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A Facile And Efficient Method For One Pot Synthesis of 3, 4 -Dihydropyrimidin-2-(1h)-Ones/ Thiones Under Solvent Free Condition

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Abstract:

We reported Simple and efficient methodology for synthesis of 3,4 -Dihydropyrimidin-2-(1H)-ones/ thiones and their derivatives using aryl aldehyde, ethyl acetoacetate, urea in presence of ceric ammonium sulphate under solvent free condition. Compared to other classical Biginelli reaction condition the present method has advantage of giving good yield, short reaction time, easy work-up, mild reaction condition.

Keywords:

3,4 -Dihydropyrimidin-2-(1H)-ones/ thiones, Biginelli reaction, short reaction time, easy work-up, mild reaction condition.

1. INTRODUCTION:

Mostly heterocyclic compounds have been synthesized mainly because of exhibiting wide range of biological and pharmaceutical applications. These heterocyclic compounds plays important role in the field of medicinal chemistry and act as key template for the development of different therapeutic agents, [1]. Dihydropyrimidone and its derivativatives have received very much importance as they are core structure of many biological active molecules and additionally several alkaloid isolated from marine involved dihydropyrimidone substructure, [2]. The 3,4 -dihydropyrimidin-2-(1H)-ones and its sulphur containing analogue earned special position in the medicinal field because of its versatile biological activities,[3-9] such as anti-viral, anti-tumour, anti-bacterial, anti-microbial, anti-hypertensive, anti-inflammatory, analgesic agents. Additionally dihydropyrimidone exhibited important therapeutic and pharmacological properties as they are integral backbone of several calcium channel blocker, [10]. Therefore

synthesis of 3,4 -dihydropyrimidin-2-(1H)-ones and its sulphur containing analogue have great interest for organic as well medicinal chemist.

Dihydropyrimidone and its derivatives are product of Biginelli reaction which is one pot multicomponent cyclocondensation of benzaldehyde, urea and ethyl acetoacetate under vigorous acidic condition utilizing conc. HCl in presence of ethanol. The procedure for synthesis of Dihydropyrimidone and its derivatives was firstly reported by Italian chemist Pietro Bigenelli in 1893,[11]. However this reaction gives moderate yield of desired product, [12]. Consequently several amended reaction protocol have been reported in the journal either by modification in the procedure, utilization of solid phase or combinatorial approach, [13]. The basic general structure of 3, 4-dihydropyrimidin-2-(1h)-ones/ thiones is described in figure 1.

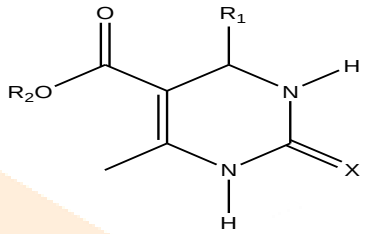


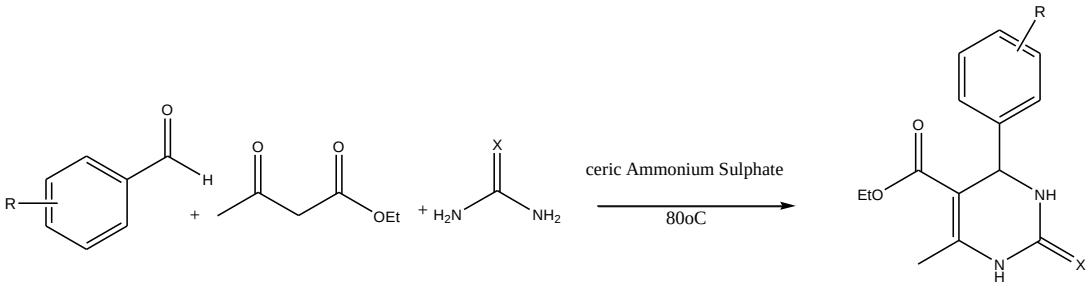
Figure1.

