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# $Ca(OH)_2/CaO$ as a green catalyst for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones derivatives

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**Abstract:** $Ca(OH)_2/CaO$ which shows excellent catalytic activity, is used as solid base catalyst for the rudimental investigation of its catalytic behavior for synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones. The reactions were carried out at room temperature under solvent free condition. This method have some advantages such as inexpensive, non-toxic and eco-friendly, good to excellent yield, mild reaction condition, and high product purity.

**Keywords:** $Ca(OH)_2/CaO$, 3,4-Dihydropyrimidin-2(1*H*)-ones, Eco-friendly catalyst, Green process.

## Introduction

Dihydropyrimidinones derivatives have many biological activities such as antimicrobial activity and cytotoxicity [1,2], antitumor activities [3,4], antioxidative [5], antidiabetic activity [6], picomolar sodium iodide symporter inhibitors [7], antiproliferative activity [8], antifungal and antitubercular [9], inhibitory activity against HIV-1 replication [10], calcium channel blockers [11], antiarrhythmic activity [12], antileishmanial [13], aspergillosis [14], antihypertensive [15], anticancer [16], cytotoxicity screening against HepG2 and HeLa cell lines [17]. Dihydropyrimidinones derivatives due to their interesting antibacterial activities [18,19], against Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa and Salmonella typhi and antifungal activity against Candida albicans, Aspergillus flavus, Rhizopus and Mucor [20] grab scientists attention in recent years.

One methods has been reported for the synthesis of dihydropyrimidinones derivatives via a three-component condensation of aldehyde, β-ketoester or β-diketone and urea to synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones derivatives. Due to the importance of the Biginelli reaction products, much work on improving the yields and reaction conditions has been actively pursued. For example, modification and improvements include using Lewis acids, both protic and metallic Lewis acids. On the other hand, this condensation was found to be equally effective when Lewis acids were replaced by a strong Brönsted base (KOH) [21] and triphenylphosphine as Lewis base [22] but in this case the reaction involves two steps. This simple procedure reported herein the use of triphenylphosphine (TPP) for the one-pot Biginelli reaction [23]. Current study investigates the $Ca(OH)_2/CaO$ as a heterogeneous catalyst in the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones derivatives.

## Results and discussion

Initially, we have examined the synthesis of 5-ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-

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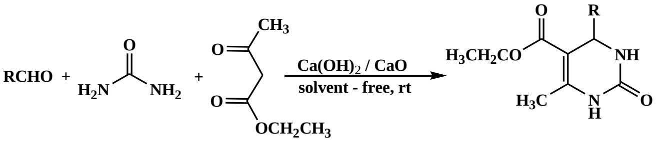
dihydropyrimidin-2(1*H*)-one using 4-methylbenzaldehyde (10 mmol), ethyl acetoacetate (10 mmol), urea (12.5 mmol) and $Ca(OH)_2/CaO$ as the catalyst under various conditions (Scheme **1**, Table **1**). We have found that the best conditions are $Ca(OH)_2/CaO$ (1.5 g) was stirring at room temperature under solvent free condition for 3 hours.



**Scheme 1:** synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones from an aldehyde, *β*-ketoester and urea.

Only 48% yield of product was obtained when $Ca(OH)_2$ was utilized as catalyst (entries 3). The application of CaO resulted in the yield of 55% (entry 8). As the reaction was performed at a $Ca(OH)_2/CaO$ 0.75(g) / 0.75(g), the complete conversion of the starting material to the desired product with the yield of 75% was obtained within 2 h. When the catalyst loading of $Ca(OH)_2/CaO$ was increased to 0.30(g) / 1.20(g), a considerably higher yield was observed (entry 14).

It was observed that in the absence of catalyst, the product of the reaction was only monitored by TLC. It was found that the best conditions could be achieved using $Ca(OH)_2/CaO$ (0.30(g) / 1.20(g) under solvent-free conditions at room temperature (rt) for 2 hours. Solvents that were used in representative sets of these reactions in refluxing ethanol and water for 2 h provided the desired product in 72 and 69% yield respectively (Table **1**, entry 16-18). It was noticed that if toluene and ethyl acetate were used as a reaction medium, the product of the reaction was only monitored by TLC and in the yield of trace.

**Table 1:** The synthesis of 5-ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1*H*)-one under various conditions. [a]

| Entry | Catalyst (g) | Solvent | Conditions | Time (min) | Yield$^a$ (%) |
|---|---|---|---|---|---|
| 1 | $Ca(OH)_2$ 1.50(g) | Water | rt | 120 | 35 |
| 2 | $Ca(OH)_2$ 1.50(g) | Water | Reflux | 120 | 47 |
| 3 | $Ca(OH)_2$ 1.50(g) | Solvent free | rt | 120 | 48 |
| 4 | $Ca(OH)_2$ 1.50(g) | Ethanol | rt | 120 | 38 |
| 5 | $Ca(OH)_2$ 1.50(g) | Ethanol | Reflux | 120 | 45 |
| 6 | CaO 1.50(g) | Water | rt | 120 | 18 |
| 7 | CaO 1.50(g) | Water | Reflux | 120 | 43 |
| 8 | CaO 1.50(g) | Solvent free | rt | 120 | 55 |
| 9 | CaO 1.50(g) | Ethanol | rt | 120 | 32 |
| 10 | CaO 1.50(g) | Ethanol | Reflux | 120 | 62 |
| 11 | $Ca(OH)_2/CaO$ 0.75(g) / 0.75(g) | Solvent free | rt | 120 | 75 |
| 12 | $Ca(OH)_2/CaO$ 1.00(g) / 0.50(g) | Solvent free | rt | 120 | 70 |
| 13 | $Ca(OH)_2/CaO$ | Solvent free | rt | 120 | 81 |

