



## One-Pot Multi-Component Synthesis of Dihydropyrimidinones via Biginelli Condensation

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### Abstract

Three-component reactions have emerged as useful methods because the combination of three components to generate new products in a single step is extremely economical, among the multi-component reactions. A green, simple, efficient, and cost-effective procedure has been carried out by the synthesis of dihydropyrimidinones in Biginelli's condensation of ethyl cyanoacetate, aldehyde and urea or thiourea.  $\text{H}_3\text{BO}_3$ ,  $\text{H}_2\text{C}_2\text{O}_4$ ,  $\text{Me}_3\text{SiCl}$  (TMSCl) using as catalyst and compared product yield. Products were characterized with IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and mass spectroscopy.

**Keywords:** Biginelli reaction, Dihydropyrimidinones, One-Pot Synthesis, Ethyl cyanoacetate.

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### Introduction

A number of N-Containing heterocyclic compounds possess a wide spectrum of applications in various fields like medicine, industry, pharmacology and analytical chemistry [1-3]. Some of these derivatives also act as antibacterial, anticancer, antimicrobial, antiviral, antihelminthic, insecticidal, and Herbicidal compounds [4-5]. These are

widely used as anticonvulsant, antifungal, antitubercular, antimalarial, antihypertensive and anti-inflammatory agents [6]. Some of the examples are Omeprazole, Esomeprazole, Lansomeprazole, Olanzapine, and Temocapril. Polyfunctionalized dihydropyrimidines (DHPMs) synthesis is challenging and an important task for organic chemists. Pyrimidines or pyrimidinones can be prepared within the laboratory using

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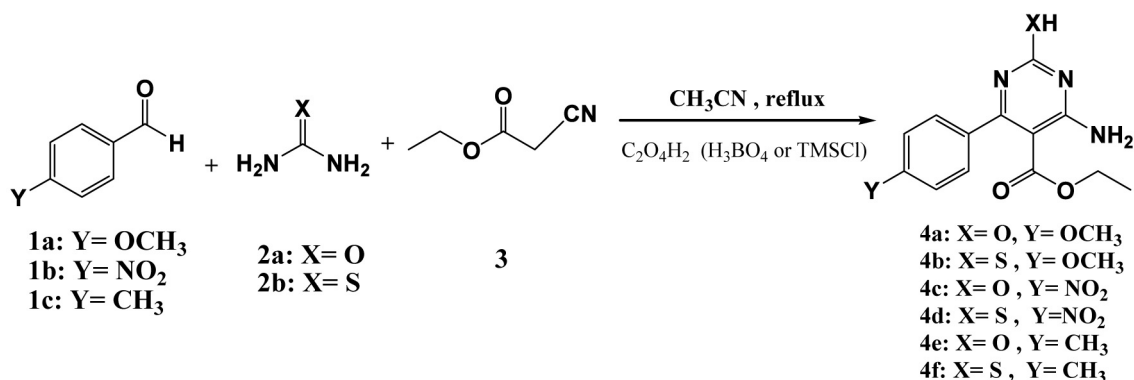
different methods. Among the different methods Biginelli method is most popular one [7]. The other methods are rely on condensation of carbonyls with amines for example the synthesis of 2-Thio-6-methyluracil using ethylacetoacetate and thiourea.[8].

The Biginelli reaction [9-12] is an acid-catalyzed, three-component reaction between a  $\beta$ -ketoester, an aldehyde and urea constitutes a rapid and facile synthesis of dihydropyrimidinones, which are interesting compounds with a potential for pharmaceutical application. Several workers are published for synthesis of Biginelli compounds using solid-phase protocols[13,14].

