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$CrCl_3 \cdot 6H_2O$ As an Environmentally Friendly and Efficient Catalyst for One-Pot, Synthesis of 2-oxo- and 2-thio-1,2,3,4-Tetrahydropyrimidines Under Solvent-Free Conditions

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Abstract

A one-pot, simple, and eco-friendly synthesis of 2-oxo- and 2-thio-1,2,3,4-tetrahydropyrimidines using a Biginelli condensation between β-keto esters (methyl or ethyl acetoacetate), aromatic benzaldehydes, and urea or thiourea in the presence of $CrCl_3 \cdot 6H_2O$ as an environmentally friendly and mild catalyst under solvent-free conditions has been performed. Based on reaction of benzaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), and urea (1.5 mmol), as well as 15 mol% of $CrCl_3 \cdot 6H_2O$ catalyst, the 82% yield was reached within 30 minute reaction time. The advantages of this methodology are solvent-free conditions, ease of handling, one-pot nature, low-cost, environmental friendliness, simple purification of products, and short reaction time.

Abstrak

$CrCl_3 \cdot 6H_2O$ sebagai Katalis yang Ramah Lingkungan dan Efisien untuk Sintesis Satu-bejana dari 2-oxo- dan 2-thio-1,2,3,4-Tetrahidropirimidin pada Kondisi Bebas Pelarut. Sintesis satu-bejana, sederhana, dan ramah lingkungan dari 2-okso dan 2-tio-1,2,3,4-tetrahidropirimidin menggunakan kondensasi Biginelli antara β-keto ester (metil atau etil asetoasetat), benzaldehida aromatik, dan urea atau tiourea dengan adanya $CrCl_3 \bullet 6H_2O$ sebagai katalis yang ramah lingkungan pada kondisi bebas pelarut telah dilakukan. Berdasarkan reaksi dari benzaldehida (1.0 mmol), etil asetoasetat (1.0 mmol), dan urea (1.5 mmol) serta katalis $CrCl_3 \cdot 6H_2O$ (15 %mol), dicapai 82 %*yield* dalam waktu reaksi selama 30 menit. Keuntungan dari metodologi ini adalah kondisi bebas pelarut, kemudahan penanganan, sifat satu-bejana, murah, ramah lingkungan, pemurnian produk sederhana, dan waktu reaksi yang singkat.

Keywords: 2-Oxo- and 2-thio-1,2,3,4-tetrahydropyrimidines, environmental friendly synthesis, solvent-free conditions, $CrCl_3 \cdot 6H_2O$ (chromium(III) chloride hexahydrate), Biginelli condensation reactions

Introduction

In recent years, organic chemists have focused their attention towards multi-component reactions (MCRs) [1-3] for the synthesis of heterocyclic compounds due to a broad range of notable advantages such as mildness, environmentally friendliness, one-pot operation, low-cost, atom-economy, and simple work-up. Due to numerous important biological and pharmaceutical activities, 2-oxo- and 2-thio-1,2,3,4-tetrahydropyrimidines are important targets among synthetic heterocyclic compounds. Typically, these compounds have been used as calcium channel blockers and α-1a-antagonists [4], as well as antihypertensive [5], anticancer [6], anti HIV [7], antibacterial and antifungal [8], antiviral [9], antioxidative [10], and anti-inflammatory [11] agents. Recently, numerous protocols for the preparation of these compounds that include Lewis and Brønsted acid catalysts have been reported [12-22]. Based on the above considerations, and in continuation of our efforts to develop simple methodologies, as well as our interest in applications of mild and efficient catalyzed organic reactions [23-30], we report herein $CrCl_3 \cdot 6H_2O$ (chromium(III) chloride hexahydrate) as a clean, mild, and efficient catalyst for the synthesis of 2-oxo- and 2-thio-1,2,3,4-tetrahydropyrimidines by means of a three-component Biginelli reaction [31] between β-keto esters, aldehyde derivatives, and urea/thiourea under thermal and solvent-free conditions, with high to excellent yields (Figure 1).