Now a days numerous method have been reported for the synthesis of dihydropyrimidone derivatives using aldehyde, urea and ethyl acetoacetate in presence of lewis acid like $AlCl_3$,[14], zinc chloride,[15], copper chloride,[16], ferric and nickel chloride,[17], polyphosphate ester,[18], iodine,[19], ammonium dihydrogen phosphate,[20], indium (III) bromide,[21], P_2O_5/SiO_2,[22] as a catalyst. However some of these one pot synthesis generally required strong protic acid, prolonged reaction time, excess of organic solvent, low yield, thus there is scope for development of facile and efficient method for synthesis of dihydropyrimidone derivatives.

2. EXPERIMENTAL-

The commercially available chemicals and reagents were utilized directly without further purification. The melting point were recorded on digital melting/boiling point apparatus of Labtronics make and found uncorrected and compared with reported literature. Thin layer chromatography was accomplished on precoated plates of TLC silica gel 60 F_{254}. 30% ethyl acetate in hexane solvent was used for TLC. Visualization was made with UV light (254 or 365nm).The ^1H NMR spectra were recorded on Bruker- 500 MHz spectrometer in $CDCl_3$ solvent using TMS as an internal standard and chemical shift is given as a delta.

In a 50 ml round bottom flask a mixture of benzaldehyde (1), ethyl acetoacetate (2) and urea (3) was taken in presence of a ceric ammonium sulphate. The reaction mixture was heated at 80^0C and completed in 30 min. (figure 2.)



1 2 3 4

Figure 2.

The reaction is monitored by TLC and after completion of reaction, the mixture was poured in crushed ice and the solid product was obtained is filtered and dried through the Buchner funnel. The crude product was recrystallized in ethanol solvent. To optimize the reaction condition we have studied role of catalyst ceric ammonium sulphate using different mole ratio. The observation shows that 10 % mole catalyst were found to be suitable for reaction conditions.

From the above observations and result obtained with benzaldehyde, ethyl acetoacetate and urea, we have elaborate the methodology to various aromatic aldehydes which having electron withdrawing and donating substituent at different position which is reacted with ethyl acetoacetate urea or thiourea to give corresponding derivatives with excellent yields. All the reaction were carried out in presence of catalyst ceric ammonium sulphate (10 mol%) at 80^0C. The aldehyde with electron withdrawing substituents react relatively slower rate than aldehyde with electron donating substituents. In general all reaction completed between 50 to 60 min.at 80^0C. The product with dihydropyrimidone derivatives were obtained in 70-90 % yields. (Table 1.). The compounds were confirmed by their ^{1}H NMR analysis.

Table 1. ceric ammonium sulphate catalysed synthesis of DHPMs derivatives

Entry	Comp.	R	X	Time min	M.P. ^{o}C found	M.P. ^{o}C reported[ref]	Yield %
	4a	H	O	50	201-203	203-205[22]	86
	4b	4-NO_2	O	55	211-213	212-214[22]	88
	4c	4-F	O	55	178-180	180-183[11]	90
	4d	4-OMe	O	50	198-200	199-201[22]	85
	4e	4-Br	O	50	208-209	209-211[20]	88
	4f	4-Me	O	60	217-219	218-220[22]	92
	4g	H	S	50	207-209	208-210[22]	88
	4h	4-NO_2	S	55	220-222	-	88
	4i	4-F	S	60	201-203	-	85
	4j	4-OMe	S	50	218-220	-	86
	4k	4-Br	S	55	193-195	-	82
	4l	4-Me	S	60	187-190	189-191[22]	88

Spectral Data of Compound

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

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08 (t, 3H, J = 7.15 Hz, CH_3), 3.97 (q, 2H, J = 7.15 Hz, OCH_2), 2.24 (s, 3H, CH_3), 7.21–7.34 (m, 5H, ArH), 5.13 (d,1H, J = 3.3 Hz, CH), 9.18 (s, 1H,NH), 7.73 (s, 1H, NH)

