Available online at www.pelagiaresearchlibrary.com

Pelagia Research Library

Der Chemica Sinica, 2017, 8(2):247-253

ISSN : 0976-8505
CODEN (USA): CSHIA5

SiO2.TTC: Efficient Catalyst for Synthesis of 3,4-Dihydropyrimidine-2(1H)-ones/Thiones

Vishvanath D Patil*, Prathamesh V Gidh and Amruta M Salve

Organic Chemistry Research Laboratory, Department of Chemistry, C.K.Thakur A.C.S. College New Panvel, Raigad, Maharashtra, India

ABSTRACT

Efficient method has been developed to synthesize various 3,4-dihydropyrimidinones. Dihydropyrimidinone derivatives were synthesized with excellent yield by using aldehyde, ethylacetoacetate and urea or thiourea with silica supported Titanium trichloride. The reaction carried out under room temperature. This method is a very easy and rapid for synthesis of dihydropyrimidinone derivatives.

Keywords: SiO_2.TTC, 3,4-Dihydropyrimidin-2(1H)-ones, Urea/thiourea.

INTRODUCTION

Dihydropyrimidone and their derivatives have been useful for natural, synthetic, pharmacological, therapeutic and bioorganic chemistry mainly due to their wide range of biological activities and its applications [1-7]. Research in multicomponent reactions (MCRs) is an encoring and hot topic in organic chemistry, as there advantages in preparations of heterocyclic compounds and in drugs discovery procedures [8]. These organic compounds show different activities as calcium channel blocks, antihypertensive agents, alpha antagonists of neuropeptids etc. Various synthetic methods have been reported by different pharmacists such as acids [9-13], microwave variants [14-27], $Mn(OAc)_2$ [28-32] LiBr [33,34], ammonium salt [35], on reagents like CAN and clay [36]. But most of the methods have limitations in terms of yields, catalyst loading, stability, long reaction time etc. causing disposal. In continuation of our research on the introduction of more efficient solid supportive catalyst in organic synthesis.

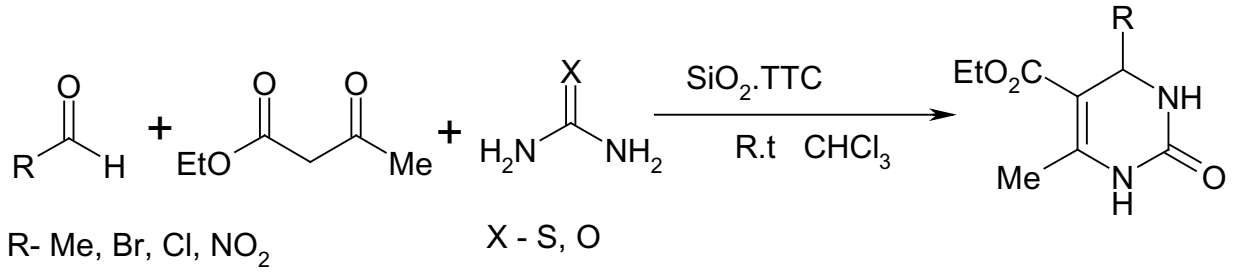
MATERIALS AND METHODS

All the chemicals and solvents were purchased from Merckand Sigma Aldrich. All reagents are received which are purified by distillation and recrystallization. The reaction was monitored by TLC.

The spot were detected either under UV light or by placing in an iodine chamber. Melting points were determined in pen capillaries methods.

General procedure for synthesis of 3,4-Dihydropyrimidin-2(1H)-ones/thiones

Aromatic aldehyde (1 mmol), ethylacetoacetate (1 mmol), urea/thiourea (1 mmol) and SiO_2.TTC (10%) were stirred in round bottom flask for 5-30 min with solvent Chloroform (1 ml) at room temperature. The development of reaction was monitored by thin-layer chromatography. The completion of reaction confirmed with TLC. After drying it was purified by recrystallization from hot alcohol and further purification by column chromatography. The product obtained after the usual workup were characterised using spectroscopic techniques **Scheme 1**.



Scheme 1: Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones/thiones

RESULTS AND DISCUSSION

The optimum condition for the synthesis of 3,4-Dihydropyrimidon-2(1H)-ones or thiones derivatives were established by considering a reaction between aldehyde, ethylacetoacetate, urea or thiourea with SiO_2.TTC (Silica supported titanium trichloride) using chloroform as a solvent. The product obtained was confirmed by melting points and spectral data.

