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CHROMIUM (III) NITRATE NONAHYDRATE: AN ENVIRONMENTALLY BENIGN AND EFFICIENT HETEROGENEOUS CATALYST FOR FACILE ONE-POT BIGINELLI SYNTHESIS OF 3,4-DIHYDROPYRIMIDIN-2-(1*H*)-ONE/THIONE DERIVATIVES UNDER SOLVENT-FREE CONDITIONS

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Abstract: The use of chromium(III) nitrate nonahydrate ($Cr(NO_3)_3 \cdot 9H_2O$) as an efficient, mild and economical catalyst for the one-pot three-component Biginelli synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one/thione derivatives in the reaction between β-keto esters (methyl or ethyl acetoacetate), aromatic aldehydes (benzaldehye derivatives) and urea or thiourea under thermal and solvent-free conditions with good yields and short reaction times is reported. The most benefits of this synthetic method include the use of an efficient, eco-friendly, inexpensive and non-toxic catalyst, as well as the solvent-free conditions. All products were characterized by ^{1}H NMR spectroscopy and melting point determination.

***Keywords*:** Chromium(III) nitrate nonahydrate ($Cr(NO_3)_3 \cdot 9H_2O$); Environmentally benign heterogeneous catalyst; Biginelli reaction; 3,4-Dihydropyrimidinone/thiones; Solvent-free conditions; One-pot synthesis.

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Introduction

In recent years, multicomponent domino reactions (MCRs)[1-5] have become useful tools for the synthesis of heterocyclic compounds due to a wide range of benefits including atom-economy, mild and environmentally friendly, low-cost and one-pot operation.

Organic compounds containing nitrogen heterocycles are important compounds in medicinal chemistry. Recently, Biginelli reactions[6] have attracted much interest in the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one/thione derivatives because of their special pharmaceutical and biological activities. For example, these compounds have found use as calcium channel blockers, α-1a-antagonists,[7] and also as antihypertensive,[8] anticancer,[9] anti-HIV,[10] antibacterial, antifungal,[11] antiviral,[12] antioxidative[13] and anti-inflammatory[14] agents. The dihydropyrimidine unit can also be found in nature, and some dihydropyrimidine-containing alkaloids are shown in Figure 1.

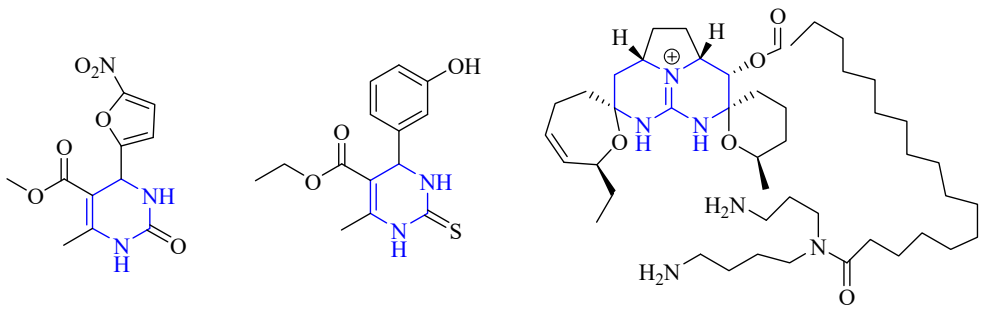


Figure1. Batzelladine alkaloids containing the dihydropyrimidine unit.

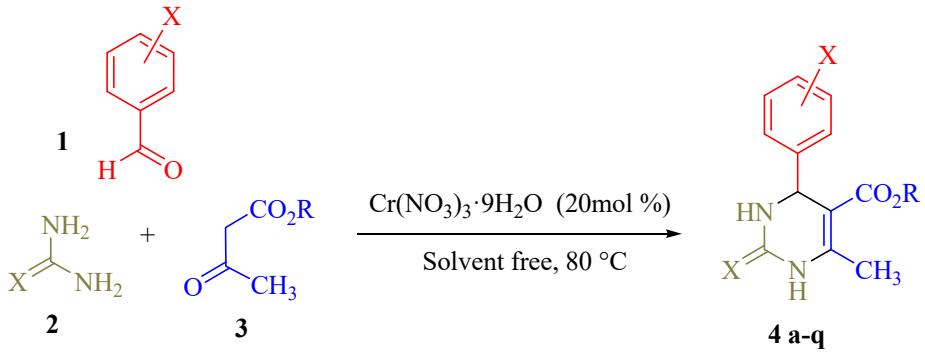
Several reported protocols for the preparation of dihydropyrimidine-containing compounds include the use of Brønsted or Lewis acid catalysts such as Calcium Fluoride,[15] copper(II) sulfamate,[16] bakers' yeast,[17] hydrotalcite,[18] hexaaquaaluminium(III) tetrafluoroborate,[19] TBAB[20] and copper (II) tetrafluoroborate,[21] [Btto][*p*-TSA],[22] triethylammonium

acetate,[23] or *p*-dodecylbenzenesulfonic acid.[24] Some of the limitations of these methodologies include low yields, the use of toxic organic solvents and catalysts, harsh reaction conditions and expensive materials.

