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A One Pot Green Synthesis of 3, 4 Dihydropyrimidin-2-(1H)-ones Catalyzed By CuO-SnO2 Under *Solvent-Free* Conditions

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Abstract: An efficient green synthesis of 3,4-dihydropyrimidin-2-(1H)-ones/thiones (DHPMs) using CuO/SnO_2 as heterogeneous catalyst from an aldehyde, *β*-keto ester and urea/thiourea under *solvent-free* conditions is described. A variety of aldehydes were studied with *β* -keto ester and urea giving good to excellent yield of corresponding 3,4-dihydropyrimidin-2-(1H)-ones. This protocol has advantage of excellent yield, reusability, inexpensive and short reaction time at room temperature. The synthesized catalyst can be reused up to 5 consecutive cycles without any significant decrease in the yield.

Keywords: *DHPMs, green synthesis, MCRs, Mixed metal oxides, MMOs*

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I. INTRODUCTION

The one pot, high yield procedures owed to reliable synthetic methods which form the base of early steps of drug discovery by high throughput screening or fragment based design and also represents 'hit-to-lead' optimization **[1, 2]** Though the combinatorial synthetic methodology passing through advances in molecular biology, the rate of introduction of new medicines has been decreased markedly over past two decades **[3]**. The heterocyclic ring comprise to the most medicines in use but the number of easily accessible and suitably functionalized heterocyclic building blocks for synthesis of structurally diverse libraries are rather limited.Therefore the medicinal and synthetic chemists attract towards development of new, rapid and green synthetic routes of such compounds **[4]**. No doubt, the most efficient strategies involve multicomponent reactions (MCRs), which have arise as an important tool to introduce the huge diversity of chemical space covered by compounds, reliable synthetic methods, selectivity, atom economy and convergence. Therefore, the design and development of new MCRs for the generation of In 1893, the Italian chemist Pietro Biginelli (University of Florence) for the first time reported the synthesis of dihydropyrimidinones by acid catalyzed cyclocondensation reaction of ethylacetoacetate (1), benzaldehyde (2) and urea (3) **[9]**.

The reaction was carried out by simple heating a mixture of these three component dissolved in ethyl alcohol with catalytic amount of HCl at reflux condition. The product of this important one pot, three component synthesis was precipitated on cooling and was identified as 3,4 dihydropyrimidine – 2 (1H) – one (4) (**Fig.1) [10].** This reaction nowadays reffered to as the "Biginelli dihydropyrimidinone synthesis".

heterocycles get much importance **[5, 6]**. The synthetic modifications in which highly functionalized organic molecules can be produced from easily available substrates via atom efficient reactions are of great importance for organic chemists. The expeditious domino and multicomponent reactions are examples of such types of conversions **[7]**. A special class of tandem sequential reactions represents the MCRs.

MCRs are defined as one-pot reactions in which more than two components are combine to form a new product, incorporating essentially most of moieties from all components.

MCRs are well appreciated due to their simple procedures, superior atom economy, high convergence and highly ever increasing number of accessible backbones **[8]**. MCRs are emerged as an established protocol for facile construction of complex and structurally variable target molecules in one pot fashion from at least three different simple building blocks. Such type of reactions offers remarkable advantage over conventional linear multi-step synthesis.

It was observed that DHPMs exhibit similar pharmacological properties to DHP calcium channel modulators of the nifedipine type and much activity has been encountered in this area during 1980s and 1991s **[11]**. Other than calcium channel modulation, DHPM derivatives also shows another biological activities e.g. α_{1a} adrenoceptor selective antagonists useful for treatment of benign prostatic hyperplasia **[12]**. Again the pharmacological activity in the field of α_1 adrenergic antagonists is based on activity found earlier in dihydropyridine (DHP) series of compounds. But the fact is DHPMs are much more than just being azanalogs of Hantzsch type DHPs **(Fig. 1).**

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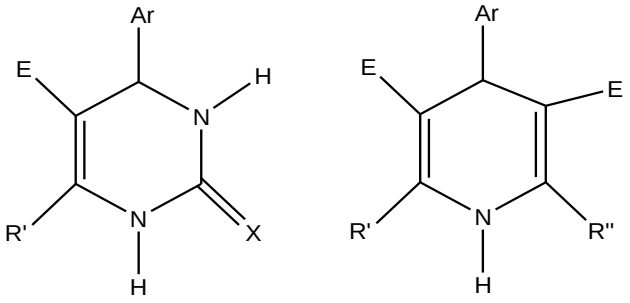

a. DHPM b. DHP

Fig. 1: Structural comparison of Biginelli dihydropyrimidinones (a, DHPMs) and Hantzsch dihydropyridines (b, DHPs).

I. THE REVIEW OF RECENT LITERATURE INDICATES THAT, BIGINELLI COMPOUNDS VIZ. DIHYDROPYRIMIDINONES (DHPMS) WERE NOT PREPARED IN PRESENCE OF CUO-SNO_2 CATALYST UNDER SOLVENT FREE CONDITIONS. HENCE IT WAS THOUGHT OF INTEREST TO DEVELOP THE GREEN PROTOCOL TO PREPARE DHPMS THROUGH CYCLOCONDENSATION OF ALDEHYDE, UREA AND B-KETOESTER. HENCE IN THE PRESENT STUDY, THE GREEN PATHWAY IS DEVELOPED BY CYCLOCONDENSATION OF ALDEHYDE, UREA AND B-KETOESTER IN PRESENCE OF CUO-SNO_2 CATALYST UNDER SOLVENT FREE CONDITIONS TO YIELD DIHYDROPYRIMIDINONES.