Several workers have been reported the synthesis of DHPMs including classical conditions with microwave irradiation and by using Lewis acids as well as protic acids as promoters such as Conc.HCl,  $\text{BF}_3 \cdot \text{OEt}_2$ , PPE, KSF clay,  $\text{InCl}_3$ ,  $\text{LaCl}_3$ , lanthanide triflate,  $\text{H}_2\text{SO}_4$ , ceric ammonium nitrate (CAN),  $\text{Mn}(\text{OAc})_3$ , ion-exchangeresin, 1-n-butyl-3-methylimidazoliumtetrafluoroborate ( $\text{BMImBF}_4$ ),  $\text{BiCl}_3$ ,  $\text{LiClO}_4$ ,  $\text{InBr}_3$ ,  $\text{FeCl}_3$ ,  $\text{ZrCl}_4$ ,  $\text{Cu}(\text{OTf})_2$ ,  $\text{Bi}(\text{OTf})_3$ ,  $\text{LiBr}$ , ytterbium triflates,  $\text{NH}_4\text{Cl}$ ,  $\text{MgBr}_2$ ,  $\text{SiO}_2/\text{NaHSO}_4$ , DDQ, and other reagents have been found to be effective. However, this so-called Biginelli reaction often suffers from low yields practically in case of substituted

aromatic and aliphatic aldehydes. Even though high yields could be achieved by following complex multi-step procedures, these methods lack the simplicity of original one-pot Biginelli protocol. Therefore, Biginelli reaction continues to attract the attention of researchers for the discovery of milder and more efficient procedures for the synthesis of dihydropyrimidinones. Biginelli compounds exhibits a diverse range of biological activities. Aryl-substituted 3,4-dihydropyrimidin-2(1H)-one and their derivatives are important class of substances in organic and medicinal chemistry.

In this report, we describe Biginelli's condensation with benzaldehyde derivatives (1a-c), urea(thiourea) (2a,2b) and ethyl cyanoacetate(3) and using one of these three catalysts  $\text{H}_3\text{BO}_3$ ,  $\text{H}_2\text{C}_2\text{O}_4$ ,  $\text{Me}_3\text{SiCl}$  with High-efficiency and simple method. Here, in Biginelli reaction we've carried out,  $\beta$ -ketoester compounds have been used instead of  $\beta$ -cyanoester compound. According to the previous data gained in this area, so far no Biginelli reaction has been performed with  $\beta$ -cyano carbonyl. Regarding the obtained products, in these reactions the cyano group converts into amino group during the reaction and in the cyclization that is itself significant (Figure1).



**Figure 1.** A view of the reactions conducted in this article.

## Experimental

### General

Reactions were monitored by TLC using silica gel coated plates and ethyl acetate/hexane solutions as the mobile phase. Melting points were measured using Electrothermal 870 THERMOICOTNEXUS apparatus. FT-IR spectra were recorded using KBr disks on a Bomem-MB 100 infrared spectrometer and absorptions are reported as wave numbers (cm<sup>-1</sup>). NMR spectra were obtained on a FT-NMR Bruker Spectro Spin DRX-300 or 500 MHz instrument as DMSO-d<sub>6</sub>. Mass spectra were obtained on a MS Model 5973 Network apparatus at ionization potential of 70 eV. Elemental analyses were performed using a Thermo Finnigan Flash EA 1112 instrument. All other reagents were purchased from commercial sources and were freshly used after being purified by standard procedures.

### Typical procedure for synthesis

A solution of benzaldehyde derivatives (p-nitro, p-methyl and p-methoxy (2 mmol),

(thio)urea (3 mmol), ethylcyanoacetate (2 mmol), and TMSCl (H<sub>3</sub>BO<sub>3</sub> or H<sub>2</sub>C<sub>2</sub>O<sub>4</sub>) (0.2 mmol) were dissolved in acetonitrile (10 ml) and boiled under reflux condition for the time specified in Table 1 until TLC showed complete disappearance of benzaldehyde derivatives. Reaction mixture was poured into cold water (20 mL) and stirred for 15 min. The precipitates were filtered and washed with cold water (2 × 10 mL) and then with 90% ethanol (15 mL) to give pure products. Products were characterized by analyzing their <sup>1</sup>H NMR, <sup>13</sup>C NMR, IR, and mass spectra and their purity was confirmed by elemental analysis.