4b: 5-Ethoxycarbonyl-4-(4-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.19 (t, 3H, J=7.5 Hz, CH_3), 4.10 (q, 2H, J=7.5 Hz, OCH_2), 2.37 (s, 3H, CH_3), 7.51 (d, 2H, J=7.0 Hz, ArH), 8.19 d, 2H, J=7.0 Hz, ArH), 5.53 (d, 1H, J=3.0 Hz, CH), 7.32 (s, 1H, NH), 5.62 (s, 1H, NH)

4c: 5-Ethoxycarbonyl-4-(4-fluorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.17 (t, 3H, J=7.0 Hz, CH_3), 4.08 (q, 2H, J=7.0 Hz, OCH_2), 2.35 (s, 3H, CH_3), 7.20 (d, 2H, J=7.0 Hz, ArH), 6.83 (d, 2H, J=7.0 Hz, ArH), 5.33 (d, 1H, J=3.0 Hz, CH), 8.17 (s, 1H, NH), 7.53 (s, 1H, NH)

4d: 5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09 (t, 3H, J=6.8 Hz, CH_3), 3.96 (q, 2H, J=6.8Hz, OCH_2), 2.23 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 7.15-6.84 (m, 4H, ArH), 9.14 (s, 1H, NH), 7.66 (s, 1H, NH)

4e: 5-Ethoxycarbonyl-4-(4-bromophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.04 (t, 3H, J = 6.9 Hz, CH_3); 3.93 (q, 2H, J = 6.9 Hz, OCH_2), 2.20 (s, 3H,CH3), 7.48 (d, 2H, J =8.1 Hz, ArH), 7.14 (d, 2H, J = 8.1 Hz, ArH), 5.07 (d, 1H, J =2.8 Hz, CH), 9.20 (s, 1H, NH), 7.73 (s, 1H, NH)

4f: 5-Ethoxycarbonyl-4-(4-methylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.06 (t, 3H,J = 6.7 Hz, CH_3), 3.95 (q, 2H, J = 6.7 Hz, OCH_2), 2.22 (s,3H, CH_3), 2.30 (s, 3H, Ar-CH3), 7.23 (d, 2H, J= 8.6Hz, ArH), 7.12 (d, 2H, J= 8.6 Hz, ArH), 9.20 (s, 1H, NH),7.73 (s, 1H, NH)

4g: 5-Ethoxycarbonyl-4-(phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09 (t, 3H, J=7.0 Hz, CH_3), 4.00 (q, 2H, J=7.0 Hz, OCH_2), 2.28 (s, 3H, CH_3), 7.19-7.35 (m, 5H, ArH), 5.16 (d, 1H, J=3.5 Hz), 10.33 (s, 1H, NH), 9.64 (s, 1H, NH)

4h: 5-Ethoxycarbonyl-4-(4-nirtophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.12 (t, 3H, J=7.1 Hz, CH_3), 4.0 (q, 2H, J=7.1 Hz, OCH_2), 2.30 (s, 3H, CH_3), 7.45-8.25 (m, 4H, ArH), 5.26 (s, 1H, CH), 10.40 (s, 1H, NH), 9.62 (s, 1H, NH)

4j: 5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione.

^{1}H NMR (500 MHz, $CDCl_3$): δ1.17 (t, 3H, J=7.5 Hz, CH_3), 4.08 (q, 2H, J=7.5 Hz, OCH_2), 2.35 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 6.98-7.30 (m, 4H, ArH), 5.39 (d, 1H, J=2.5 Hz, CH), 7.47 (s, 1H, NH), 5.51 9s, 1H, NH)

4k: 5-Ethoxycarbonyl-4-(4-bromophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.18 (t, 3H, J=7.0 Hz, CH_3), 4.10 (q, 2H, J=7.0 Hz, OCH_2), 2.36 (s, 3H, CH_3), 7.16-7.45 (m, 4H, ArH), 5.36 (d, 1H, J=3.0 Hz, CH), 8.11 (s, 1H, NH), 7.64 (s, 1H, NH)

4l: 5-Ethoxycarbonyl-4-(4-methylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.10 (t, 3H, J=7.0 Hz, CH_3), 4.00 (q, 2H, j=7.0 Hz, OCH_2), 2.25 (s, 3H, CH_3), 2.27 (s, 3H, Ar-CH_3), 7.07-7.16 (m, 4H, ArH), 10.27 (s, 1H, NH), 9.58 (s, 1H, NH)

