



One - pot synthesis of dihydropyrimidinones catalyzed by Ni (acac)₂: a new catalyst for the Biginelli reaction

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ABSTRACT

We report herein the use of Nickel acetyl acetonate [Ni(acac)₂] as a new catalyst for the one-pot Biginelli reaction coupling of β-ketoester, aldehydes and urea (or thiourea) to afford the corresponding dihydropyrimidinones/thiones.

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Keywords

Dihydropyrimidinones,
Biginelli cyclocondensation,
Nickel acetyl acetate.

Introduction

A general and practical chemistry route to the Biginelli cyclocondensation reaction using Nickel acetyl acetate as the catalyst (10% mol). This method provides an efficient and much improved modification of original Biginelli reaction reported in 1893, in terms of high yields, short reaction times, and simple work-up procedure, and it has the ability to tolerate a wide variety of substitutions in all three components, which is lacking in existing procedures.

The preparation of combinational libraries of heterocyclic compounds by solid phase synthesis is of great interest for accelerating lead discovery in pharmaceutical¹ such as antibacterial, antiviral, antitumor and anti-inflammatory activities. Some of them have been successfully used as calcium channel blockers, antihypertensive agents, α-1a-antagonists and neuropeptide Y (NPY) antagonists² Moreover several alkaloids containing the dihydropyrimidinones core unit have been isolated from marine source, which also shows interesting biological properties.³ Among these most notably are the batzelladine alkaloids, which have been found to be potent HIV gp-120-CD4 inhibitors⁴. Reaction of three components in THF containing polyphosphate ester (PPE)⁵ and acetonitrile with iodotrimethylsilane (TMSI)⁶ also furnished good yield. For example, modification and improvements include using Lewis acids such as BF₃-OEt₂⁷, FeCl₃ and HCl⁸, LaCl₃·7H₂O,⁹ La(OTf)₃¹⁰

Yb(OTf)₃¹¹, ZrCl₄¹², BiCl₃¹³, Mn(OAc)₃¹⁴, LiClO₄¹⁵, H₃BO₃¹⁶ and polyphosphate ester¹⁷ Many other synthetic methods for preparing these compounds have been reported including classical conditions with microwave¹⁸ and ultrasound irradiation^{19,20}.

Nickel acetyl acetate is also known as bis (acetylacetone) nickel (II). It has been used as a catalyst for oligomerization, reduction, cross-coupling, oxidation, conjugate addition, addition to multiple bonds and rearrangement reactions. It is commercially available. Alternatively, it can be prepared from potassium acetylacetate and nickel (II)

chloride²¹. As part of our continued interest in the Biginelli reaction²², we report here our preliminary investigation dealing with the use of Nickel acetyl acetate as a catalyst under neutral conditions preserving the simplicity of Biginelli's one-pot reaction (Scheme 1). Herein we disclose the first example of an efficient synthetic protocol for the preparation of 3, 4-dihydropyrimidinones using Nickel acetyl acetate as an organopromoter. Nickel acetyl acetate is used because it is nontoxic, relative noncorrosiveness, safe to handle, and easily biodegraded. The toolbar and its menus

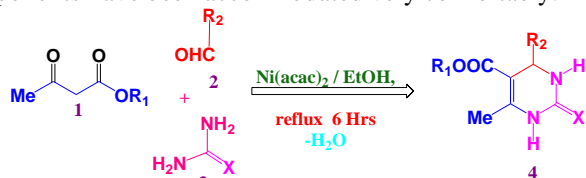
The art of performing efficient chemical transformation coupling three or more components in a single operation by a catalytic process avoiding stoichiometric toxic reagents, large amounts of solvents, and expensive purification techniques represents a fundamental target of the modern organic synthesis²³.

Biginelli reaction first reported in 1893, involving acid catalyzed one-pot cyclocondensation of aldehydes, dicarbonyl compound and urea or thiourea is a simple and direct approach for their synthesis. However limitations associated with this method are poor yields particularly in case of substituted aldehydes and use of strong acidic conditions. Thus, Biginelli's reaction for the synthesis of dihydropyrimidinones has received renewed interest, and several improved procedures have recently been reported, consequently, there is scope for further renovation towards mild reaction conditions, increased variation of the substituent's in all three components, and better yields.