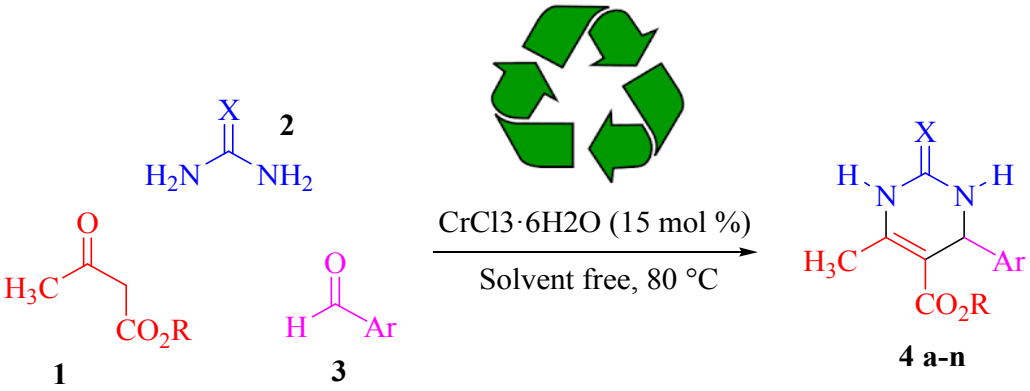


Figure 1. Synthesis of 2-oxo and 2-thio-1,2,3,4-Tetrahydropyrimidines

Material and Methods

Melting points of all compounds were determined using an Electrothermal 9100 apparatus. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker DRX-400 Avance instrument with DMSO-d_6 as solvent. All reagents and solvents were purchased from Merck, Fluka, and Acros chemical companies and used without further purification.

General procedure for preparation of 2-oxo- and 2-thio-1,2,3,4-tetrahydropyrimidines (4a-n). A mixture of aldehyde (1 mmol), β-keto ester (1 mmol), urea or thiourea (1.5 mmol), and $CrCl_3 \cdot 6H_2O$ (15 mol %) was heated with stirring at 80 °C. After completion of the reaction, as judged by thin-layer chromatography (TLC), the reaction mixture was cooled, poured into 4 °C water, and stirred for 5 min. The solid was filtered, washed with cold water, filtered, and recrystallized from ethanol to afford pure products (**4a-n**). Spectral data for some of these known products are included in the supplementary material.

Results and discussion

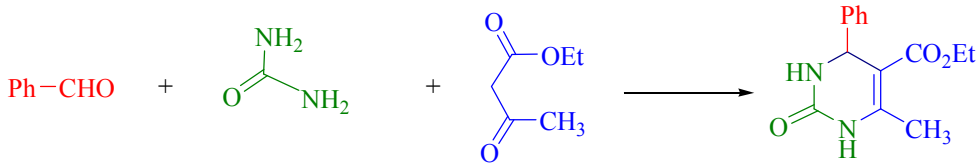
Initially, we performed a three-component Biginelli condensation reaction of benzaldehyde (**3**, 1.0 mmol), urea (**2**, 1.5 mmol), and ethyl acetoacetate (**1**, 1.0 mmol) in the presence of $CrCl_3 \cdot 6H_2O$ (15 mol%) under solvent-free conditions at 80 °C. The product **4a**, was found in 82%. Encouraged by this result, we chose this reaction as a model to study the reaction conditions further for the synthesis of 2-oxo- and 2-thio-1,2,3,4-tetrahydropyrimidines (**4a-n**). The catalyst plays an important role in the success of the reaction in terms of the rate of the reaction and yield. In order to optimize the reaction conditions, the quantity of the catalyst required was varied. No product could be detected in the absence of the catalyst even after 4 h (Table 1, entry 1). Because the use of 5 mol% $CrCl_3 \cdot 6H_2O$ resulted in longer reaction time and lower yield than those from our initial result, the loading of catalyst was gradually increased from 5 mol% to 20 mol% (Table 1). It was found that 15 mol% of $CrCl_3 \cdot 6H_2O$ was optimal to carry out the reactions with an acceptable reaction time (Table 1, entry 4). The use of excess catalyst did not alter either the reaction time or yield of the product. We also investigated different temperatures for the model reaction (Table 1). The reaction rate increased on raising the temperature from room temperature (RT) to 90 °C, and the yield of product increased significantly (Table 1). We were gratified to find that the reaction proceeded smoothly and to mostly complete conversion of reactants at 80 °C to afford the desired product (**4a**) in 82% yield within 30 min (Table 1, entry 4). A further increase in the temperature did not affect the product yield (Table 1, entry 9).

