



**LIGHT INDUCED BIGINELLI REACTION: A CLEAN AND EFFICIENT  
PROTOCOL USING ALUMINIUM SULPHATE AS CATALYST FOR SYNTHESIS  
OF DIHYDROPYRIMIDINONES**

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**Abstract:**

In this paper we report the Biginelli reaction of aldehyde,  $\beta$ -ketoester and urea/thiourea under visible light condition using aluminium sulphate as catalyst. Compared to the classical Biginelli reaction conditions, the present method has the advantages of giving good yields, short reaction time, avoidance of the use of toxic organic solvent, reaction condition are simple, inexpensive and easily available catalyst, simple work-up procedure.

**Keywords:** Aldehyde, Aluminium sulphate, Dihydropyrimidinones, Light mediated,  $\beta$ -keto ester

**Introduction:**

The multicomponent reactions are key process in organic synthesis and medicinal chemistry<sup>i</sup>. The diversity, competent and rapid access to small and highly functionalized organic molecules to makes this approach is present vital interest in the construction of combinatorial libraries and optimization in drug discovery process<sup>ii</sup>.

Dihydropyrimidinones are a series of extremely important small heterocyclic molecules possessing resourceful pharmaceutical properties<sup>iii</sup>. Dihydropyrimidinone are well recognized to shows a wide range of biological activities such as antiviral, antitumor, antibacterial, anti-inflammatory, antihypertensive, Calcium channel blocker, antifungal, antioxidant, antitubercular, antifilarial, analgesic, anti-epileptic, antimalarial, antileishmanial<sup>iv, v</sup>. Pyrimidinone derivatives are found as core units in many marine alkaloids (batzelladine and carambine), which have been found to be potent to HIV-gp-120 CD4 inhibitors<sup>vi</sup>. Thus due to enormous importance in pharmacological and biological activities of this class of compounds, research interest towards this area is increasing day by day. This in turn increases the attempts to develop various versatile, safe and quick methods for their synthesis. The classical Biginelli reaction suffers from the drawbacks like harsh reaction conditions, long reaction time, and low to moderate yields that are often encountered when using substituted aromatic or aliphatic aldehydes. This has led to multistep synthetic strategies that produce somewhat better yields but lack the simplicity of one-pot synthesis. In order to improve the efficiency of the Biginelli reaction, various methods were developed for the synthesis of dihydropyrimidinone<sup>vii-xi</sup>. However, some of these methods suffer from drawbacks like use

of heavy toxic metal salt, expensive catalyst, long reaction, use of toxic organic solvent. Thus, development of simple, valuable, fair, high yielding and eco-friendly approaches using new catalysts for the synthesis of these molecules is an important task of organic chemists.

Photochemical reactions are attractive area in organic synthesis. Photochemical reactions using light in environment friendly conditions like water, aqueous ethanol or solvent free reaction is generally considered as a clean and green procedure<sup>xii</sup>. This type of photo-activation of substrate very often minimizing the formation of byproducts and requires much lesser time corresponds to thermal methods and due to this fact, photochemical reactions motivate chemist to do research and some excellent reviews, research paper have been published<sup>xiii</sup>.

### Results and Discussion:

In a preliminary study, Ethyl acetoacetate (1a), urea (2a), benzaldehyde(3a) sulphate in the 1:1:1 mole ratio in presence of aluminium sulphate (20mmole) under visible light. The progress of the reaction was monitored by TLC. As the time moves reaction proceed in forward direction and the reaction was found to be complete within 85 minutes affording Dihydropyrimidinones (4a) in 92% yield. The structure of the product is confirmed by spectroscopy method. In <sup>1</sup>HNMR spectra, the proton at the 4-position of the dihydropyrimidinones rings appears as singlet at 5.67 ppm and the 4- carbon appears around 48.9. This proton and carbons are coming from benzaldehyde, the aldehyde proton appears at 9ppm and this peak is disappearing in product which confirms the bond formation between C-2 carbon of ethyl acetoacetate, urea and aldehyde carbon. In <sup>13</sup>CNMR the carbonyl group appear in the expected region around 195.3-197.2.

In order to study the scope of this protocol, a series of DHPMs were synthesized using aromatic aldehydes carrying both electron donating or withdrawing substituent's and heterocyclic aldehydes were subjected to reaction with β-keto esters, urea under the optimized reaction conditions. Thiourea has been used with similar success to provide the corresponding dihydropyrimidin-2(1H)-thiones which are also of much interest with regard to biological activity. The reaction proceeds smoothly to give the corresponding dihydropyrimidinones in excellent yields and the results are given in Table 1.

