(9), Li(OTf)(10), Ln(OTf) (11),hetropoly acid(12), TMSCl (13), hexa-aqualuminium (III) tetrafluroborate (14) as well as ionic liquid were made in classical Biginelli reaction. Although these methods are quite satisfactory, many of them have employed considerable amount of hazardous organic solvent either for carrying out reaction at higher temperature and using costly reagents. Furthermore these methods are not suitable in terms of recent trends in progress chemistry; due to the use of metallic catalyst. Therefore a method using an environmentally benign catalyst is desirable. Which should be high regio specific and chemo selective as well as having no toxicity to air and water compatibility and operation simplicity.

MATERIALS AND METHODS

All melting points were measured using an Electro-Thermal apparatus and were uncorrected. FT-IR spectra were recorded using KBr disk on Perkin Elmer FT-IR KBr spectrophotometer as thin films with ν_{\max} in inverse centimeter. ¹H and ¹³C NMR spectra were recorded on a BrukerAvance II 400 NMR spectrometer using CDCl₃ and DMSO-*d*₆ as solvents and tetramethylsilane (TMS) as internal standard. Chemical shifts being reported in parts per million (δ) relative to TMS. Mass spectra were obtained using electron impact (EI) at an ionizing potential of 70eV.

Purity of the compounds was checked by thin layer chromatography which was performed on aluminum sheet Silica Gel 60 F₂₅₄ (Merck). The spots were visualized by exposure to UV light and iodine vapors.

General Procedure:-

Equimolar mixture (0.2 mole each) of aldehyde, β -keto ester, and urea was taken in round bottom flask. To it 0.5 gm (0.15 mole) LDH catalyst and 10 ml ethanol was added and the reaction mixture was refluxed for 4 hours. The reaction mixture was filtered to remove the catalyst and filtrate was poured into ice cold water and stirred for 15 minutes. Then content were filtered and washed with cold water to remove excess urea if any. The solid so obtained was the corresponding 3,4-dihydropyrimidin-(2H)-one. It was then re-crystallized by ethanol to get pure product. Product formation was confirmed by the comparison with authentic sample, physical constant and IR, ¹H NMR spectral analyses.

Ethyl-4-(phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidine carboxylate (A):-

Solid M.P. - 203°C, Reported 202-204 °C^[15], IR: 3171 (-NH-), 3114 (-NH-), 1651 (C=O), 1670(C=O), 2901 (-C-H), 2937, 2984 (-C-H), 1251, 1282(C-O) ¹H NMR: (3.25 d 3H), (3.17, t 2H), (4.2, q, 2H), (5.3, s 2H), (7.2-7.4 Ar-H, 5H).

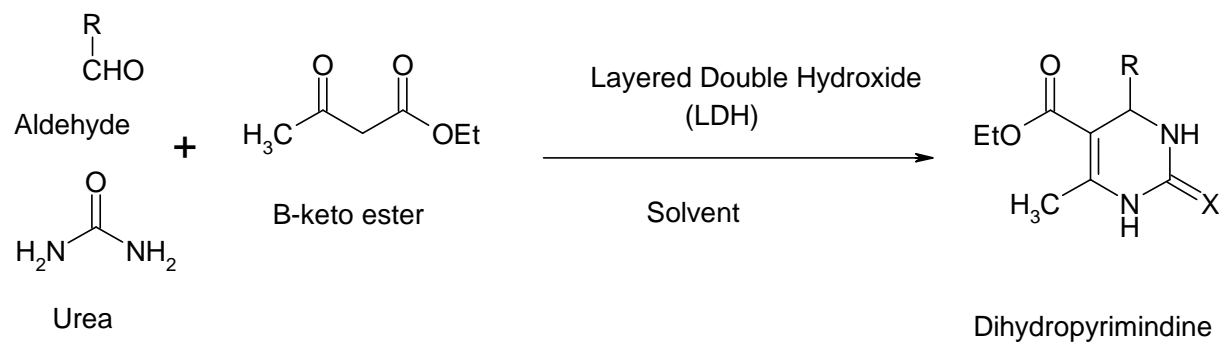
Ethyl-4-(phenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate(I):-

Yellowish solid, mp 208°C, Reported 208-209 °C^[15] IR : 3244 (c=c), 3115 (N-H), 2979 (C-H), 1725, 1702 (C=O), 1649 (C-S), 1290, 1270 (C-O) NMR: 1.1, d 3H), (4.20, q, 2H), 3.17 (t, 2H), (5.3 s, 2H), 7.2-7.4 (Ar-H, 5H).

