Ruthenium(III) Chloride-Catalyzed One-Pot Synthesis of 3,4-Dihydropyrimidin-2-(1*H*)-ones under Solvent-Free Conditions

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Abstract: Ruthenium(III) chloride efficiently catalyzes the three-component Biginelli reaction of an aldehyde, a β-keto ester, and urea or thiourea under solvent-free conditions to afford the corresponding 3,4-dihydropyrimidine-2-(1*H*)-ones in excellent yields.

Key words: pyrimidinones, ruthenium, aldehyde, Biginelli reaction, solvent-free conditions, heterocycles

At the beginning of the new century, green chemistry has become a major driving force for organic chemists to develop environmentally benign routes to a myriad of materials.[1] The possibility of performing multi-component reactions under solvent-free conditions with solid catalysts could enhance their efficiency from an economic as well as ecological point of view, so solvent free chemical reactions have received much attention. These reactions offer several advantages in preparative procedures, such as environmental compatibility, simplifying work-up, formation of cleaner products, enhanced selectivity, reduction of byproducts, a reduction in the waste produced, and much improved reaction rates.[2]

Dihydropyrimidinones and their sulfur analogs have been reported to possess diverse pharmacological properties such as antiviral, antibacterial, and antihypertensive activity, as well as efficacy as calcium channel modulators, and α-1a-antagonists.[3–6] The batzelladine alkaloids containing the dihydropyrimidine core unit are particularly notable, as they recently were found to be potent HIV gp-120-CD_4 inhibitors.[7] Therefore, due to the importance of these compounds as synthons in organic synthesis, many methods for preparing such compounds have been developed, and the Biginelli reaction has gained particular importance for ongoing research programs.[8–15] However, many of these reported methods have drawbacks such as long reaction times, low yields of products, harsh reaction conditions, the use of stoichiometric reagents, difficulties in work-up, the use of toxic and inflammable solvents, and incompatibility with other functional groups in the molecules. Therefore, there is a need to develop new methods using less hazardous solvents, or even better, those that do not need solvents at all.

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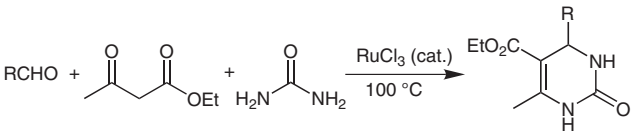
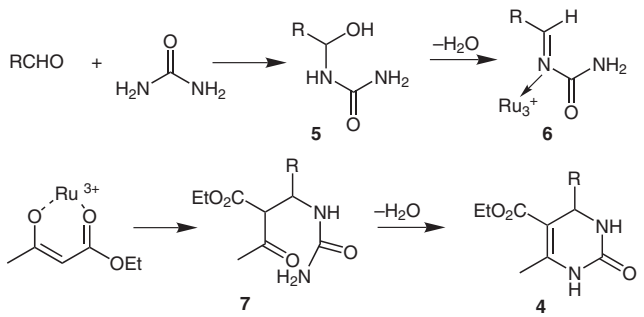
In this communication, we report a simple and efficient method for the synthesis of dihydropyrimidinones using a catalytic amount of $RuCl_3$ at 100 °C under solvent-free conditions. Recently, we have reported that $RuCl_3$ is a mild Lewis acid for both the acetylation of alcohols[16] and the chemoselective synthesis of acetals from aldehydes.[17] The reaction of benzaldehyde and urea with ethyl acetoacetate in the presence of a catalytic amount of $RuCl_3$ at 100 °C afforded the desired dihydropyrimidinone in 91% yield (Scheme 1). We also examined this reaction in different solvents, but the reaction gave better yields under neat conditions (Table 1). Thus, several activated and deactivated aromatic aldehydes and aliphatic aldehydes underwent the reaction to give the corresponding dihydropyrimidinones in good yields. The experimental procedure is very simple, convenient, and has the ability to tolerate a variety of other functional groups such as methoxy, nitro, hydroxy, halides, and olefins under the reaction conditions. Thiourea was used as one of the ingredients with similar success to provide the corresponding 3,4-dihydropyrimidin-2(1*H*)-thiones, which are also of interest with respect to their biological activities. For instance, monastrol (entry 18, Table 2), a mitotic kinesin Eg5 motor protein inhibitor and a potential anticancer drug lead, was obtained in 89% yield.[18,19] The results have been summarized in Table 2, which clearly indicates the generality and scope of the reaction with respect to various aromatic, heterocyclic, unsaturated, and aliphatic aldehydes.



Scheme 1

We propose a mechanism of the Ru(III)-catalyzed reaction as shown in Scheme 2. The aldehyde reacts with urea to form an acyl imine intermediate **6**, which is activated by Ru(III). Subsequent addition of the β-carbonyl compound, followed by cyclization and dehydration, affords the dihydropyrimidinone **4**.