### *Ethyl-4-amino-2-hydroxy-6-(4-methoxyphenyl) pyrimidine-5-carboxylate (4a)*

Light yellow, Yield 80%, m.p. 164-168 °C. IR (KBr) ν cm<sup>-1</sup>: 3500(NH<sub>2</sub>), 3400(NH<sub>2</sub>), 3300(OH), 1700(C=O), 1690(C=N), 1640, 1300, 1090(C-O), 1011; <sup>1</sup>H NMR (500 MHz), DMSO-d<sub>6</sub>: δ 8.78 (br.s, OH), 8.27(d, J=8 Hz, 2H Ar), 7.11(d, J=8 Hz, 2H Ar), 4.26(q,

$J=7.1\text{Hz}$ , 2H), 3.93(s, 3H, OMe), 2.04(br.s, 2H,  $\text{NH}_2$ ), 1.26(t,  $J=7.1\text{ Hz}$ , 3H);  $^{13}\text{C}$  NMR (500 MHz) DMSO- $d_6$ :  $\delta$  166, 161,157, 153, 128, 125, 114, 89, 61, 56, 14. MS(m/e): 284( $\text{M}^+$ ; 10%), 190 (40%), 160(10%), 76(80%), 59(50%), 43(90%); Anal. Calcd for  $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_4$ : C, 58.13; H, 5.23; N, 14.53 %; Found: C, 58.16; H, 58.18;N, 14.39% .

*Ethyl4-amino-2-mercapto-6-(4-methoxyphenyl)pyrimidine-5-carboxylate (4b)*

Light yellow, Yield 70%, m.p. 174-178 °C. IR (KBr)  $\nu$   $\text{cm}^{-1}$ ; 3500( $\text{NH}_2$ ), 3400( $\text{NH}_2$ ), 2550(SH), 1700(C=O), 1688(C=N), 1648, 1300, 1099(C-O);  $^1\text{H}$  NMR (500 MHz), DMSO- $d_6$ :  $\delta$  8.5 (br.s, SH), 8.27(d,  $J=8\text{ Hz}$ , 2H Ar), 7.11(d,  $J=8\text{ Hz}$ , 2H Ar), 4.31(q,  $J=7.1\text{Hz}$ , 2H), 3.85(s, 3H, OMe), 2.15(br.s, 2H,  $\text{NH}_2$ ), 1.26(t,  $J=7.1\text{ Hz}$ , 3H);  $^{13}\text{C}$  NMR (500 MHz) DMSO- $d_6$ :  $\delta$ 177,163, 162,154, 153, 124, 116, 115, 90, 62, 56, 14. Anal. Calcd for  $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_3\text{S}$ : C, 55.07; H, 4.95; N, 13.76 %. Found: C, 55.35; H, 5.1;N,13.70%.

*Ethyl4-amino-2-hydroxy-6-(4-nitrophenyl)pyrimidine-5-carboxylate (4c)*

Yellow, Yield 85%, m.p. 190-193 °C. IR (KBr)  $\nu$   $\text{cm}^{-1}$ ; 3500( $\text{NH}_2$ ), 3400( $\text{NH}_2$ ), 3300(OH), 1700(C=O), 1688(C=N), 1511,1561(N-O) 1648, 1343(N-O), 1089 (C-O), 1011;  $^1\text{H}$  NMR (500 MHz), DMSO- $d_6$ :  $\delta$  8.56 (s, OH), 8.43(d,  $J=8\text{ Hz}$ , 2H Ar), 8.27(d,  $J=8\text{ Hz}$ , 2H Ar), 4.30(q,  $J=7.1\text{Hz}$ , 2H),2.52(br.s, 2H,  $\text{NH}_2$ ),

1.36(t,  $J=7.1\text{ Hz}$ , 3H);  $^{13}\text{C}$  NMR (500 MHz) DMSO- $d_6$ :  $\delta$  161, 153, 146,137, 132, 124, 115, 105, 63, 14. Anal. Calcd for  $\text{C}_{13}\text{H}_{12}\text{N}_4\text{O}_5$  : C, 51.32; H, 3.98; N, 18.41%. Found: C,51.65,H, 3.79, N, 18.56%.