To study the generality of this process, several examples illustrating this novel and general method for the synthesis of dihydropyrimidinones were studied and are summarized in Table 1.

Many of the pharmacologically relevant substitution patterns on the aromatic ring could be introduced with high efficiency. A variety of substituted aromatic, aliphatic, and heterocyclic aldehydes carrying either electron-donating or -withdrawing substituent's afforded high yields of products in high purity. Acid sensitive aldehydes such as furfural worked

well without the formation of any side products. Thiourea has been used with similar success to provide the corresponding dihydropyrimidine-(2*H*)-thiones, which are also of much interest with regard to biological activity. Thus, variations in all three components have been accommodated very comfortably.



Scheme 1

The three component condensation reactions proceeded smoothly in refluxing ethanol and were completed within 8-12 h depends on the substituted aldehydes. Many pharmacologically important moieties may be substituted on the aromatic ring with high efficiency under the Nickel acetyl acetonate catalyzed conditions. Aromatic aldehydes carrying either electron-donating or withdrawing substituent's afforded high yields of products in high purity, this method is effective for the preparation of DHPMs. Another important feature of this procedure is the survival of a variety of functional groups such as ether, nitro, hydroxy, halides, etc., under the reaction conditions. The advantage of the $Ni(acac)_2$ for this reaction lies in its simplicity. This method utilizes readily available or preparation of reagents at low cost and also affords high yields of DHPMs in short reaction times.

This procedure offers easy access to substituted dihydropyrimidinones with a variety of substitution patterns. Among the various solvents such as acetonitrile, methanol, THF and ethanol used for the transformation, ethanol and methanol were found to be the best. The results summarized in Table 1 reveal the scope and generality of the reaction with respect to various aldehydes, β -ketoester and urea or thiourea. It is presumed that the reaction may proceed through the imine intermediate formed from the aldehyde and urea, stabilized by the Nickel ion followed by the addition of the β -ketoester enolate and cyclodehydration to afford the dihydropyrimidine.

In conclusion, we have developed a simple and general method for the synthesis of dihydropyrimidinones using the inexpensive and easily available Nickel acetyl acetonate as catalyst and neutral free conditions. The method offers several advantages including high yields, short reaction times and a simple experimental workup procedure, which makes it a useful process for the synthesis of dihydropyrimidinones.

6-Methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-Pyrimidine-5-carboxylic acid ethyl ester (4a): Solid, mp 208–209°C; 1H NMR (DMSO- d_6): δ 1.12 (t, 3H, $J=7.5$ Hz, CH_3), 2.28 (s, 3H, CH_3), 4.03 (q, 2H, $J=7.5$ Hz, OCH_2), 5.17 (d, 1H, $J=3.0$ Hz, H-4), 7.22–7.41 (m, 5H, H atom), 7.78 (brs, 1H, NH), 9.22 (brs, 1H, NH). IR (KBr): 3242, 3116, 1725, 1700, 1647 cm^{-1} .

6-Methyl-4-(4-nitro-phenyl)-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (4d): Solid, mp 210–212°C; 1H NMR (DMSO- d_6): δ 1.07 (3H, t, 3 $J=6.8$ Hz, CH_3), 2.26 (3H, s, CH_3), 3.97 (2H, q, 3 $J=5.4$ Hz, OCH_2), 5.27 (1H, s, CH), 7.50 (2H, d, 3 $J=7.3$ Hz, atom), 7.87 (1H, s, NH), 8.20 (2H, d, 3 $J=7.2$ Hz, atom), 9.33 (1H, s, NH); ^{13}C NMR: δ 14.5, 18.3, 54.2, 59.8, 98.7, 124.2, 128.1, 147.2, 149.8, 152.2, 152.5, 165.5; IR (KBr) : 3215, 1731, 1707, 1641 cm^{-1} ; MS m/e 305 (M^+ 25), 276 ($M^+-C_2H_5$, 92), 260 ($M^+-C_2H_5CO_2$, 20), 183 (100).