In summary, we have developed a simple and efficient method for the synthesis of dihydropyrimidinones using a catalytic amount of $RuCl_3$ under solvent-free conditions. Moreover, the mild reaction conditions, short reaction



Scheme 2

Table 1 Formation of DHPM in Different Solvents[a] and Solvent-Free Conditions[b]

Entry	Solvent	Time (h)	Yield[c] (%)
1	MeCN	8	78
2	EtOH	9	62
3	CH_2Cl_2	10	46
4	H_2O	6	25
5	THF	10	40
6	solvent-free	0.5	91

[a] Reflux temperature.
[b] 100 °C.
[c] Benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (1.5 mmol), and $RuCl_3$ (5 mol%) were used.

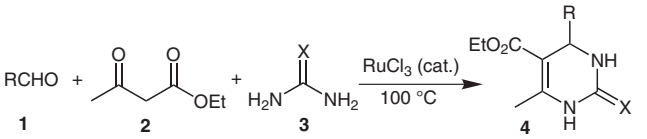
times, high yields of the products, ease of work-up, compatibility with various functional groups, and the ecologically clean procedure, will make the present method a useful and important addition to the present methodologies for heterocyclic synthesis.

NMR spectra were recorded on a Bruker ARX 300 (300 MHz) instrument. Low resolution MS (CI, EI) were recorded on a Finnigan 4000 mass spectrometer. HRMS (EI, CI, ESI) were recorded on a Finnigan MAT XL95 mass spectrometer. The reactions were monitored by TLC, and visualized with UV light followed by development using phosphomolybdic acid (15%) in EtOH. All solvents and reagents were purchased from Aldrich in high-grade quality, and used without any further purification. All yields refer to isolated products. All products are known and were identified by comparison of their spectral data and physical properties with those of authentic samples.[3–15]

General Procedure

A mixture of aldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (1.5 mmol), and $RuCl_3$ (5 mol%) was heated with stirring at 100 °C for an appropriate time (Table 2). After completion of the reaction (TLC), the reaction mixture was cooled to r.t., and then poured onto crushed ice (5 g). The solid separated was filtered under suction, washed with ice-cold H_2O. Finally, solid product was recrystallized from hot EtOH to give the pure product.

Table 2 $RuCl_3$-Catalyzed Synthesis of Dihydropyrimidinones and Thio-Derivatives



Entry	R	X	Time (min)	Yield[a] (%)
1	Ph	O	30	91
2	4-$MeOC_6H_4$	O	45	93
3	4-ClC_6H_4	O	40	87
4	4-$NO_2C_6H_4$	O	72	84
5	4-HOC_6H_4	O	85	80
6	4-MeC_6H_4	O	50	90
7	3-$MeOC_6H_4$	O	55	87
8	4-$NO_2C_6H_4$	O	78	85
9	2,4-$(OMe)_2C_6H_3$	O	40	92
10	PhCH=CH	O	55	89
11	1-Naphthyl	O	70	86
12	2-Furfuryl	O	45	90
13	*n*-Pentyl	O	90	76
14	*n*-Hexyl	O	95	74
15	Ph	S	50	86
16	3-$MeOC_6H_4$	S	50	89
17	4-ClC_6H_4	S	60	91
18	3-HOC_6H_4	S	65	89

[a] Yields refer to isolated products that were characterized by comparison of their mp, IR and ^1H NMR spectra with those of authentic samples.

Selected Spectral Data

5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (Entry 2, Table 2)

^1H NMR (300 MHz, DMSO-d_6): δ = 1.16 (t, *J* = 7.2 Hz, 3 H), 2.24 (s, 3 H), 3.76 (s, 3 H), 3.98 (q, *J* = 7.2 Hz, 2 H), 5.10 (d, *J* = 3.2 Hz, 1 H), 6.79 (d, *J* = 8.7 Hz, 2 H), 7.17 (d, *J* = 8.7 Hz, 2 H), 7.25 (br s, 1 H), 8.94 (br s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 13.8, 17.6, 53.4, 54.7, 58.6, 99.5, 113.3, 127.1, 136.9, 147.5, 152.1, 158.3, 165.2.

MS: *m*/*z* = 290 (M^+), 261, 217, 155, 77, 42.

5-Ethoxycarbonyl-4-(4-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (Entry 4, Table 2)

^1H NMR (300 MHz, DMSO-d_6): δ = 1.10 (t, *J* = 7.2 Hz, 3 H), 2.27 (s, 3 H), 3.98 (q, *J* = 7.2 Hz, 2 H), 5.29 (d, *J* = 3.2 Hz, 1 H), 7.51 (d, *J* = 9 Hz, 2 H), 7.89 (br s, 1 H), 8.19 (d, *J* = 9 Hz, 2 H), 9.33 (br s, 1 H).

5-Ethoxycarbonyl-4-(3-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione (Entry 16, Table 2)

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.13 (t, *J* = 6.2 Hz, 3 H), 2.28 (s, 3 H), 3.74 (s, 3 H), 4.01 (q, *J* = 6.2 Hz, 2 H), 5.18 (d, *J* = 2.8 Hz, 1 H), 6.85 (m, 3 H), 7.28 (t, *J* = 9 Hz, 1 H), 9.70 (br s, 1 H), 10.37 (br s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.3, 17.6, 54.3, 55.3, 59.9, 101.2, 112.8, 118.6, 130.4, 145.2, 145.7, 159.6, 165.3, 174.4.

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