*Ethyl4-amino-2-hydroxy-6-(4-nitrophenyl)pyrimidine-5-carboxylate (4d)*

Light yellow, Yield 85%, m.p. 205-208 °C. IR (KBr)  $\nu$   $\text{cm}^{-1}$ ; 3500( $\text{NH}_2$ ), 3400( $\text{NH}_2$ ), 2550(SH), 1700(C=O), 1617(C=N), 1591,1510 (N-O) 1469, 1444(N-O), 1060 (C-O);  $^1\text{H}$  NMR (500 MHz), DMSO- $d_6$ :  $\delta$  8.51(d,  $J=8\text{ Hz}$ , 2H Ar), 8.19(d,  $J=8\text{ Hz}$ , 2H Ar), 8.07 (s, SH) 4.34(q,  $J=7.1\text{Hz}$ , 2H),2.09 (br.s, 2H,  $\text{NH}_2$ ), 1.32(t,  $J=7.1\text{ Hz}$ , 3H);  $^{13}\text{C}$  NMR (500 MHz) DMSO- $d_6$ :  $\delta$  161, 153, 150,138, 132, 125, 115, 105, 63, 14. Anal. Calcd for  $\text{C}_{13}\text{H}_{12}\text{N}_4\text{O}_4\text{S}$ : C, 48.74; H, 3.78; N, 17.49%. found: C, 49.01;H, 37.79, N.3.85.

*Ethyl 4-amino-2-hydroxy-6-p-tolylpyrimidine-5-carboxylate (4e)*

Light yellow, Yield 72%, m. p. 200-205 °C. IR (KBr)  $\nu$   $\text{cm}^{-1}$ ; 3500( $\text{NH}_2$ ), 3400( $\text{NH}_2$ ), 3300(OH), 3000( $\text{CH}_3$ ), 1700(C=O), 1690(C=N), 1640, 1300, 1090(C-O), 1011;  $^1\text{H}$  NMR (500 MHz), DMSO- $d_6$ :  $\delta$  8.50 (br.s, OH), 8.35(d,  $J=8\text{ Hz}$ , 2H Ar), 8.18(d,  $J=8\text{ Hz}$ , 2H Ar), 4.27 (q,  $J=7.1\text{Hz}$ , 2H), 2.34(s, 3H, Me), 3.25(.s, 2H,  $\text{NH}_2$ ), 1.27(t,  $J=7.1\text{ Hz}$ , 3H);  $^{13}\text{C}$  NMR (500 MHz) DMSO- $d_6$ :  $\delta$  166, 161,156, 153, 139,130,127, 114, 90,56,24,

14. Anal. Calcd for  $C_{14}H_{15}N_3O_3$ : C, 61.53; H, 5.53; N, 15.38; %; Found: C, 61.30; H, 5.45, N, 15.20%. Calcd for  $C_{14}H_{15}N_3O_2SC$ , 58.11; H, 5.23; N, 14.52%; Found: C, 57.90; H, 5.44, N, 15.77%.

*Ethyl 4-amino-2-mercapto-6-p-tolylpyrimidine-5-carboxylate (4f)*

Light yellow. Yield 72% ; m. p. 220-224 °C. IR (KBr)  $\nu$   $cm^{-1}$ : 3500(NH<sub>2</sub>), 3400(NH<sub>2</sub>), 3300(OH), 3000(CH<sub>3</sub>), 1700(C=O), 1690(C=N), 1640, 1300, 1095(C-O), 1015; <sup>1</sup>H NMR (500 MHz), DMSO-d<sub>6</sub>:  $\delta$  8.44 (br.s, SH), 8.34(d, *J*=8 Hz, 2H Ar), 8.18(d, *J*=8 Hz, 2H Ar), 4.27 (q, *J*=7.1Hz, 2H), 2.35(s, 3H, Me), 3.05(.s, 2H, NH<sub>2</sub>), 1.27(t, *J*=7.1 Hz, 3H); <sup>13</sup>C NMR (500 MHz) DMSO-d<sub>6</sub>:  $\delta$  178, 163, 155, 138, 130, 139, 127, 114, 105, 56, 24, 14. Anal.