Due to the special pharmaceutical and biological properties of 3,4-dihydropyrimidin-2-(1*H*)-one/thione derivatives and their potential applications, the development of mild, simple and environmentally safe syntheses of these compounds has become a major aim of our researches and finally, we have found $Cr(NO_3)_3 \cdot 9H_2O$ as an economical, efficient and environmentally benign heterogeneous catalyst. $Cr(NO_3)_3 \cdot 9H_2O$ as catalyst in organic compounds synthesis also has the advantage of being an inexpensive and non-toxic reagent. In this paper, an eco-friendly, simple and mild one-pot approach for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one/thione derivatives using chromium(III) nitrate nonahydrate as a mild and efficient catalyst by means of a three-component Biginelli reaction between β-keto esters, aldehyde derivatives and urea/thiourea under thermal and solvent-free conditions is reported with excellent yields.

Results and Discussion

We describe herein an environmentally benign, one-pot three component synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one/thione derivatives through the reaction of aldehydes derivatives (**1**, 1.0 mmol), urea/ thiourea (**2**, 1.5 mmol) and ethyl/methyl acetoacetate (**3**, 1.0 mmol) in the presence of $Cr(NO_3)_3 \cdot 9H_2O$ under solvent-free and thermal conditions (Scheme 1).



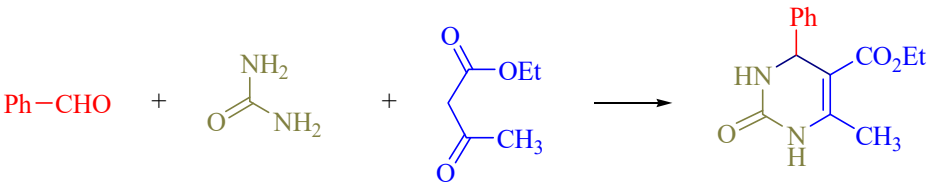
Scheme 1. Synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one/thione derivatives.

Our initial work started with screening of catalyst loading in order to identify optimal reaction conditions for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one/thione derivatives. The catalyst played a crucial role in the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one/thione derivatives. Various reaction media were screened (catalyst-free, 5, 10, 15, 20 and 25 mol%) using the model reaction (Table 1). It was found that the best results were obtained with 20 mol% of catalyst (Table 1, entry 5). The reaction was completed within 25 min and the product was obtained in 87% yield.

We have also examined the effect of temperature on the reaction outcome. Thus, various temperature values were tested, starting from rt to 90°C. The product yield steadily increased until a temperature value of 80°C. A higher amount of catalyst did not increase product yields (Table 1, entry 12). Therefore, our optimized conditions are the use of 20 mol% of catalyst at 80°C under solvent-free condition (Table 1, entry 5). Having the optimized reaction conditions for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one/thione derivatives (**4a-q**) using 20 mol% $Cr(NO_3)_3 \cdot 9H_2O$ as the catalyst under solvent-free conditions at 80°C, we subsequently applied

them for a variety of aldehydes, urea/ thiourea and ethyl/methyl acetoacetate (Table 2).

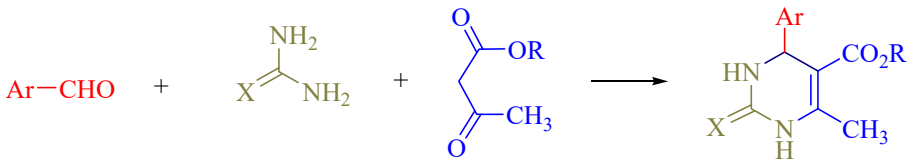
Table 1. Optimization of the reaction condition on the synthesis of **4a** [a].



