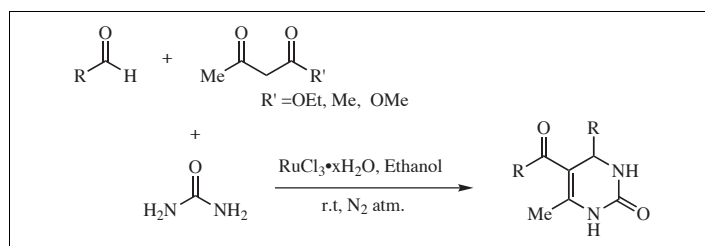


Ruthenium-Catalyzed Biginelli Condensation: A Simple and Efficient One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones under Mild Reaction Conditions

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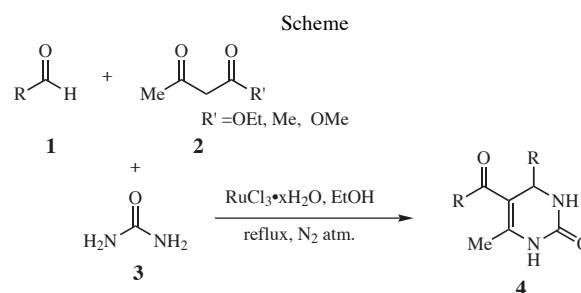
Ruthenium trichloride was found to be an efficient catalyst for the first time for the synthesis of a variety of 3,4-dihydropyrimidin-2(1*H*)-ones by cyclocondensation of an aldehyde, β -dicarbonyl compound and urea in excellent yields under mild reaction conditions.

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3,4-Dihydropyrimidinones are synthetically important building blocks in the realm of natural and synthetic organic chemistry due to their therapeutic and pharmacological properties including antiviral, antitumor, antibacterial and anti-inflammatory activities [1]. The Biginelli reaction, first reported in 1893 and reviewed recently, involving one-pot cyclocondensation of ethyl acetoacetate, benzaldehyde and urea in the presence of strong acid, is a direct and simple method for the preparation of dihydropyrimidinones [2], however this method suffers from the drawback such as the lower yields of the desired products (20-40 %) particularly in case of substituted aldehydes and loss of sensitive functional groups during the reaction. Therefore the development of improved methodology for this reaction has received considerable interest in recent years. In this context a variety of improved procedures using catalysts such as lewis acids [3], triflates [4], silica-sulfuric acid [5], silica supported sodium hydrogen sulfate [6], iodine-alumina [7], poly(4-vinylpyridine-co-divinylbenzene)-Cu(II) complex [8], L-proline [9] and silver salts of heteropoly acids [10] have been reported in the literature. However, in spite of their potential utility many of these methods suffers from the drawbacks such as the use of strong acidic conditions, longer reaction times, tedious work-up and lower yields of the products, leaving scope for further development of an efficient and versatile catalyst for Biginelli reaction.

Owing to the widest scope of oxidation states among the transition metals, ruthenium has proved to be the most versatile catalyst in synthetic organic chemistry and has been extensively used in various synthetic transformations

[11]. To the best of our knowledge there is no literature report on the use of ruthenium as catalyst for Biginelli type condensation. In continuation of our studies herein [12], we wish to report for the first time a very simple, facile and efficient ruthenium catalyzed Biginelli condensation for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones in excellent yields under mild conditions (Scheme).



A variety of aliphatic, aromatic and heterocyclic aldehydes were reacted with urea and β -dicarbonyl compound in ethanol using ruthenium trichloride hydrate ($\text{RuCl}_3 \cdot x\text{H}_2\text{O}$) as catalyst to afford corresponding 3,4-dihydropyrimidin-2(1*H*)-ones [13], these results are presented in Table. All the aldehydes studied were smoothly converted to their corresponding 3,4-dihydropyrimidin-2(1*H*)-ones in excellent yields, which were identified by comparing their physical (mps) and spectral data (^1H NMR and IR) with those of authentic samples [3,14,15,16]. To evaluate the catalytic effect of ruthenium trichloride, the blank experiment was carried

out under similar reaction conditions using benzaldehyde, ethyl acetoacetate and urea as substrates. The reaction was found to be very slow in the absence of catalyst. The use of acetyl acetone as 1,3-dicarbonyl moiety in place of ethyl acetoacetate also gave similar results Table (entry 11-14). The effect of various solvents was also studied for the formation of dihydropyrimidinone using benzaldehyde, ethyl acetoacetate and urea as substrates. Among the various solvents such as THF, acetonitrile, ethanol and benzene studied, ethanol was found to be the best solvent.