| | | | | | |
|---|---|---|---|---|---|
| | 0.50(g) / 1.00(g) | | | | |
| 14 | $Ca(OH)_2/CaO$<br>0.30(g) / 1.20(g) | Solvent free | rt | 120 | 88 |
| 15 | $Ca(OH)_2/CaO$<br>0.30(g) / 1.20(g) | Water | rt | 120 | 57 |
| 16 | $Ca(OH)_2/CaO$<br>0.30(g) / 1.20(g) | Water | Reflux | 120 | 69 |
| 17 | $Ca(OH)_2/CaO$<br>0.30(g) / 1.20(g) | Ethanol | rt | 120 | 53 |
| 18 | $Ca(OH)_2/CaO$<br>0.30(g) / 1.20(g) | Ethanol | Reflux | 120 | 72 |
| 19 | $Ca(OH)_2/CaO$<br>0.30(g) / 1.20(g) | Solvent free | rt | 150 | 89 |
| 20 | $Ca(OH)_2/CaO$<br>0.30(g) / 1.20(g) | Solvent free | rt | 100 | 72 |

[a] 4-Methylbenzaldehyde (10 mmol), ethyl acetoacetate (10 mmol), urea (12.5 mmol) were applied.

Next, the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones derivatives was studied and summarized in Table **2**. In all cases, the three-component reaction proceeded smoothly to give the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones in moderate to good yields. In summary, we have described $Ca(OH)_2/CaO$ is an efficient, catalyst for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones derivatives. All of the products were characterized by FT-IR and $^1H$-NMR.

**Table 2:** The synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones derivatives in the presence of $Ca(OH)_2/CaO$ (0.30(g) / 1.20(g)) via Scheme **1**.[a]

| **Ent.** | **R** | **Time (min)** | **Yield[a]** | **Mp (°C)** | **mp°C Ref.** |
|---|---|---|---|---|---|
| 1 | $2\text{-}NO_2\text{-}C_6H_4$ | 130 | 88 | 216-218 | 218-220[24] |
| 2 | $4\text{-}NO_2\text{-}C_6H_4$ | 100 | 89 | 212-213 | 211[25] |
| 3 | $4\text{-}Cl\text{-}C_6H_4$ | 135 | 87 | 213-214 | 214-215[24] |
| 4 | $4\text{-}MeO\text{-}C_6H_4$ | 150 | 85 | 203-204 | 203-205[26] |
| 5 | $3\text{-}MeO\text{-}C_6H_4$ | 150 | 83 | 220-221 | 220-221[27] |
| 6 | $4\text{-}Me\text{-}C_6H_4$ | 120 | 88 | 215-216 | 214[25] |
| 7 | $C_6H_5$- | 130 | 87 | 206-207 | 204[25] |
| 8 | 2-Furyl | 150 | 82 | 201-202 | 203-205[24] |

| | | | | | |
|---|---|---|---|---|---|
| 9 | Isopropyl | 150 | 83 | 195-197 | 196-197[26] |
| 10 | $C_6H_5$-$CH_2CH_2$- | 120 | 82 | 156-157 | 156-157[27] |
| 11 | $C_6H_5$-C=C- | 130 | 81 | 229-230 | 229-230[27] |

[a] Isolated yield

## Conclusion

In conclusion, $Ca(OH)_2/CaO$, which shows excellent catalytic activity, is used as solid base catalyst for the rudimental investigation of its catalytic behavior for synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones from an aldehyde, *β*-ketoester and urea as well as the mechanism of this reaction over $Ca(OH)_2/CaO$. The reactions were carried out at room temperature under solvent free condition. This method have some advantages such as inexpensive, non-toxic and eco-friendly catalyst, good to excellent yield, mild reaction condition, and high product purity.

## Experimental

The materials were purchased from Sigma–Aldrich and Merck and were used without any additional purification. Products were characterized by FT-IR, $^1$H-NMR and comparison of their physical properties with those reported in the literature. FT-IR spectra were run on a Bruker, Eqinox 55 spectrometer. A Bruker (DRX-500 Avanes) NMR was used to record the $^1$H NMR spectra.

*General procedure for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones derivatives at room temperature under solvent free condition:*

A mixture of aldehyde (10 mmol), ethyl acetoacetate (10 mmol), urea (12.5 mmol) and $Ca(OH)_2/CaO$ (1.50g) was stirring at room temperature under solvent free condition. After completion of reaction, the product was dissolved to methanol and filtered to recover the catalyst. The solvent was evaporated and the crude product recrystallized from 85% ethanol..

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