Having optimized reaction conditions for the synthesis of 2-oxo- and 2-thio-1,2,3,4-tetrahydropyrimidines (**4a-n**) to 15 mol% $CrCl_3 \cdot 6H_2O$ as the catalyst under solvent-free conditions at 80 °C we subsequently applied these conditions to a variety of aldehydes, urea/thiourea, and ethyl/methyl acetoacetate. The results are summarized in Table 2.

Although different mechanistic pathways have been previously proposed [22], we believe that the reaction may proceed through an initial *N*-acylimine **B** formed from aldehyde **3** and urea **2** (Figure 2). The coordination of the lone-pair of the nitrogen atom in the *N*-acylimine **B** with the Lewis acid could lead to the in situ formation of an *N*-carbamoyliminium ion **C**, which is sufficiently electrophilic to react with the enol form of ethyl acetoacetate **A**, affording the open chain intermediate **D**. Further intramolecular cyclization, with elimination of H_2O, produces the 2-oxo- and 2-thio-1,2,3,4-tetrahydropyrimidines **4**.

Comparison of catalytic ability some of catalysts reported in the literature for synthesis of 2-oxo- and 2-thio-1,2,3,4-tetrahydropyrimidines is shown in Table 3.

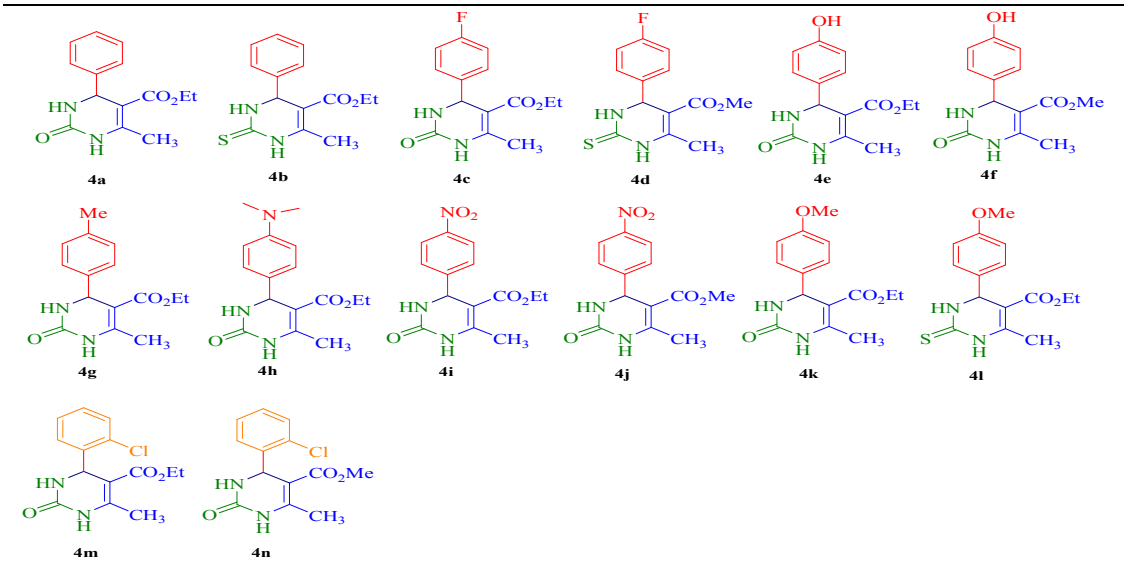
Table 1. Optimization of The Reaction Condition on The Synthesis of 4a