3. RESULTS AND DISCUSSION-

General Procedure for Preparation of DHPMs Derivatives

A mixture of aldehyde (4.71 mmol), ethyl acetoacetate (7.0 mmol) and urea (7.0 mmol) was stirred in presence of a ceric ammonium sulphate (10 mol%) as a catalyst at 80^{0}C under solvent free condition for a period of appropriate time (50 to 60 min) mentioned in table 1. The progress of reaction was monitored by thin layer chromatography (TLC). After completion of reaction which is indicated by TLC, the reaction mixture was cooled to room temperature and crushed ice added into the mixture. The reaction mixture stirred for 20 min. then white crystalline crude solid product is obtained which then filtered through vaccum pump using Buchner filtration. The crude product was recrystallized in ethanol solvent and then pure product was confirmed by ^{1}H NMR spectral analysis. The amount of catalysts can be optimized by varying its concentration and 10 mol% concentration of ceric ammonium sulphate gives a better yield in short reaction time.

Optimization of Reaction Condition:

Comparison with different catalyst for the synthesis of 4a.

To examine efficiency of the catalyst ceric ammonium sulphate, we compare it with different reported catalyst such as methane sulfonic acid, P_2O_5, chlorosulfonic acid, P_2O_5/SiO_2, $ZnCl_2$, I_2. from this it was observed that ceric ammonium sulphate catalyst work very well and required 50-60 min. time at 80^{0}C under solvent free condition for synthesis of 4a using benzaldehyde, ethyl acetoacetate and urea which is indicated in table 2. entry 7.

Table 2. comparison of reaction condition and time with reported method versus present method.

Entry	Catalyst	Solvent	Condition	Time min	Reference
1	Methanesulfonic acid	ethanol	reflux	60	14
2	P_2O_5	ethanol	reflux	240	15
3	Chlorosulfonic acid	solvent free	60^{0}c	30	16
4	P_2O_5/SiO_2	solvent free	85^{0}c	120	17
5	$ZnCl_2$	solvent free	80^{0}c	20	18
6	I_2	solvent free	90^{0}c	15	19
7[a]	**ceric ammonium sulphate 10 mol%**	**solvent free**	**80^{0}c**	**50**	**This work**

[a]reaction condition: benzaldehyde (4.71mmol), ethyl acetoacetate (7.0 mmol) and urea (7.0 mmol) was taken in presence of a 10mol% ceric ammonium sulphate.

***Optimization of amount of catalyst for reaction*:**

To optimized amount of catalyst, we carried out some reactions by changing the concentration of catalyst ceric ammonium sulphate for synthesis of 4a from benzaldehyde, ethyl acetoacetate and urea under solvent free condition. from this we conclude that 10 mol% of ceric ammonium sulphate was the most suitable amount of catalyst showing maximum yield (86%) in minimum possible time (50 min.) which is indicated in table 3. entry 5. with increase in percentage of catalyst 12 mol% we observed that there is no increase in yield of product which is indicated in entry-

6. from above observations we synthesized all other derivatives with 10 mol% amount of catalyst ceric ammonium sulphate.

Table 3. optimization of amount of catalyst[a]:

Entry	Catalyst in mol %	Time min	Yield %
1	2	80	50
2	4	70	60
3	6	60	70
4	8	50	80
5	**10**	**50**	**86**
6	12	50	86

[a]reaction condition: benzaldehyde (4.71 mmol), ethyl acetoacetate (7.0 mmol) and urea (7.0 mmol) was taken in presence of ceric ammonium sulphate.

4. CONCLUSION

In summery we have developed general practical way for synthesis of dihydropyrimidone derivatives using ceric ammonium sulphate with excellent yield using non-toxic, eco-friendly catalyst. The present method has advantage of mild reaction condition, easy work-up, short reaction time and excellent yield are advantages of this work without use of expensive and hazardous solvent.

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