4-(2,4-Dichloro-phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (4e): Solid, mp 245–247°C. 1H NMR (DMSO- d_6): δ 9.33 (brs, N1-H), 7.77 (br s, N3-H), 7.31–7.57 (m, Ar-H), 5.60 (s, C4-H), 3.90 (q, OCH_2CH_3 , $J=7.2$ Hz), 2.29 (s, C6- CH_3), 1.02 (t, OCH_2CH_3 , $J=7.2$ Hz); IR (KBr): 3219, 3104, 2969, 1699, 1641 cm^{-1} ; MS m/e 328 (M^+ , 6.69), 330 ($M^+ +2$, 4.10), 299 (47.18), 293 (68.72), 255 (40.00), 183 (100.00), 155 (32.82), 137 (25.64). Anal. calcd for $C_{14}H_{14}Cl_2N_2O_3$: C, 51.06; H, 4.26; N, 8.51. Found: C, 51.32; H, 4.43; N, 8.24.

4-(2-Chloro-phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (4f): Solid, mp 252–254°C; 1H NMR (DMSO- d_6): δ 2.31 (s, 3H, CH_3), 3.47 (s, 3H, OCH_3), 5.71 (s, 1H, CH), 7.33–7.41 (m, 4H, Ar-H), 7.81 (s, 1H, NH), 9.15 (s, 1H, NH); IR (KBr): 3215, 3080, 1687, 1641 cm^{-1} ; MS m/e : 281.3.

4-(4-Hydroxy-phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (4h): Solid, Mp 198–200°C; 1H NMR (DMSO- d_6): δ 1.18 (t, $J=7.5$ Hz, 3H, CH_3), 2.28 (s, 3H, CH_3), 4.0 (q, $J=7.5$ Hz, 2H, $-OCH_2$), 5.18 (s, 1H), 6.7 (d, $J=8.9$ Hz, 2H, Ar), 7.09 (d, $J=8.9$ Hz, 2H, Ar), 7.25 (s, 1H), 8.95 and 9.0 (2s, 2H, brs. NH); IR (KBr): 3520, 3230, 3150, 1705, 1690 cm^{-1} ; MS m/e = 276 (10) (M^+), 248 (100), 231 (28), 204 (80), 168 (87), 136 (48). Anal. calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.83; N, 10.17. Found: C, 60.81; H, 5.78; N, 10.11

4-Furan-2-yl-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (4j): Solid, mp 211–213°C; 1H NMR (DMSO- d_6): δ 1.30 (t, 3H, $J=6.6$ Hz), 2.34 (s, 3H), 4.20 (q, 2H, $J=6.8$ Hz), 5.20 (d, 1H, $J=3.0$ Hz), 7.60 (s, 1H), 7.83 (brs, 1H, NH), 9.20 (s, 1H, NH); IR (KBr): 3349, 3228, 3123, 2978, 2841, 1659, 1506, 1461, 1278, 1059, 927, 871, 761 cm^{-1} ; MS m/e : 250 (m^+ , 42), 221 (100), 177 (92), 110 (26), 95 (12), 57 (19).

6-Methyl-2-oxo-4-styryl-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (4k): Solid, mp 229–230°C; 1H NMR (DMSO- d_6): δ 1.22 (t, 3H, $J=7.0$ Hz), 2.23 (s, 3H), 4.12 (q, 2H, $J=7.0$ Hz), 4.85 (d, 1H, $J=3.0$ Hz), 6.26 (d, 1H, $J=14.0$ & 5.0 Hz), 7.38 (d, 2H, $J=7.0$ Hz), 7.43 (d, 2H, $J=7.0$ Hz), 7.68 (brs, 1H, NH), 9.24 (brs, 1H, NH); IR (KBr): 3297, 3241, 3091, 2976, 2842, 698, 1508, 1493, 1371, 1223, 1137, 1051, 963, 769 cm^{-1} ; MS m/e : 286 (m^+ , 27), 259 (100), 224 (66), 196 (31), 149 (22), 103 (16), 91(10), 84.