Entry	$CrCl_3.6H_2O$ (mol %)	Temperature(^{0}C)	Time(min)	Isolated Yields (%)
1	Catalyst-free	80	240	----
2	5	80	60	37
3	10	80	45	59
4	**15**	**80**	**30**	**82**
5	15	rt	240	----
6	15	40	60	36
7	15	60	45	54
8	15	70	40	69
9	15	90	30	82
10	20	80	30	83

Reaction conditions: benzaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea (1.5mmol) and $CrCl_3.6H_2O$ was heated under various temperatures for the appropriate time

Table 2. Synthesis of 2-oxo(thio)-1,2,3,4-Tetrahydropyrimidines



Entry	Ar	R	X	Product	Time (min)	Yield %[a]	M.p.˚C	Lit. M.p.˚C
1	C_6H_5	C_2H_5	O	**4a**	30	82	201-203	200-202[17]
2	C_6H_5	C_2H_5	S	**4b**	35	81	208-210	208-210[17]
3	4-F-C_6H_4	C_2H_5	O	**4c**	25	85	173-176	174-176[16]
4	4-F-C_6H_4	CH_3	S	**4d**	35	82	209-211	208-210[16]
5	4-OH-C_6H_4	C_2H_5	O	**4e**	40	76	227-230	230-232[16]
6	4-OH-C_6H_4	CH_3	O	**4f**	35	78	244-246	245-246[12]
7	4-Me-C_6H_4	C_2H_5	O	**4g**	30	83	203-205	204-205[12]
8	4-$(Me)_2N$-C_6H_4	C_2H_5	O	**4h**	35	81	253-255	255-257[15]
9	4-O_2N-C_6H_4	C_2H_5	O	**4i**	30	86	209-211	207-209[17]
10	4-O_2N-C_6H_4	CH_3	O	**4j**	25	83	213-215	214-216[17]
11	4-OMe-C_6H_4	C_2H_5	O	**4k**	30	83	201-203	202-203[15]
12	4-OMe-C_6H_4	C_2H_5	S	**4l**	35	80	150-153	150-152[17]
13	2-Cl-C_6H_4	C_2H_5	O	**4m**	35	81	221-223	220-223[18]
14	2-Cl-C_6H_4	CH_3	O	**4n**	30	82	249-251	248-252[18]