Entry	$Cr(NO_3)_3 \cdot 9H_2O$ (mol %)	Temperature (°C)	Time (min)	Isolated Yields (%)
1	Catalyst free	80	420	No product
2	5	80	60	41
3	10	80	40	56
4	15	80	30	72
5	**20**	**80**	**25**	**87**
6	20	rt	420	No product
7	20	40	60	36
8	20	50	45	53
9	20	60	30	61
10	20	70	30	74
11	20	90	25	87
12	25	80	25	88

[a] Reaction conditions: benzaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea (1.5mmol) and $Cr(NO_3)_3 \cdot 9H_2O$ were heated at various temperatures for the indicated amount of time.

Table 2. $Cr(NO_3)_3 \cdot 9H_2O$ catalyzed synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one/thione derivatives.



Entry	Ar	R	X	Product	Time (min)	Yield %[a]	M.p. °C	Lit. M.p. °C[b]
1	C_6H_5	C_2H_5	O	**4a**	25	87	199-201	200-202[19]
2	C_6H_5	C_2H_5	S	**4b**	25	84	210-212	208-210[19]
3	4-MeO-C_6H_4	C_2H_5	O	**4c**	30	89	201-203	202-203[18]
4	4-MeO-C_6H_4	C_2H_5	S	**4d**	35	88	151-153	150-152[19]
5	3-MeO-C_6H_4	C_2H_5	O	**4e**	30	87	207-209	205-206[17]
6	4-F-C_6H_4	C_2H_5	O	**4f**	20	92	172-174	174-176[20]
7	4-F-C_6H_4	CH_3	S	**4g**	25	89	209-211	208-210[20]
8	4-$(Me)_2N$-C_6H_4	C_2H_5	O	**4h**	35	84	256-258	255-257[18]
9	2-Cl-C_6H_4	C_2H_5	O	**4i**	35	80	222-224	220-223[16]
10	2-Cl-C_6H_4	CH_3	O	**4j**	30	85	252-254	248-252[16]
11	3-Cl-C_6H_4	C_2H_5	O	**4k**	35	82	191-193	191-193[16]
12	4-Cl-C_6H_4	C_2H_5	O	**4l**	35	76	213-215	214-215[18]
13	4-Me-C_6H_4	C_2H_5	O	**4m**	25	89	205-207	204-205[17]
14	4-O_2N-C_6H_4	C_2H_5	O	**4n**	25	86	206-208	207-209[19]
15	4-O_2N-C_6H_4	CH_3	O	**4o**	25	91	212-214	214-216[19]
16	4-HO-C_6H_4	C_2H_5	O	**4p**	45	74	230-232	230-232[20]
17	4-HO-C_6H_4	CH_3	O	**4q**	40	78	246-248	245-246[16]

[a] Isolated yield.
[b] All known products previously reported in literature were characterized by comparison of m.p. and NMR spectra.

A comparison between the catalytic activities of some of previously reported catalysts for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one/thione derivatives is shown in Table 4. This study reveals that chromium(III) nitrate nonahydrate has the potential to be an alternative eco-

friendly, cost effective and environmentally benign catalyst for the Biginelli reaction. In addition, the use of solvent-free conditions with excellent yields and short reaction times are notable advantages of this present methodology.

Table 4. Comparison of catalytic ability some of catalysts reported in the literature for synthesis of **4a**[a].

Entry	Catalyst	Conditions	Time/Yield (%)	References
1	Bakers' yeast	Room temperature	24h/84	[17]
2	Hydrotalcite	Solvent-free, 80 °C	35 min/84	[18]
3	$[Al(H_2O)_6](BF_4)_3$	MeCN, Reflux	20 h/81	[19]
4	$Cu(BF_4)_2.xH_2O$	Room temperature	30 min/90	[21]
5	[Btto][*p*-TSA]	Solvent-free, 90 °C	30 min/96	[22]
6	triethylammonium acetate	Solvent-free,70 °C	45min/90	[23]
7	*p*-dodecylbenzenesulfonic acid	Solvent-free, 80 °C	3 h/94	[24]
8	$Cr(NO_3)_3{\cdot}9H_2O$	Solvent-free, 80 °C	25 min/87	This work

[a] Based on reaction of benzaldehyde, ethyl acetoacetate and urea.

Experimental

General

The melting points of all compounds were determined using an Electro thermal 9100. ^{1}H NMR spectra were recorded on a Bruker DRX-400 Avance instrument using DMSO-d_6 as solvent. All reagents and solvents were purchased from Merck or Fluka and used without further purification.