The scope of aldehyde component was first investigated by the reaction with urea (entries A-H) and thus aldehyde bearing different types of substituent's underwent the reaction to give good to excellent yields. The thiourea was then used in similar way to afford corresponding dihydropyrimidine-2(1H)-one in good yields (entries I-K). The reaction conversion and product outcome showed no effect of substituent on the product yields.

RESULTS AND DISCUSSION

In this communication we wish to describe an improved method for the Biginelli condensation using layered double hydroxide (LDH) as easily synthesized, economical, easy to handle and isolate as well as eco-friendly catalyst.



Where $\chi = \text{O, S}$

Reaction Scheme

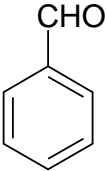
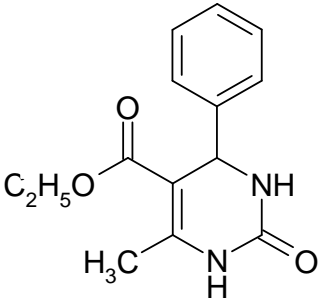
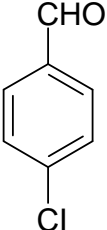
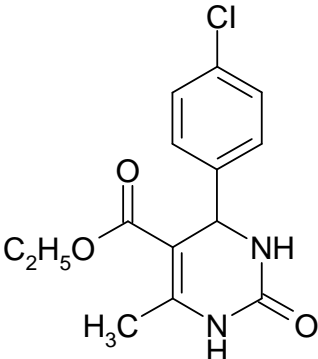
Comparison of different catalysts used for the synthesis of dihydropyrimidine

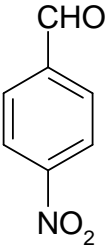
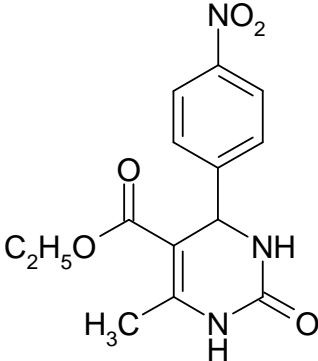
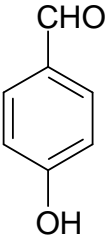
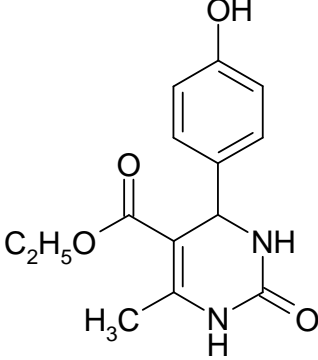
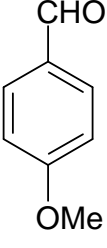
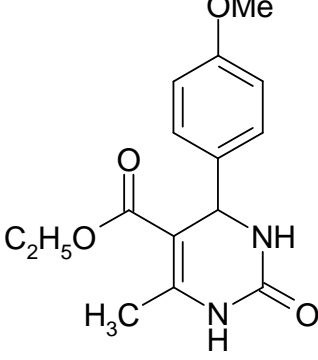
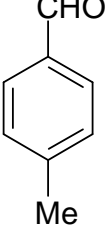
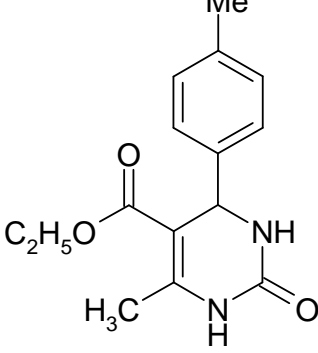
Entry	Catalyst	Time	Temperature	Yield (%)
1	FeCl ₃ / tetra acetyl orthosilicate	9 hrs.	Reflux in Ethanol	78
2	triflates	45 sec.	MW Irradiation	90
3	metal bromide	4 hrs	Reflux in Ethanol	80
4	polyoxometalate	5 hrs	Reflux in Ethanol	75
5	strontium(II) nitrate	6 hrs	Reflux in Ethanol	78
6	cerium (III) chloride	6 hrs	Reflux in Ethanol	91
7	Li triflates	11 hrs	Stirring	83
8	Ln triflates	12 hrs	Stirring	85
9	hetopoly acid	3 hrs	Reflux in Ethanol	90
10	TMSCl	3 hrs	Reflux in Ethanol	87
11	hexaaqualuminium (III) tetrafluoroborate	60 sec.	MW Irradiation	92
12	LDH	4 hrs	Reflux in Ethanol	88