Isolated yield

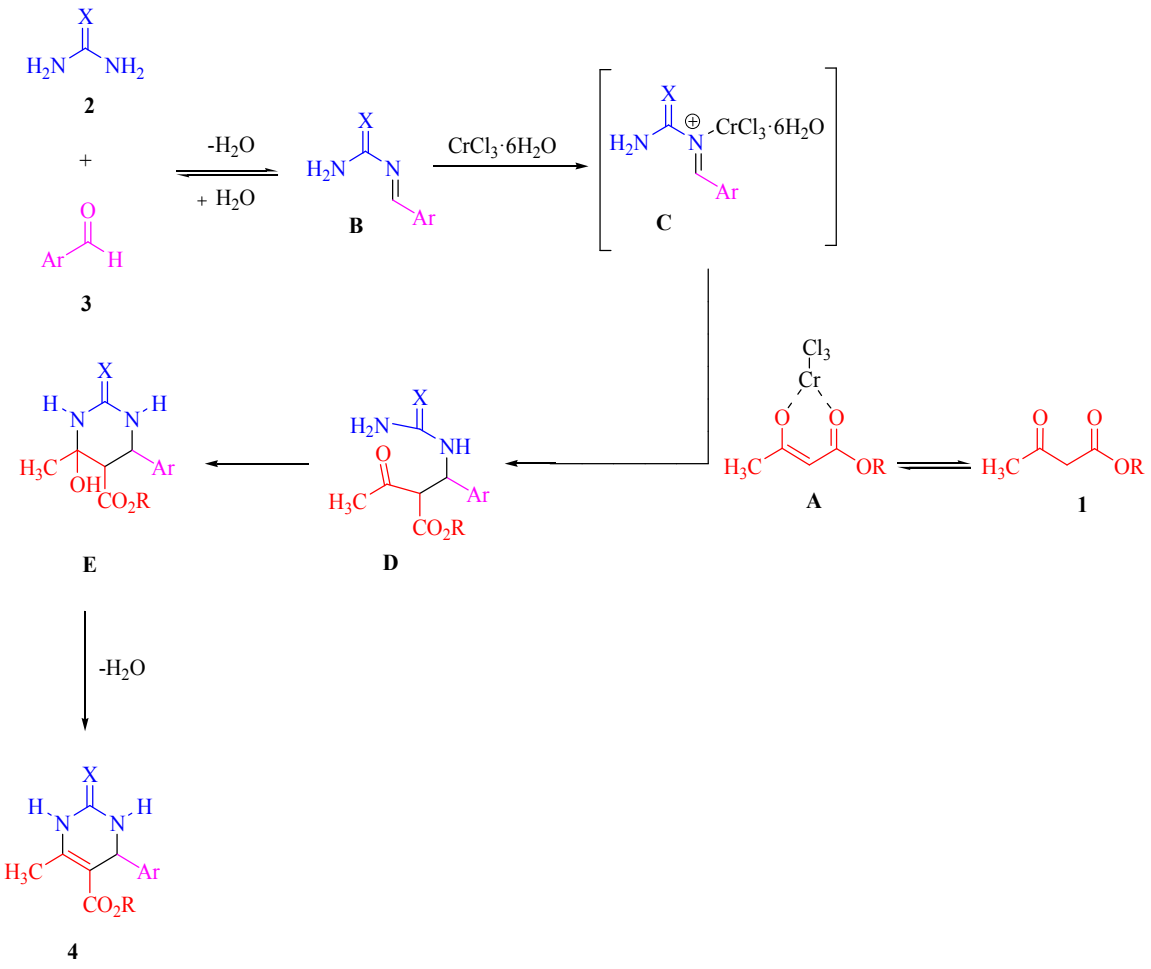


Figure 2. Proposed Mechanistic Route for the Synthesis of 2-oxo(thio)-1,2,3,4-Tetrahydropyrimidines

Table 3. Comparison of Catalytic Ability some of Catalysts Reported in the Literature for Synthesis of 2-oxo(thio)-1,2,3,4-tetrahydropyrimidines

Entry	Catalyst	Conditions	Time/Yield (%)	References
1	bakers' yeast	Room temperature	24h/84	[12]
2	$Cu(BF_4)_2.xH_2O$	Room temperature	30 min/90	[14]
3	Hydrotalcite	Solvent-free, 80 °C	35 min/84	[15]
4	$[Al(H_2O)_6](BF_4)_3$	MeCN, Reflux	20 h/81	[17]
5	[Btto][*p*-TSA]	Solvent-free, 90 °C	30 min/96	[19]
6	triethylammonium acetate	70 °C	45min/90	[20]
7	*p*-dodecylbenzenesulfonic acid	Solvent-free, 80 °C	3 h/94	[21]
8	$CrCl_3.6H_2O$	Solvent-free, 80 °C	30 min/82	This work

Based on reaction of benzaldehyde; ethyl acetoacetate and urea.

Conclusions

In summary, the use of $CrCl_3·6H_2O$ (chromium(III) chloride hexahydrate) as an efficient and readily available catalyst for the simple and clean synthesis of diverse of 2-oxo- and 2-thio-1,2,3,4-tetrahydropyrimidines under solvent-free conditions has been developed. The use of an environmentally friendly, non-toxic, and inexpensive catalyst, along with short reaction times and high to excellent yields, provides a compelling method to prepare these biologically active compounds.

Acknowledgments

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