### Result and discussion

The efficiency of the reaction is affected mainly by the amount of catalysts (Table 1). No product was obtained in the absence of the catalyst even after 5h (entry 1) indicating that the catalyst is necessary for the reaction. The yield of product increased by excess use of catalyst. The optimal amount of catalyst was 0.06 g (entry 5) for H<sub>3</sub>BO<sub>3</sub>, 0.09 g for H<sub>2</sub>C<sub>2</sub>O<sub>4</sub> 0.09 g (entry 10) and for TMSCl 0.02 g (entry 13); increasing the amount of the catalysts beyond this value did not increase the yield noticeably (entries 6, 11, 14, 15, 16) (Table 1).

**Table 1.** Effect of the amounts of catalyst on the yield reaction for 5 h reaction time<sup>a</sup>.

Entry	Catalyst	Catalyst(g)	Yield <sup>b</sup> (%)	entry	catalyst	Catalyst(g)	Yield <sup>b</sup> (%)
1	none	---	0	9	H <sub>2</sub> C <sub>2</sub> O <sub>4</sub>	0.08	60
2	H <sub>3</sub> BO <sub>3</sub>	0.03	60	10	H <sub>2</sub> C <sub>2</sub> O <sub>4</sub>	0.09	66
3	H <sub>3</sub> BO <sub>3</sub>	0.04	65	11	H <sub>2</sub> C <sub>2</sub> O <sub>4</sub>	0.1	66
4	H <sub>3</sub> BO <sub>3</sub>	0.05	72	12	TMSCl	0.01	65
5	H <sub>3</sub> BO <sub>3</sub>	0.06	78	13	TMSCl	0.02	80
6	H <sub>3</sub> BO <sub>3</sub>	0.07	78	14	TMSCl	0.03	80
7	H <sub>2</sub> C <sub>2</sub> O <sub>4</sub>	0.03	50	15	TMSCl	0.04	80
8	H <sub>2</sub> C <sub>2</sub> O <sub>4</sub>	0.06	55	16	TMSCl	0.05	80

<sup>a</sup>Reaction conditions: p-methoxybenzaldehyde (2mmol), Ethylcyano acetate (2mmol), and Urea/thiourea (3mmol), in 10 ml CH<sub>3</sub>CN. <sup>b</sup>Isolated yields.