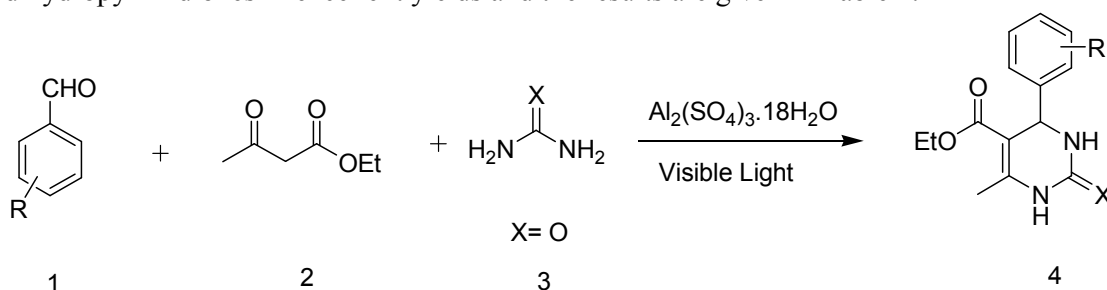


Figure 1 Synthesis of Dihydropyrimidinone using aluminium sulphate as catalyst under visible light irradiation

Table 1. Synthesis of substituted dihydropyrimidinones/thiones using aluminium sulphate as a catalyst under visible light condition<sup>a</sup>

Entry	Aldehyde	X	Product (4)	Time in minutes	% Yield <sup>b</sup>	M. P.
1	Benzaldehyde	O	4a	85	92	200-204
2	4-chlorobenzaldehyde	O	4b	70	89	211-215
3	4-methoxybenzaldehyde	O	4c	105	81	208-211

4	4-bromobenzaldehyde	O	4d	74	82	236-238
5	4-hydroxybenzaldehyde	O	4e	95	80	192-195
6	4-nitrobenzaldehyde	O	4f	60	86	208
7	4-N,N-dimethylbenzaldehyde	O	4g	120	70	245-247
8	4-methylbenzaldehyde	O	4h	80	85	218-221
9	3-hydroxybenzaldehyde	O	4i	90	87	162-163
10	3-nitrobenzaldehyde	O	4j	84	84	225-227
12	2-hydroxybenzaldehyde	O	4l	135	72	198-200
13	2-nitrobenzaldehyde	O	4m	150	64	208-210

a: Reaction condition: 1mmol of substituted benzaldehyde, 1mmol of ethyl acetoacetate, 1mmol of urea, 0.2mmol of aluminium sulphate under visible light irradiation; b: isolated yield after purification

Notably, this protocol is compatible with a wide range of functional groups such as methoxy, halides, nitro, hydroxyl, *N, N*-dimethyl-, and acid sensitive compound like cinnamaldehyde, furfural aldehyde could afford the corresponding products in excellent yield as well.

#### Conclusion:

In summary, here I reported an efficient synthesis of dihydropyrimidinones and dihydropyrimidinethiones using aluminium sulphate as a catalyst under visible condition. The mild reaction conditions, rapid formation of product, high yields, inexpensive and easily available catalyst, are some notable merits of this method. Moreover, compatibility with the environment, more efficiency and easy separation of catalyst after synthesis are considered as another merit of this method.

#### Experimental:

All reagents, chemicals and solvents were purchased from Loba, Merck, SRL and Sigma Aldrich. TLC (pre-coated silica gel 60 F254) was used to monitor the progress of the reaction. Melting points were recorded by open capillary method and are uncorrected. IR spectra were recorded as KBr pellets using shizmude FTIR. The <sup>1</sup>HNMR spectra were obtained on a Bruker DRX-300 Avance instrument using DMSO *d*<sub>6</sub> as solvent and TMS as internal standard at 300MHZ. All products are known compounds and their authenticity was ensured on the basis of spectroscopic data and on comparison with authentic samples.

**General Procedure for the Synthesis of Dihydropyrimidinones:** A mixture of aldehyde (1mmol), ethyl acetoacetate (1mmol), urea (1mmol) and Al<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> 18H<sub>2</sub>O (0.2mmol, 20mol %) in a reaction flask was stirred well, irradiated with a 500W tungsten lamp (Philips India Ltd.). The reaction mixture was irradiated for specified time (see Table 1). The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled, added to 20mL ice cold water, solid was precipitated, filtered on a suction pump, washed with water and dried. A pure sample was obtained by recrystallization from ethanol.

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Received on March10, 2016.