6-Methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (4l): Solid, mp 191–192°C; 1H NMR (DMSO- d_6): δ 1.19 (t, $J=7.3$ Hz, 3H, CH_3), 2.27 (s, 3H, CH_3), 4.08 (q, $J=7.3$ Hz, 2H, $-OCH_2$), 5.22 (s, 1H, CH), 7.23 (m, 5H, Ar), 9.25 and 9.9 (2s, 2H, 2brs. NH); IR (KBr): 3259, 3195, 3100, 1710, 1690 cm^{-1} ; MS m/e = 276 (65) (M^+), 237 (45), 204 (100), 172 (35), 142 (20).

4-(4-Hydroxy-phenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (4m): Solid, mp 195–198°C; 1H NMR (DMSO- d_6): δ 1.18 (t, $J=7.5$ Hz, 3H, CH_3), 2.25 (s, 3H, CH_3), 4.0 (q, $J=7.5$ Hz, 2H, $-OCH_2$), 5.10 (s, 1H, CH), 6.65 (d, $J=9.1$ Hz, 2H, Ar), 7.00 (d, $J=9.1$ Hz, 2H, Ar), 9.10 (br. s, 1H, OH), 9.15 and 9.8 (2br. s, 2H, NH); IR (KBr) = 3450, 3190, 3040, 1705, 1650 cm^{-1} ; MS m/e = 292 (25) (M^+), 264 (28), 220 (20), 200 (15), 142 (25), 50 (100).

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- General procedure for Ni(acac)₂-mediated preparation of dihydropyrimidinones 4a*: a solution of β -keto ester (1, 10 mmol), the appropriate aldehydes (benzaldehyde) (2, 10 mmol), urea or thiourea (3, 15 mmol), Ni(acac)₂ (5 mmol) in Ethanol (20 mL) was heated under reflux for 7 h. After cooling, the reaction mixture was poured onto 50 g of crushed ice. Stirring was continued for several minutes; the solid products were filtered, washed with cold water (2 \times 50 mL) and a mixture (1:1) of ethanol-water (2 \times 20 mL) and subsequently dried. All the products are known compounds which were characterized by IR and ¹H NMR spectral data and their mps compared with literature reported melting points.

Table 1. Ni(acac)₂-catalyzed synthesis of dihydropyrimidinones/thiones 4 via Scheme 1

Entry	X	R ₁	R ₂	Reaction Time/Hour	Yields	MP °C Found
4a	O	C ₆ H ₅	OEt	7	92	208-209
4b	O	4-CH ₃ C ₆ H ₄	OEt	10	85	225-226
4c	O	4-CH ₃ OC ₆ H ₄	OEt	10	80	199-202
4d	O	4-NO ₂ C ₆ H ₄	OEt	7	90	210-212
4e	O	2,4-(Cl) ₂ -C ₆ H ₃	OEt	6	65	245-247
4f	O	2-Cl-C ₆ H ₄	OEt	10	75	252-254
4g	O	3-NO ₂ C ₆ H ₄	OEt	8	70	227-228
4h	O	4-(OH)-C ₆ H ₄	OEt	12	80	198-200
4i	O	4-F-C ₆ H ₄	OEt	12	75	190-192
4j	O	2-Furyl-	OEt	9	80	211-213
4k	O	C ₆ H ₅ -CH=CH-	OEt	6	85	229-230
4l	S	C ₆ H ₅	OEt	10	80	191-192
4m	S	4-(OH)-C ₆ H ₄	OEt	11	75	195-198
4n	S	4-(OCH ₃)-C ₆ H ₄	OEt	10	92	140-145

Standard conditions: All the reactions were carried out using of β -keto ester (1), the appropriate aldehyde (2), urea or thiourea (3), Ni(acac)₂ in ethanol was heated under reflux for 5 h