The effectiveness of solid supportive catalyst SiO_2.TCC was determined with respect to its leading amounts. There was no improvement in yield with increasing amount from 0.10 mmol of catalyst (**Table 1**, Entry 3).

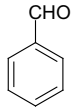
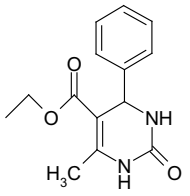
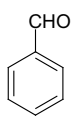
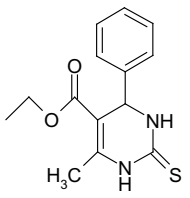
Thus, the most appropriate amount for anhydrous SiO_2.TTC as a catalyst was found to be 0.1 mmol as per results summarized in **Table 1**.

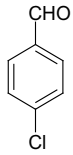
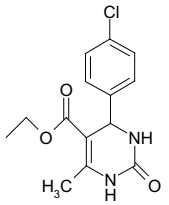
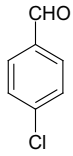
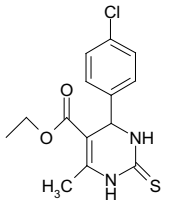
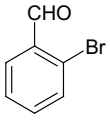
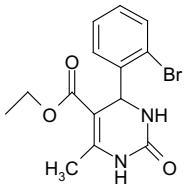
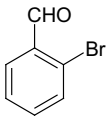
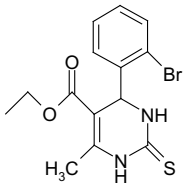
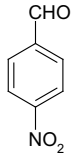
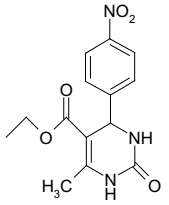
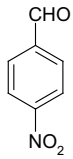
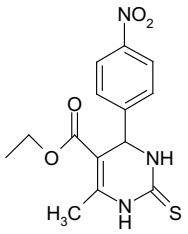
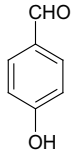
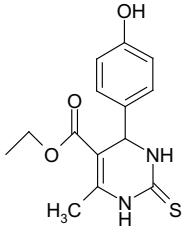
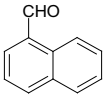
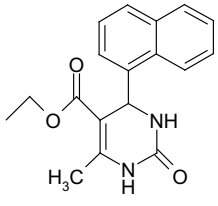
Table 1: Investigation of catalytic effects for synthesis of 3,4-Dihydropyrimidine -2(1H) ones/thiones.

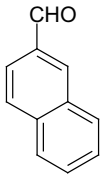
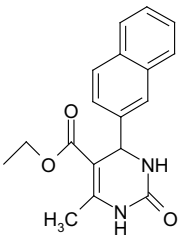
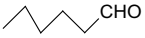
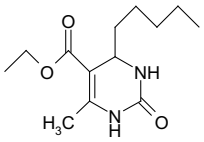
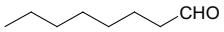
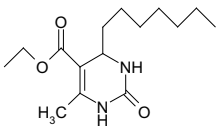
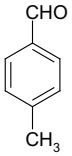
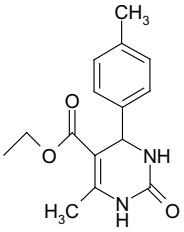
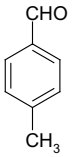
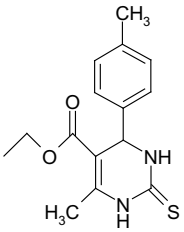
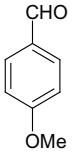
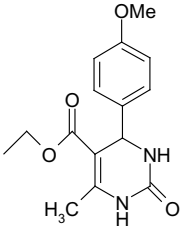
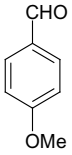
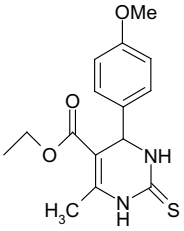
Entry	SiO2.TTC (mmol %)	Time (min.)	Yield[a] (%)
1	0.01	15	55
2	0.05	15	65
3	0.10	05	92
4	0.15	05	92
5	0.20	05	92
[a]Isolated yield of corresponding product			

As summarized in **Table 2**, aromatic/aliphatic aldehydes with electron-donating or electron withdrawing groups, ethylacetoacetate and urea/thiourea in presence of SiO_2.TTC were reacted, resulting in corresponding 3,4-dihydropyrimidin-2(1H)-ones/thiones in good to excellent yields.

Table 2: Synthesis of diydrohyropyrimidones catalysed by SiO_2.TTC.

