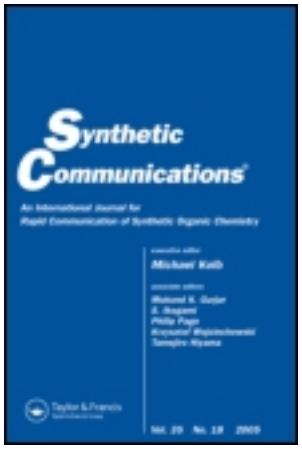


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# $FeCl_3$ Immobilized in Al-MCM 41: An Efficient Catalyst System for the Biginelli Reaction

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# $FeCl_3$ IMMOBILIZED IN Al-MCM 41: AN EFFICIENT CATALYST SYSTEM FOR THE BIGINELLI REACTION

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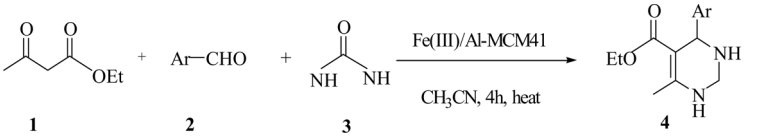
## GRAPHICAL ABSTRACT




1 2 3 4

**Abstract** *$FeCl_3$ immobilized on Al-MCM-41 was found to be an efficient catalytic system for the one-pot synthesis of 3,4-dihyropyrimidinone derivatives. This is a facile and high-yielding reaction for synthesis of the 3,4-dihyropyrimidinone. The catalyst exhibited remarkable reactivity and is reusable.*

**Keywords** Biginell; 3,4-dihyropyrimidinone; Fe(III)/Al-MCM-41; three-component condensation

## INTRODUCTION

Multicomponent reactions are useful and efficient methods in organic synthesis. The major advantages of these reactions are (1) a single purification step, (2) greater yields yields than stepwise assembly, (3) the use of simple and diverse precursors to construct complex molecules, and (4) the use of only a single promoter or catalyst. Thus, the development of new multicomponent reactions is a popular area of research in current organic chemistry and is also acceptable from a green chemistry point of view.[1]

3,4-Dihydropyrimidin-2(1H)-ones (DHPMs) have been reported to possess diverse pharmacological activities such as antiviral, antibacterial, and anti-hypertensive activity,[2] as well as efficiency as calcium channel modulators and $\alpha_{1a}$-antagonists.[3] Several marine alkaloids possess anti-inflammatory and antitumor pharmacological activities.[4] In particular, the batzelladine alkaloids have been found to be potent HIV gp-120-CD4 inhibitors.[5]

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The simple and direct method for the synthesis of DHPMs reported by Biginelli in 1893 involves the one-pot condensation of an aldehyde, a β-ketoester, and a urea under strongly acidic conditions. However, this method suffers from poor yields, especially in the cases of aliphatic and some substituted aromatic aldehydes. Several improved protocols by modification of the classical one-pot approach for the preparation of DHPMs have been reported recently.[6] However, some of the reported methods also suffer from drawbacks such as unsatisfactory yields, cumbersome product isolation procedures, and environmental pollution.[7] The synthesis of DHPM derivatives involving the use of a number of catalysts, such as $InBr_3$,[8] tetrabutylammonium bromide (TBAB),[9] polystyrene-poly(ethylene glycol)-sulfonic acid (PS-PEG-$SO_3H$),[10] and $CaF_2$,[11] have been reported.

## RESULTS AND DISCUSSION

Among the various metals, iron (Fe) is the most abundant in nature and is an indispensable species of nearly all organisms. Nature has evolved a number of metalloenzymes such as the heme-containing cytochrome P450 and the non-heme monooxygenase. Transition-metal complexes can be stabilized, either encapsulated or grafted within microporous (zeolites) or mesoporous materials (MCMs).[12–14] They have numerous potential applications as catalysts, photocatalysts, and gas sensors.

In this investigation, we decided to synthesize 3,4-dihydropyrimidinones via ethyl acetoacetate **1**, aldehydes **2** and urea **3** using Fe(III)/Al-MCM-41 as a heterogeneous and recyclable catalyst (Scheme 1).

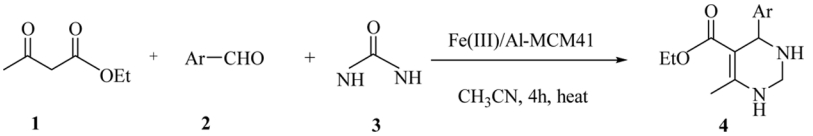
We examined the reaction using various aldehydes, urea, and ethyl acetoacetate under reflux, and the results are summarized in Table 1.

Several aromatic aldehydes carrying either electron-releasing or electron-withdrawing substituents in the *ortho, meta*, and *para* positions afforded good yields of the products. An important feature of this procedure is the survival of a variety of functional groups such as hydroxyl, nitro, ethers, halides and groups under the reaction conditions.