General procedure for preparation of 3,4-dihydropyrimidin-2-(1H)-one/thione derivatives (4a-q)

A mixture of aldehyde derivatives (**1**, 1.0 mmol), urea/thiourea (**2**, 1.5 mmol) and ethyl/methyl acetoacetate (**3**, 1.0 mmol) was heated under solvent-free conditions at 80°C for the appropriate amount of time in the

presence of $Cr(NO_3)_3 \cdot 9H_2O$ (20 mol%). After reaction completion (monitored by TLC), the mixture was cooled to rt and cold water was added. The precipitate was separated by filtration and crystallized from ethanol to afford the pure products (**4a- q**). Spectral data of the products are presented below:

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one ***(4a)***

M.p. 199-201 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.10 (3H , t, *J*= 7.2 Hz, $\underline{CH_3}CH_2$), 2.26 (3H, s, CH_3), 3.99 (2H, q, *J*=7.2 Hz, CH_2O), 5.15 (1H, s, $H_{benzylic}$), 7.26 (3H, d, *J*= 7.2 Hz, H_{Ar}), 7.33 (2H, t, *J*=7.2 Hz, H_{Ar}), 7.76 and 9.21 (2H, 2s, 2NH).

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-thione ***(4b)***

M.p. 210-212 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.11 (3H , t, *J*= 7.2 Hz, $\underline{CH_3}CH_2$), 2.31 (3H, s, CH_3), 4.02 (2H, q, *J*=7.2 Hz, CH_2O), 5.19 (1H, s, $H_{benzylic}$), 7.23 (2H, d, *J*=7.2 Hz, H_{Ar}), 7.28 (1H, t, *J*=7.2 Hz, H_{Ar}), 7.36(2H, t, *J*=7.2 Hz, H_{Ar}), 9.68 and 10.36 (2H, 2s, 2NH).

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

M.p.201-203°C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.11 (3H , t, *J*= 9.6 Hz, $\underline{CH_3}CH_2$), 2.24(3H, s, CH_3), 3.73 (3H, s, OCH_3), 3.99 (2H, q, *J*=9.6 Hz, CH_2O), 5.09 (1H, s, $H_{benzylic}$), 6.89 (2H, d, *J*= 8.4Hz, H_{Ar}), 7.15(2H, d, *J*= 8.8Hz, H_{Ar}), 7.70 and 9.18 (2H, 2s, 2NH).

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

M.p. 151-153; ^{1}H NMR (400 MHz, DMSO-d_6): 1.11 (3H , t, *J*= 9.6 Hz, $\underline{CH_3}CH_2$), 2.29 (3H, s, CH_3), 3.73 (3H, s, OCH_3), 4.00 (2H, q, *J*=9.6 Hz, CH_2O), 5.14 (1H, s, $H_{benzylic}$), 6.68-7.31 (4H, m, H_{Ar}), 7.77 and 9.25 (2H, 2s, 2NH).

5-Ethoxycarbonyl-6-methyl-4-(4-fluorophenyl)-3,4-dihydropyrimidin-2(1H)-one ***(4f)***

M.p.172-174°C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.11 (3H , t, *J*= 9.6 Hz, $\underline{CH_3}CH_2$), 2.25(3H, s, CH_3), 3.99 (2H, q, *J*=9.6 Hz, CH_2O), 5.14 (1H, s, $H_{benzylic}$), 7.13-7.20 (2H, m, H_{Ar}), 7.24-7.29 (2H, m, H_{Ar}), 7.78 and 9.25 (2H, 2s, 2NH).

5-Ethoxycarbonyl-6-methyl-4-(N, N-Dimethylphenyl)-3,4-dihydropyrimidin-2(1H)-one ***(4h)***

M.p. 256-258 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.12 (3H, t, *J*= 9.2 Hz, $\underline{CH_3}CH_2$), 2.26 (3H, s, CH_3), 2.85 (6H, s, $2CH_3$), 3.99 (2H, q, *J*=9.2 Hz, CH_2O), 5.04 (1H, s, $H_{benzylic}$), 6.66 (2H, d, *J*=11.6 Hz, H_{Ar}), 7.42 (2H, d, *J*=11.6Hz, H_{Ar}), 7.61 and 9.11 (2H, 2s, 2NH).

5- Ethoxycarbonyl-6-methyl-4-(2-chlorophenyl)-3,4-dihydropyrimidin-2(1H) –one ***(4i)***

M.p. 222-224 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.00 (3H , t, *J*= 9.2 Hz, $\underline{CH_3}CH_2$), 2.31 (3H, s, CH_3), 4.02 (2H, q, *J*=9.2 Hz, CH_2O), 5.63 (1H, s, $H_{benzylic}$), 7.25-7.34 (3H, m, H_{Ar}), 7.41 (1H, d, *J*=8.8 Hz, H_{Ar}), 7.73 and 9.29(2H, 2s, 2NH).