Entry	Aldehyde[a]	X	Product[b]	Time (Min)	Yield[c] (%)
1		O		05	92
2		S		30	90

3		O		05	91
4		S		25	89
5		O		25	90
6		S		25	88
7		O		05	95
8		S		25	84
9		S		25	92
10		O		25	90

11		O		25	89
12		O		50	80
13		O		50	84
14		O		15	92
15		S		25	90
16		O		15	90
17		S		25	88

[a]The substrate was treated with aldehyde (1mmol), Ethylacetoacetate (1 mmol),Urea/Thiourea (1 mmol) in presence of anhydrous SiO_2.TTC as a catalyst at room temperature.
[b]All products were identified by their IR and ^{1}HNMR spectra.
[c]Isolated Yields.

Three components reacted smoothly in presence of solid supportive SiO_2.TTC with $CHCl_3$ gave good yields of corresponding products (**Table 2**). SiO_2.TTC was proved to be an efficient catalyst under mild conditions. Various

aromatic aldehydes containing either electron donating or withdrawing substituents at different position reacted well under present reaction condition (**Table 2**) proving the wide scope and generality of the protocol. The nature and substitution pattern of different substituents affected the course of reaction in terms of time and yields. These aromatic aldehyde having electron withdrawing groups gave excellent yields, in short reaction time (**Table 2**, Entry 7) but those with electron donating substitution gave comparatively low yields with slow reaction rate (**Table 2**, Entry 3,14,16). Further aldehydes with o-substituents were found to be less reactive (**Table 2**, Entry 5,6) aliphatic aldehydes were less reactive even at more time (**Table 2**, Entry 12,13). The products obtained from thiourea gives moderate yields (**Table 2**, Entry 2,4,6,8,9,15,17). This proved wide scopes and generality of the present protocol. The categorization date of various ^{1}H, NMR, IR achieved for various compounds are given in **Table 2**.

Characterization

(i) 4-(4-Chlorophenyl) 3,4-dihydro-6-phenylpyrimidin-2(1H)-one (**Table 2,** Entry 3): Melting point 266^{o}C;

^{1}HNMR (400 MHz, DMSO); δ =8.65 (s, 1H, NH), 8.08 (s, 1H, NH), 7.53 7.33 m, (m, 9H, Ar H), 5.45(d, J 2.8 Hz, 1H, CH), 5.18 (d, 1H, J 2.8 Hz, CH)

IR (KBr) cm^{-1} 3232, 2936, 1685, 1573 and 1465

(ii) 3,4-Dihydro-4-(4-hydroxyphenyl)-6-phenylpyrimidin- 2(1H)-one (**Table 2,** Entry 9): Melting point 256^{o}C

^{1}HNMR (400 MHz, DMSO) δ=9.20 (s, 1H, NH), 8.14 7.53 (m, 9H, Ar H), 7.35 7.31 (s, 1H, NH), 7.28 (d, J 8.8 Hz, 1H, CH), 5.56 (s, 1H, OH) 5.15 (d, 1H, J 8.8 Hz, CH);

IR (KBr) cm^{-1} 3386, 2922, 1626, 1519 and 1445

(iii) 3,4-Dihydro-4-(4-methoxyphenyl)-6-phenylpyrimidin-2(1H)-one (**Table 2,** Entry 16):

^{1}HNMR (400 MHz, DMSO) δ=12.06 (s, 1H, NH), 9.35 (s, 1H, NH), 8.38 7.22 (m, 9H, Ar H), 6.95 (d, J 8.7 Hz, 1H, CH), 5.47 (d, 1H, J 8.7 Hz, CH), 3.75 (s, 3H, OCH_3);

IR (KBr) cm^{-1} 3382, 2936, 1614, 1522, 1418

CONCLUSION

In this research paper, we successfully developed a simple and highly efficient one pot synthesis of 3,4-Dihydropyrimidin-2(1H)-ones or thiones derivatives from easily available starting materials using SiO_2.TTC. We developed multi components reaction of ethyl acetoacetate, aromatic aldehydes, and urea/thiourea using SiO_2.TTC catalyst. This protocol is attractive in terms economy, short reaction times, simple easy workup make this procedure a useful addition to modern synthetic methods are few of the advantages of this procedure.

ACKNOWLEDGEMENT

The authors acknowledge the kind support to this work by Principal Dr. S.T. Gadade C.K.Thakhur A.C.S. College, New Panvel, Raigad, Maharaahtra, India.