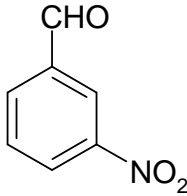
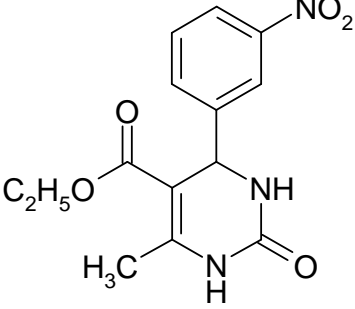
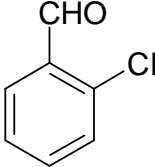
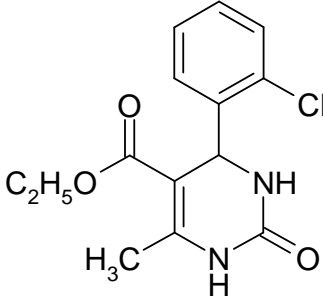
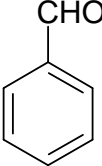
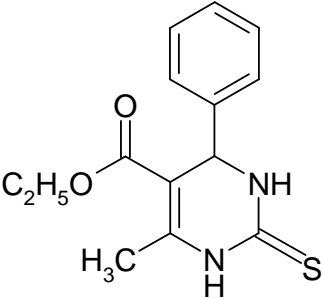
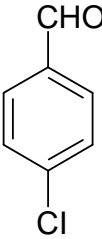
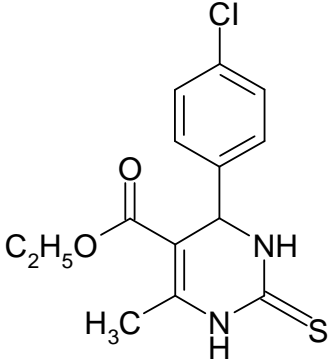
LDH is known as Layered double hydroxide catalyst. It is prepared by dissolving Mg(NO₃)₂.6H₂O and Al(NO₃)₃.9H₂O in equimolar amount in a double distilled water and then adding drop wise 50% NaOH and maintaining pH close to 10.

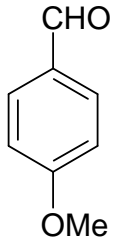
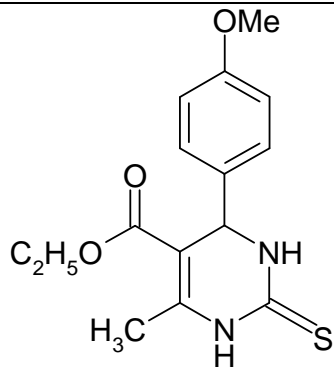
In a typical general procedure, a mixture of aldehyde, ethylacetoacetate and urea were made to react in ethanol in the presence of LDH catalyst as shown in reaction scheme. The reaction progress was monitored by thin layer chromatography (TLC). When the reaction was complete, confirmed by conversion of aldehyde by TLC, the catalyst was removed by filtration. The product was recovered by pouring the reaction mixture in water.

After establishing the optimum conditions, we have applied this method to various other aldehydes with ethylacetoacetate and urea/thiourea and the results are shown in Table 1. In general, the reaction with different aldehydes gave very good yields ranging from 72% to 88%. The scope of this methodology was found to be applicable to a variety of aromatic aldehydes bearing electron withdrawing or electron donating groups present on aromatic system. In all cases the reaction was completed in 4-5 hours' time at reflux temperature. The important feature of this procedure is the tolerance of variety of functional groups, such as nitro, hydroxyl, halide and ethers.

Entry	Aldehyde	Product	Yield	MP (°C)	MP Reported (°C)
A			88%	203	202-204 ^[15]
B			86%	210	210-212 ^[15]

C			85%	211	212-214 ^[15]
D			82%	225	225-226 ^[15]
E			80%	205	202-204 ^[15]
F			81%	214	215-216 ^[15]

G			82%	225	226-227 ^[15]
H			84%	217	216-218 ^[15]
I			85%	208	208-209 ^[15]
J			73%	183	180-182 ^[15]

K			72%	138	136-138 ^[15]
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CONCLUSION

Inorganic catalyst LDH utilized in classical heating method for three-component condensation of β -keto ester, aldehyde, and urea or thiourea to yield the corresponding biologically active 3,4-dihydropyrimidin-2(1H)-one. The protocol was found to be rapid, simple, eco-friendly and high product yielding.

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