Although the detail mechanism of this reaction is not clear at this stage the reaction probably involves the *in situ* formation of acylimine intermediate by the reaction of urea and aldehyde, which undergoes the subsequent addition to β -dicarbonyl compound followed by cyclization and dehydration to yield dihydropyrimidinone **4** as proposed using lewis acids [17].

In conclusion the present procedure describes for the first time the use ruthenium tichloride as an extremely mild and high efficient catalyst for the synthesis of a variety of 3,4-dihydropyrimidin-2(1*H*)-ones in excellent yield under mild conditions by three component condensation of an aldehyde, 1,3-dicarbonyl compound and urea in one-pot. The simplicity of the system, easy workup and excellent yields make this method an attractive and facile tool for the Biginelli reaction.

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[13] Typical experimental procedure: A solution of benzaldehyde (5 mmol, 535 mg), urea (5 mmol, 300 mg) and ethylacetoacetate (5 mmol, 650 mg) in ethanol (10 ml) was stirred until urea got dissolved completely. Ruthenium trichloride hydrate (5 mol %, 0.25 mmol, 52 mg) was then added to the reaction mixture and it was further stirred for 5 min. followed by refluxing for 4 h under nitrogen blanket. The progress of the reaction was monitored by TLC (SiO₂) using ethyl

Table

Ruthenium-catalyzed Synthesis of Dihydropyrimidin-2(1*H*)-ones

Entry	Product	R	R'	Reaction time/h	Yield ^a (%)	Mp (°C) Found (lit) [ref]
1	4a	C ₆ H ₅	OEt	4.0	95	201(202) [14]
2	4b	4-CH ₃ C ₆ H ₄	OEt	4.5	85	214-15 (215) [3]
3	4c	4-CH ₃ OC ₆ H ₄	OEt	4.5	82	199-200 (201) [15]
4	4d	4-NO ₂ C ₆ H ₄	OEt	5.0	80	208-09 (210) [15]
5	4e	4-ClC ₆ H ₄	OEt	4.5	79	211 (212-13) [15]
6	4f	2-ClC ₆ H ₄	OEt	5.0	75	222 (223-4) [15]
7	4g	n-CH ₃ CH ₂ CH ₂	OEt	6.0	75	151-2 (153-55) [3]
8	4h	2-Furyl	OEt	4.5	83	204-05 (205) [14]
9	4i	(CH ₃) ₂ CH	OEt	5.5	75	193-4 (195) [15]
10	4j	n-CH ₃ (CH ₂) ₂ CH ₂	OEt	6.5	70	156 (157-8) [15]
11	4k	C ₆ H ₅	Me	4.5	94	208 (209-12) [14]
12	4l	4-NO ₂ C ₆ H ₄	Me	5.0	82	234-5 (235-7) [15]
13	4m	4-CH ₃ OC ₆ H ₄	Me	5.0	79	189-90 (190-93) [15]
14	4n	2-Furyl	Me	6.0	80	209-10 (210-12) [16]

[a] Isolated Yields.

acetate/ hexane (4:6) as eluent. After completion the reaction mixture was cooled at room temperature, the solid that separated was collected by filtration, washed with water and recrystallized from ethanol to give 5-ethoxy-carbonyl-6-methyl -4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one in 95 % yield, mp. 201 °C (202 °C) [14]. Similarly other aldehydes were reacted with urea and β -dicarbonyl compound and their reaction times and yields are presented in Table.

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