REFERENCES

[1] Meshram GA, Patil VD (**2009**) A simple and efficient method for sulfonylation of amines, alcohols and phenols with cupric oxide under mild conditions. *Tetrahedron Lett* 50: 1117-1121.

[2] Patil VD, Sutar NR, Patil KP (**2016**) Synthesis of 2,4,5-Triaryl-1H-Imidazoles using anhydrous PbCl2. *J Chem Pharm Res* 8: 728-732.

[3] Domling A (**2006**) Recent developments in isocyanide based multicomponent reactions in applied chemistry. *Chem Rev* 106: 17-89.

[4] Akritopoulou-Zanze I, Djuric SW (**2007**) Recent advances in the development and application of post-Ugi transformation. *Heterocycles* 73: 125-147.

[5] Akritopoulou-Zanze I (**2008**) Isocyanide-based multicomponent reactions in drug discovery. *Curr Opinion Chem Biol* 12: 324-331.

[6] Hulme, C (**2005**) Applications of Multicomponent Reactions in Drug Discovery-Lead Generation to Process Development.

In Multicomponent Reactions. Zhu J; Bienayme H, Eds., Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, pp: 311-341.

[7] Hulme C, Gore V (**2003**) "Multi-component reactions : emerging chemistry in drug discovery" 'from xylocain to crixivan'. *Current Med Chem* 10: 51-80.

[8] Atwal KS, Swanson BN, Unger SE, Floyd DM, Moreland S, et al. (**1991**) Dihydropyrimidine calcium channel blockers. 3. 3-Carbamoyl-4-aryl-1,2,3,4-tetrahydro-6-methyl-5-pyrimidinecarboxylic acid esters as orally effective antihypertensive agents. *J Med Chem* 34: 806-811.

[9] Biginelli P (**1893**) Synthesis of 3,4-dihydropyrimidin-2(1H)-ones. *Gazz chim Ital* 23: 360-416.

[10] Patil AD, Kumar NV, Kokke WC, Bean MF, Freyer AJ, et al. (**1995**) Novel Alkaloids from the Sponge Batzellasp: Inhibitors of HIV gp120-Human CD4 Binding. *Eur J Org Chem* 60: 1182-1188.

[11] Heys L, Moorea CG, Murphy PJ (**2000**) The guanidine metabolites of Ptilocaulisspiculifer and related compounds; isolation and synthesis. *J Chem Soc Rev* 29: 57.

[12] Tu S, Fang F, Miao C, Jiang H, Feng Y, et al. (**2003**) One-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones using boric acid as catalyst. *Tetrahedron Lett* 44: 6153.

[13] Hu EH, Sidler DR, Dolling Ulf-H (**1998**) Unprecedented Catalytic Three Component One-Pot Condensation Reaction: An Efficient Synthesis of 5-Alkoxycarbonyl- 4-aryl-3,4-dihydropyrimidin-2(1H)-ones. *J Org Chem* 63: 3454-3457.

[14] Ranu BC, Hazra A, Jana UJ (**2000**) Indium (III) chloride-catalyzed one-pot synthesis of dihydropyrimidinones by a three-component coupling of 1, 3-dicarbonyl compounds, aldehydes, and urea: an improved procedure for the Biginelli reaction. *J Org Chem* 65: 6270-6272.

[15] Yadav JS, Reddy BVS, Srinivas R, Venugopal C, Ramalingam T (**2001**) LiClO4-catalyzed one-pot synthesis of dihydropyrimidinones: an improved protocol for Biginelli reaction. *Synthesis* 2001: 1341-1345.

[16] Ramalinga K, Vijayalakshmi P, Kaimal TNB (**2001**) Bismuth(III)-catalyzed synthesis of dihydropyrimidinones: improved protocol conditions for the Biginelli reaction. *Synlett* 2001: 863-865.

[17] Reddy V, Mahesh M, Raju PVK, Babu TR, Reddy VVN (**2002**) Zirconium(IV) chloride catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones. *Tetrahedron Lett* 43: 2657-2659.

[18] Fu NY, Yuan YF, Cao Z, Wang SW, Wang JT, et al. (**2002**) Indium(III) bromide-catalyzed preparation of dihydropyrimidinones: improved protocol conditions for the Biginelli reaction. *Tetrahedron* 58: 4801-4807.

[19] Fan X, Zhang X, Zhang Y (**2002**) Samarium chloride catalysed Biginelli reaction: one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones. *J Chem Res* 2002: 436-438.