All reaction products were isolated by infrared (IR), gas chromatography (GC) mass spectrometry, and melting points and compared with those obtained from authentic samples.

The reusability of the catalyst was next checked by repeating the same model reaction three times. The results are summarized in Table 2.

To show the merits of Fe(III)/Al-MCM-41 in comparison with other reported catalysts, we summarized some of results for the preparation of 3,4-dihydropyrimidinones (**4a**) in Table 3, which shows that Fe(III)/Al-MCM-41 is an equally or more efficient catalyst with respect to reaction time and yield than previously reported ones.




**Scheme 1.** Synthesis of 3,4-dihydropyrimidinones.

**Table 1.** Synthesis of compounds **4a–g** by Fe(III)/Al-MCM-41

| Entry | Product[a] | Ar | Yield[b] (%) | Mp (°C) (lit.) |
|---|---|---|---|---|
| 1 | 4a | $C_6H_5$ | 85 | 201–203 (202–204)[7] |
| 2 | 4b | 2-$NO_2$-$C_6H_4$ | 90 | 220–223 (198–200)[11] |
| 3 | 4c | 4-Me-$C_6H_4$ | 68 | 216–219 (215–216)[9] |
| 4 | 4d | 4-OMe-$C_6H_4$ | 89 | 202–204 (201–203)[7] |
| 5 | 4e | 4-$NO_2$-$C_6H_4$ | 75 | 208–210 (208–211)[7] |
| 6 | 4f | 4-Cl-$C_6H_4$ | 89 | 212–214 (213–215)[7] |
| 7 | 4g | 3-$NO_2$-$C_6H_4$ | 75 | 227–230 (229–231)[9] |

[a]Products were characterized by comparison of their spectroscopic data (GC mass, IR, mps) and $^1$H NMR with those reported in the literature.
[b]Isolated yield.

**Table 2.** Reuse of the Fe(III)/Al-MCM-41 for synthesis of **4a**

| Entry | Time (h) | Yield (%)[a] |
|---|---|---|
| 1 | 4 | 85 |
| 2 | 4.5 | 80 |
| 3 | 5 | 75 |

[a]Isolated yield.

**Table 3.** Comparison Fe(III)/Al-MCM-41 with reported catalysts in the synthesis of **4a**

| Catalyst | Catalyst loading | Solvent | Temperature | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| AIKIT-5(10) | 150 mg | $CH_3CN$ | Reflux | 3 | 96 |
| PPE | 300 mg | THF | Reflux | 15 | 95 |
| $InBr_3$ | 10 mol% | $C_2H_5OH$ | Reflux | 7 | 98 |
| Fe(III)/Al-MCM-41 | 0.03 gr | $CH_3CN$ | Reflux | 4 | 85 |

## CONCLUSION

In conclusion, we developed an efficient and simple alternative for the preparation of 3,4-dihydropyrimidinones via Fe(III)/Al-MCM-41catalysis under mild conditions. Prominent among the advantages of this new method are operational simplicity, good yields, recyclablity of the catalyst, and an easy workup procedure.

## EXPERIMENTAL

All the chemicals were purchased from Merck Company. Melting points were measured using a Barnstead Electrothermal instrument. GC mass analysis was performed using an Agilent 6890 GC system, Hp-5 capillary 30 m × 530 μm × 1.5 μm nominal. IR spectra were recorded as KBr discs on a Brucker Tensor 27 Fourier transform (FT)–IR spectrometer. $^1$H NMR spectra were recorded on a Bruker AQS Avance 300-MHz spectrometer using tetramethylsilane (TMS) as an internal standard.

### General Procedure for the Synthesis of 3,4-Dihydropyrimidinones

A solution of ethyl acetoacetate **1** (2 mmol), aldehyde **2** (2 mmol), urea **3** (3 mmol), and Fe(III)/Al-MCM-41 (0.03 g) in acetonitrile (10 ml) was heated under reflux for 4 h. The progress of the reactions was monitored by thin-layer chromatography (TLC). The reaction mixture was poured into crushed ice with stirring. The crude product was filtered, and washed with 95% hot ethanol, the catalyst was filtered, and then the product recrystallized with hot ethanol to give **4**.

### Preparation of Catalysts Fe(III)/Al-MCM-41[15]

Al-MCM-41 (1 g) was added to $FeCl_3$ (1.5 mmol in 100 ml ethanol). The mixture was refluxed while stirring for 8 h under a nitrogen atmosphere. The solid product was then filtered, and soxhelet was extracted with enough absolute ethanol to remove the weakly adsorbed metallocomplexes on the mesoporous surface. The solid was finally dried in air at room temperature. The iron percentage present in the immobilized complex/Al-MCM-41 is 0.89%.[15b]

### General Procedure for Recyclability of the Catalyst

Next, we investigated the reusability and recycling of Fe(III)/Al-MCM-41. At the end of the reaction, the catalyst could be recovered by simple filtration. The recycled catalyst could be washed with methanol and subjected to a second run of the reaction process. To assure that catalysts were not dissolved in acetonitrile, the catalysts were weighted after filtration and before the next reaction. The results show that these catalysts are not soluble in acetonitrile. In Table 2, the comparison of efficiency of Fe(III)/Al-MCM-41 in the synthesis of **4a** after three runs is reported. As shown in Table 1, the first reaction using recovered Fe(III)/Al-MCM-41 afforded a yield similar to that obtained in the first run. In the second and third runs, the yields were gradually decreased because the active quantity of Fe(III) decreased.