5-Methoxycarbonyl-6-methyl-4-(2-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one ***(4j)***

M.p. 252-254 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 2.31 (3H, s, CH_3), 3.46 (3H, s, OCH_3), 5.62 (1H, s, $H_{benzylic}$), 7.28-7.34 (3H, m, H_{Ar}), 7.42 (1H, d, *J*=7.2 Hz, H_{Ar}), 7.72 and 9.36 (2H, 2s, 2NH).

5- Ethoxycarbonyl-6-methyl-4-(3-chlorophenyl)-3,4-dihydropyrimidin-2(1H)–one ***(4k)***

M.p. 191-193 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.11 (3H , t, *J*= 9.2 Hz, $\underline{CH_3}CH_2$), 2.26 (3H, s, CH_3), 4.01 (2H, q, *J*=9.6 Hz, CH_2O), 5.15 (1H, s,

$H_{benzylic}$), 7.19-7.26 (2H, m, H_{Ar}), 7.31-7.41 (2H, m, H_{Ar}), 7.83 and 9.30 (2H, 2s, 2NH).

5-Ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1H)-one ***(4m)***

M.p. 205-207 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.11 (3H, t, *J*= 7.2 Hz, $\underline{CH_3}CH_2$), 2.26 (6H, d, *J*=9.2 Hz, $2CH_3$), 3.99 (2H, q, *J*=7.2 Hz, CH_2O), 5.11 (1H, s, $H_{benzylic}$), 7.13 (4H, s, H_{Ar}), 7.70 and 9.17 (2H, 2s, 2NH).

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

M.p. 206-208 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.10 (3H, t, *J*= 9.6 Hz, $\underline{CH_3}CH_2$), 2.28(3H, s, CH_3), 3.99 (2H, q, *J*=9.2 Hz, CH_2O), 5.27 (1H, s, $H_{benzylic}$), 7.50-7.53 (2H, m, H_{Ar}), 7.23 (2H, d, *J*= 9.2Hz, H_{Ar}), 7.92and 9.38 (2H, 2s, 2NH).

5-Methoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one ***(4o)***

M.p. 212-214 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 2.28(3H, s, CH_3), 3.55 (3H, s, OCH_3), 5.28 (1H, s, $H_{benzylic}$), 7.52 (2H, d, *J*= 8.4Hz, H_{Ar}), 7.22 (2H, d, *J*= 8.8Hz, H_{Ar}), 7.93 and 9.40 (2H, 2s, 2NH).

5- Ethoxycarbonyl-6-methyl-4-(4-hydroxyphenyl)-3,4-dihydropyrimidin-2(1H)-one ***(4p)***

M.p. 230-232 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.11 (3H , t, *J*= 9.6 Hz, $\underline{CH_3}CH_2$), 2.50 (3H, s, CH_3), 3.98 (2H, q, *J*=9.2 Hz, CH_2O), 5.04 (1H, s, $H_{benzylic}$), 6.68-7.04 (4H, m, H_{Ar}), 7.64 and 9.13 (2H, 2s, 2NH), 9.35 (1H, s, OH).

5- Methoxycarbonyl-6-methyl-4-(4-hydroxyphenyl)-3,4-dihydropyrimidin-2(1H)-one ***(4q)***

M.p. 246-248 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 2.31 (3H, s, CH_3), 3.46 (3H, s, OCH_3), 5.04 (1H, s, $H_{benzylic}$), 6.70 (2H, d, *J*=8.8 Hz, H_{Ar}), 7.02 (2H, d, *J*=9.6 Hz, H_{Ar}), 7.67 and 9.16 (2H, 2s, 2NH), 9.36 (1H, s, OH).

Conclusions

In summary, an efficient and eco-friendly protocol for the Biginelli synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones via one-pot three-component reaction of aldehydes, urea/thiourea and ethyl/methyl acetoacetate in the presence of chromium(III) nitrate nonahydrate ($Cr(NO_3)_3 \cdot 9H_2O$), an efficient heterogeneous catalyst, under thermal and solvent-free conditions was studied. The notable advantages of the present methodology are low-cost, the use of a non-toxic, eco-friendly catalyst, good yields, short reaction times and solvent-free conditions.

Acknowledgements

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