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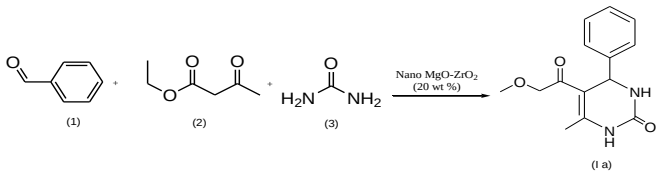
II Experimental

General

All commercially available chemicals and reagents were purchased from Aldrich and used without further purification. IR spectra were recorded on a Perkin-Elmer 1640 FT-IR instrument. The 1H- and 13C-NMR spectra were recorded on a Bruker DPX-300 NMR machine. Unless otherwise specified, CDCl3 was used as solvent. Mass spectra were recorded with a Bruker Daltonic Data Analysis 2.0 spectrometer.

Typical Experimental Procedure

In typical synthesis of dihydropyrimidinones, a mixture of β-keto ester (10 mmol), aldehydes (10 mmol), urea (15 mmol) and 20 wt. % of CuO-SnO_2 catalyst (with respect to aldehyde) were added to 25 mL flat bottom flask equipped with a refluxed condenser and magnetic stirrer. The mixture was stirred with a magnetic stirrer and refluxed for appropriate reaction time **(Table: 1).** After completion of reaction the catalyst was filtered by using sintered crucible and washed with acetone and ether successively and reused for next cycle. The crude products were obtained by recrystallisation by using ethanol.



Reaction Scheme 1: Preparation of 5–(Ethoxycarbonyl)–6–methyl–4–phenyl–3,4–dihydropyrimidin–2(1H)–one (I_a)

*Reaction conditions: Benzaldehyde = 10 mmol, Urea=15 mmol, Ethyl aceto aceatate =10 mmol, catalyst = 20 wt. % with respect to aldehyde, solvent free,Time=20 min., temp. = 25°C.

E= Ester, amide, acyl
R', R" = Alkyl
X = O, S
Ar = Substituted aryl

Preparation of CuO-SnO_2 Catalyst

$Cu(NO_3)_2.3H_2O$ (0.05 mol) and $SnCl_2.2H_2O$ (0.05 mol) were initially dissolved in 250 ml of water and then urea (0.2 mol) was added to the homogeneous mixture and transferred to an autoclave. The solution was allowed to reach to 180 °C within an hour (ramp time). The reaction was kept at this temperature for 2 hours (soak time) with an in situ pressure of 12 atmospheres. After 2 hours, it was cooled to room temperature. The product was filtered, washed with water and acetone and dried at 110°C in a hot air oven. The initial pH of the experimental solution was acidic (pH ~ 4) and the final pH was alkaline (pH ~8). The final product was pale green in color.

Results and Discussion:

In order to explore our interest for the application of mix metal oxide CuO-SnO2 in organic synthesis, we herein present a simple and efficient one-pot synthesis of dihydropyrimidinones from enolizable a mixture of β-keto ester, aldehydes and urea in presence of mix metal oxide CuO-SnO_2 **(Scheme.1)**. The present protocol provide a variety of dihydropyrimidinones which are obtained in good to excellent yields(85-95%). According to this procedure, the reaction proceeded smoothly at room temperature to afford the corresponding β-acetamidoketones in good yields. **(Table No.1)**

Table 1: List of the synthesized compounds*.

Compound	Name of the compound	Time (Min.)	Isolated yield	Melting point	
				Observed	Reported
I_a	5–(Ethoxycarbonyl)–6–methyl–4–phenyl–3,4–dihydropyrimidin–2(1H)–one	30	92	204	206
I_b	5–(Ethoxycarbonyl)–6–methyl–4–(2–methoxyphenyl)–3,4–dihydropyrimidin–2(1H)–one	30	87	258	255-257
I_c	5–(Ethoxycarbonyl)–6–methyl–4–(4–methoxyphenyl)–3,4–dihydropyrimidin–2(1H)–one	30	71	204	259-260
I_d	5–(Ethoxycarbonyl)–6–methyl-4–(2-chlorophenyl)–3,4–dihydropyrimidin–	30	90	221	209-212

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	2(1H)–one				
I_e	5–(Ethoxycarbonyl)–6–methyl–4–(4-chlorophenyl)–3,4–dihydropyrimidin–2(1H)–one	30	91	215	213-214
I_f	5–(Ethoxycarbonyl)–6–methyl–4–(2-nitrophenyl)–3,4–dihydropyrimidin–2(1H)–one	20	92	225	222-225
I_g	5–(Methoxycarbonyl)–6–methyl–4–(4-nitrophenyl)–3,4–dihydropyrimidin–2(1H)–one	20	93	208	206-207
I_h	5–(Methoxycarbonyl)–6–methyl–4–(4-hydroxyphenyl)–3,4–dihydropyrimidin–2(1H)–one	20	85	231	230-231

***Reaction conditions:** Aldehyde = 10 mmol, urea/thiourea=15 mmol, β-keto-ester =10 mmol, catalyst = 20 wt. % with respect to aldehyde, solvent free, temp. = 25°C. All compounds are well characterized by spectroscopic techniques.

Conclusion:

In conclusion, we have reported an efficient procedure for the synthesis of dihydropyrimidinones using mix metal oxide CuO-SnO2 catalyst. The major advantage of this method is that the ease of work-up. This method also offers some other merits such as clean synthesis, high yields of products, shorter reaction times and use of various substrates, which make it useful and attractive strategy for the synthesis of dihydropyrimidinones.

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