[20] Lu J, Bai Y (**2002**) Catalysis of the Biginelli Reaction by Ferric and Nickel Chloride Hexahydrates. One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones. *Synthesis* 2002: 466-470.

[21] Varela R, Alam MM, Adapa SR (**2003**) Bismuth triflate catalyzed one-pot synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones: an improved protocol for the Biginelli reaction. *Synlett* 2003: 67-70.

[22] Bose DS, Fatima L, Meryala HB (**2003**) Green Chemistry Approaches to the Synthesis of 5-Alkoxycarbonyl-4-aryl-3,4-dihydropyrimidin-2(1H)-ones by a Three-Component Coupling of One-Pot Condensation Reaction: Comparison of Ethanol, Water, and Solvent-free Conditions. *J Org Chem* 68: 587-590.

[23] Sabitha G, Reddy GSKK, Reddy CS, Yadav JS (**2003**) One-pot synthesis of dihydropyrimidinones using iodotrimethylsilane. Facile and new improved protocol for the Biginelli reaction at room temperature. *Synlett* 2003: 858-860.

[24] Paraskar AS, Dewkar GK, Sudalai A (**2003**) 3,4-Dihydropyrimidinones/thiones and their derivatives are synthesized via Biginelli routes involving an aldehyde, 1,3-dicarbonyl compound. *Tetrahedron Lett* 44: 3305.

[25] Yadav JS, Subba Reddy BV, Reddy JE, Ramalingam T (**2000**) Microwave-assisted efficient synthesis of dihydro pyrimidines: improved high yielding protocol for the Biginelli reaction. *J Chem Res* 2000: 354-355.

[26] Stadler A, Kappe CO (**2000**) Atroposelective attack of nucleophiles on 2-formyl-1-naphthamides and their derivatives: chelation and non-chelation control. *J Chem Soc Perkin Trans 1* 2000: 1363-1378.

[27] Kappe CO, Kumar D, Varma R (**1999**) Microwave-assisted high-speed parallel synthesis of 4-aryl-3,4-dihydropyrimidine-2(1H)-ones using a solventless Biginelli condensation protocol. *Synthesis* 1799-1803.

[28] Kidwai M, Saxena S, Mohan R, Venkataramanan R (**2002**) A novel one pot synthesis of nitrogen containing heterocycles: An alternative methodology to the Biginelli and Hantzsch reactions. *R J Chem Soc Perkin Trans* 1: 1845-1846.

[29] Donodoni A, Massi A (**2001**) Parallel synthesis of dihydropyrimidinones using Yb(III)-resin and polymer-supported scavengers under solvent free conditions. A green chemistry approach to the Biginelli reaction. *Tetrahedron Lett* 42: 7975-7978.

[30] Malti G, Kundu P, Guin C (**2003**) One pot synthesis of dihydropyrimidinone catalyzed by lithium bromide: an improved procedure for the Biginelli reaction. *Tetrahedron Lett* 44: 2757-2758.

[31] Reddy KR, Reddy CV, Mahesh M, Raju PVK, Reddy N (**2003**) New environmentally friendly solvent-free synthesis of dihydropyrimidinones catalysed by *N*-butyl-*N,N*-dimethylphenylethylammonium bromide. *Tetrahedron Lett* 44: 8173-8175.

[32] Bigi F, Carloni S, Frullanti B, Maggi R, Sartori G (**1999**) A revision of the Biginelli reaction under solid acid catalysis. Solvent-free synthesis of dihydropyrimidines over montmorillonite KSF. *Tetrahedron Lett* 40: 3465-3468.

[33] Wipf P, Cunningham AA (**1995**) A solid phase protocol of the Biginelli dihydropyrimidine synthesis suitable for combinatorial chemistry. *Tetrahedron lett* 36: 7819-7822.

[34] Salehi P, Dabiri M, Zolfigol MA, Fard MAB (**2003**) Silica sulfuric acid: an efficient and reusable catalyst for the one-pot synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones. *Tetrahedron Lett* 44: 2889-2891.

[35] Yadav JS, Subbareddy BV, Reddy KB, Raj KS, Prasad AR (**2001**) Ultrasound-accelerated synthesis of 3, 4-dihydropyrimidin-2 (1 H)-ones with ceric ammonium nitrate. *J Chem Soc Perkin Trans 1* 2001: 1939-1941.

[36] Mitra AK, Banerjee K (**2003**) Clay catalysed synthesis of Dihydropyrimidiniones under Solvent-free conditions. *Synlett* 10: 1509-1511.