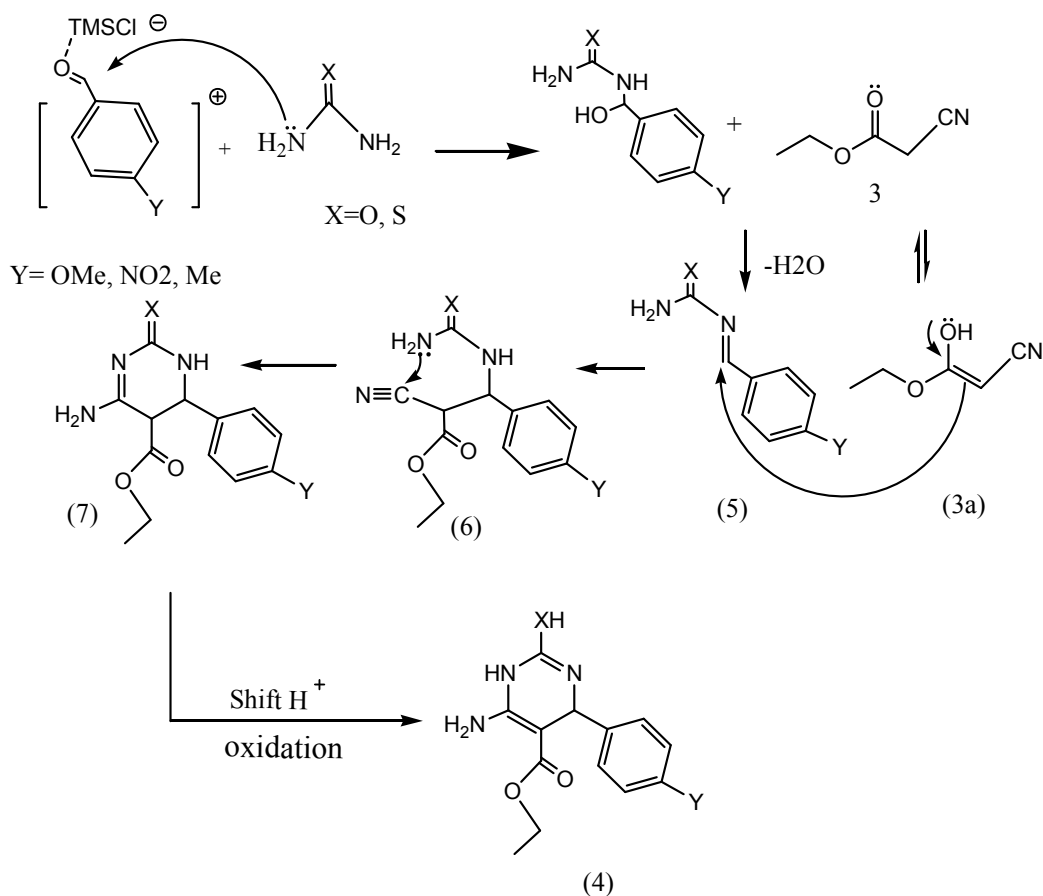
Reaction efficiency are also affected by the type of catalyst. It is clear that, reaction time and efficiency can be affected by catalyst type.

The use of TMSCl remarkably improved the yield of reaction and time of reaction completion (Table 2).

**Table 2.** Catalyst effect on reaction time and yield.

Entry	R	X	Catalyst	Time(min)	Product	Yield(%)
1	CH3	O	H3BO3	180	4e	69
2	CH3	O	H2C2O4	160	4e	62
3	CH3	O	TMSCl	150	4e	72
4	OCH3	O	H3BO3	120	4a	77
5	OCH3	O	H2C2O4	75	4a	66
6	OCH3	O	TMSCl	120	4a	80
7	OCH3	S	H3BO3	180	4b	62
8	OCH3	S	H2C2O4	150	4b	55
9	OCH3	S	TMSCl	170	4b	70
10	NO2	O	H3BO3	210	4c	77
11	NO2	O	H2C2O4	180	4c	55
12	NO2	O	TMSCl	180	4c	80
13	NO2	S	H3BO3	180	4d	79
14	NO2	S	H2C2O4	150	4d	68
15	NO2	S	TMSCl	120	4d	85

A mechanistic pathway can be suggested when Y= OMe, NO<sub>2</sub>, Me and X= O,S for the formation of the products. The fact that ethyl cyanoacetate (3), in tautomerization form (3a), is able to condense with intermediate 5 to form compound 6. Under catalytic conditions, it can consequently condense and gets oxidized to form the product (4) (Figure 2).

**Figure 2.** Proposed mechanism for the formation of compound 4.

## Conclusion

We have presented the first synthesis of novel derivatives of ethyl 4-amino-2-hydroxy(or mercapto)-6pyrimidine-5-carboxylate derivatives using mild reaction conditions with ethylcyano acetate compound using  $H_3BO_3$ ,  $H_2C_2O_4$ ,  $Me_3SiCl$  as a catalyst. High yield products are directly obtained from the reaction mixtures using a simple filtration and easily purified by washing with ethanol. The procedure is applicable to a variety of starting substrates, reactions complete in short time periods.

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