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Der Pharma Chemica, 2011, 3 (4):292-297
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

One pot synthesis of dihydropyrimidinones catalyzed by Cyanuric chloride: An improved procedure for the Biginelli reaction

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ABSTRACT

We report herein the use of Cyanuric chloride 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.

Keywords: Biginelli cyclocondensation, Cyanuric chloride, Dihydropyrimidinones.

(Dedicated to Dr. N . Srinivasan on his 50th birthday)

INTRODUCTION

A general and practical chemistry route to the Biginelli cyclocondensation reaction using Cyanuric chloride 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 pharmaceutical[1] 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) antagonists[2] 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 inhibitors[4] . 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 BF_3-OEt_2[7] $FeCl_3$ and HCl[8] $LaCl_3 7H_2O$,[9] $La(OTf)_3$[10]

$Yb(OTf)_3$[11],$ZrCl_4$[12] ,$BiCl_3$[13] ,$Mn(OAc)_3$[14] ,$LiClO_4$,[15] ,H_3BO_3[16] and polyphosphorate ester[17] Many other synthetic methods for preparing these compounds have been reported including classical conditions with microwave[18] and ultrasound irradiation[19,20].

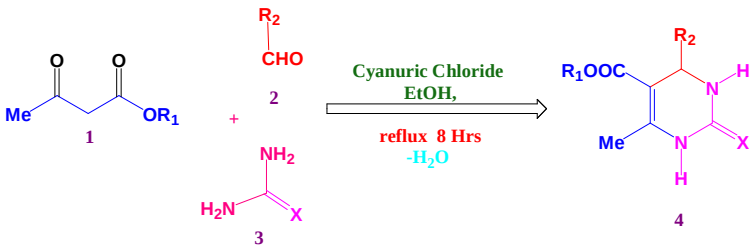
As part of our continued interest in the Biginelli reaction[21], we report here our preliminary investigation dealing with the use of Cyanuric chloride as a catalyst under neutral conditions preserving the simplicity of Biginelli's one-pot reaction **(Scheme 1)**. Herein we disclose the first example of an efficient synthetic protocol for the preparation of 3, 4-dihydropyrimidinones using Cyanuric chloride as an organopromoter.

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 synthesis[22]. Biginelli reaction first reported in 1893, involving acid catalyzed one-potcyclocondensation 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.

MATERIALS AND METHODS

Materials benzaldehydes and substituted benzaldehydes, urea or thiourea, *Cyanuric chloride*were purchased from Acros Chemical Co., and they were used as received. Ethanol freshly distilled prior to use. The other materials werecommon commercial level and used as received.

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

Cyanuric chloride 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 Cyanuric chloride for this reaction lies in its simplicity. This method utilizes readily available of reagents at low cost and also affords high yields of DHPMs in short reaction times.

*General procedure for Cyanuric chloride —mediated preparation of dihydropyrimidinones***4a:** a solution of β-keto ester (**1**, 10mmol), the appropriate aldehydes (benzaldehyde) (**2**, 10 mmol), urea or thiourea (**3**, 15 mmol), *Cyanuric chloride* (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 (2×50 mL) and a mixture (1:1) of ethanol–water (2×20 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.

RESULTS AND DISCUSSION

Thus, 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 followed by the addition of the β-ketoester enolate and cyclodehydration to afford the dihydropyrimidine.

CONCLUSION

In conclusion, we have developed a simple and general method for the synthesis of dihydropyrimidinones using the inexpensive and easily available Cyanuric chloride as catalyst. 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.

Table 1.*Cyanuric chloride* -catalyzed synthesis of dihydropyrimidinones/thiones 4 via Scheme 1

Entry	X	R_1	R_2	Reaction Time/Hour	Yields	MP ^{0}C Found
4a	O	C_6H_5	OEt	7	92	208-209
4b	O	4-$CH_3C_6H_4$	OEt	10	85	225-226
4c	O	4-$CH_3OC_6H_4$	OEt	10	80	199–202
4d	O	4-$NO_2C_6H_4$	OEt	7	90	210-212
4e	O	2,4-$(Cl)_2$-C_6H_3	OEt	6	65	245-247
4f	O	2-Cl-C_6H_4	OEt	10	75	252–254
4g	O	3-$NO_2C_6H_4$	OEt	8	70	227-228
4h	O	4-(OH)-C6H4	OEt	12	80	198-200
4i	O	4-F-C6H4-	OEt	12	75	190-192
4j	O	2- Furyl-	OEt	9	80	211-213
4k	O	C6H5-CH=CH-	OEt	6	85	229-230
4l	S	C_6H_5	OEt	10	80	191–192
4m	S	4-(OH)-C6H4	OEt	11	75	195–198
4n	S	4-(OCH_3)-C6H4	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**), Cyanuric chloride in ethanol was heated under reflux for 5

6 – Methyl – 2 -oxo-4-phenyl-1,2,3,4-tetrahydro-Pyrimidine-5-carboxylic acid ethyl ester (4a): Solid, mp 208–209°C; ^{1}H 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-pyrim idine-5-carboxylic acid ethyl ester (4d): Solid, mp 210–212°C; ^{1}H NMR (DMSO-d_6): δ H 1.07 (3H, t, 3 *J*=6.8Hz, 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. ^{1}H 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$_2$CH_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 $C_{14}H_{14}C_{l2}N_2O_3$: 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-pyri midine-5-carboxylic acid ethyl ester (4f): Solid, mp 252 –254°C ; ^{1}H 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; ^{1}H 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 ; ^{1}H 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; ^{1}H 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; ^{1}H 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=7.3Hz, 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; ^{1}H 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).

Acknowledgments
The authors thank ***Mr. K. Gopi***, Managing Director, Research and Development, Acacia Life Sciences, Hyderabad 500076, India, for financial support.

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