### Spectral Data for Selected Compounds

**5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (4a).** Mp 201–203 °C. IR (KBr): 3111, 2955, 1705, 1649, 1613 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz): δ 8.17 (s, 1H, NH), 7.25 (d, 2H, $J = 8.6$, Ar-H), 6.84 (d, 2H, $J = 8.6$, Ar-H), 5.75 (s, 1H, NH), 5.36 (d, $J = 2$ Hz, 1H), 4.08 (q, $J = 7.1$ Hz, 2H, $OCH_2$), 3.79 (s, 3H, $CH_3$), 2.35 (s, 3H, $CH_3$), 1.18 (t, $J = 7.1$ Hz, 3H, $OCH_2CH_3$).

**5-Ethoxycarbonyl-6-methyl-4(2-nitrophenyl-3,4-dihydropyrimidin-2(1H)-one (4b).** Mp 220–223 °C. $^1H$ NMR ($CDCl_3$, 300 MHz): 7.47–8.24 (m, 5H, Ar-H and NH), 5.90 (s, 1H, NH), 5.77 (s, 1H, H-4), 4.35 (q, $J = 7.5$ Hz, 2H, $OCH_2$), 2.48 (s, 3H, $CH_3$), 1.37 (t, $J = 7.5$ Hz, 3H, $OCH_2CH_3$).

**5-Ethoxycarbonyl-6-methyl-4(4-methylphenyl-3,4-dihydropyrimidin-2(1H)-one (4c).** Mp 216–219 °C. IR (KBr): 3326, 3152, 1654, 1232, 1051 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz): δ 9.15 (s, 1H, NH), 7.80 (s, 1H, NH), 7.30–7.10

(m, 4H, Ar-H), 5.09 (s, 1H, H-4), 3.96 (q, $J = 7.1$ Hz, 2H, $OCH_2$), 2.23 (s, 3H, $CH_3$), 1.08 (t, $J = 7.1$ Hz, 3H, $OCH_2CH_3$).

**5-Ethoxycarbonyl-6-methyl-4(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (4d).** Mp 216–219 °C. IR (KBr): 3223, 3106, 1710, 1668, 1605 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz): δ 7.55 (s, 1H, NH), 7.21–7.34 (m, 5H, $C_6H_5$), 5.5 (s, 1H, NH), 5.42 (d, $J = 2.4$ Hz, 1H), 4.06–4.12 (m, 2H, $OCH_2$), 2.37 (s, 3H, $CH_3$), 1.18 (t, $J = 7.1$ Hz, 3H, $OCH_2CH_3$).

**5-Ethoxycarbonyl-6-methyl-4(4-nitrophenyl-3,4-dihydropyrimidin-2(1H)-one (4e).** Mp 208–210 °C. IR (KBr): 3230, 3120, 1730, 1710, 1650 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz): δ 9.35 (s, 1H, NH), 7.89 (s, 1H, NH), 7.47–8.23 (m, 4H, Ar-H), 5.26 (s, 1H, H-4), 3.97 (q, $J = 7.0$ Hz, 2H, $OCH_2$), 2.25 (s, 3H, $CH_3$), 1.08 (t, $J = 7.0$ Hz, 3H, $OCH_2CH_3$).

**5-Ethoxycarbonyl-6-methyl-4(4-chlorophenyl-3,4-dihydropyrimidin-2(1H)-one (4f).** Mp 212–214 °C. $^1H$ NMR ($CDCl_3$, 300 MHz): δ 9.24 (s, 1H, NH), 7.78 (s, 1H, NH), 7.40–7.21 (m, 4H, Ar-H), 5.12 (s, 1H, H-4), 3.97 (q, $J = 6.9$ Hz, 2H, $OCH_2$), 2.24 (s, 3H, $CH_3$), 1.08 (t, $J = 6.9$ Hz, 3H, $OCH_2CH_3$).

**5-Ethoxycarbonyl-6-methyl-4(3-nitrophenyl-3,4-dihydropyrimidin-2(1H)-one (4g).** Mp 227–230 °C. IR (KBr): 3300, 3120, 1710, 1690, 1630 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz): δ 9.37 (s, 1H, NH), 7.90 (s, 1H, NH), 8.10–7.64 (m, 4H, Ar-H), 5.29 (s, 1H, H-4), 3.98 (q, $J = 7.0$ Hz, 2H, $OCH_2$), 2.26 (s, 3H, $CH_3$), 1.08 (t, $J = 7.0$ Hz, 3H, $OCH_2CH_3$).

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