DOI:10.7598/cst2018.1441
ISSN:2278-3458

Chemical Science Transactions
2018, **7(1),** 89-94

RESEARCH ARTICLE

A Green Approach for the Synthesis of 2,4-Dihydro-pyrimidinones Using PTSA

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Received 4 August 2017 / Accepted 24 August 2017

Abstract: A simple and efficient method has been developed for the one pot cyclocondensation of heterocyclic aldehydes, *β*-ketoester and urea by using PTSA (p-Toluenesulfonic acid) as catalyst. This method has several advantages of excellent yield, inexpensive, short reaction time, ecofriendly and attractive for large scale synthesis.

Keywords: 2-Chloro3-formylquinoline, PTSA, Urea, Dihydropyrimidinones

Introduction

Dihydropyrimidinones have been paid increasing attention, due to their various therapeutic and pharmacological properties, such as antiviral, antibacterial, antihypertensive and antitumor effects[1]. More recently, they emerged as integral backbones of several calcium channel blockers, antihypertensive agents, *α*-1a-antagonists, and neuropeptide Y(NPY) antagonists[2]. Dihydropyrimidinone derivatives are found as core units in many marine alkaloids (batzelladine and carambine), which have been found to be potent to HIV-gp-120 CD4 inhibitors[3]. Thus, synthesis of the heterocyclic nucleus contained in such compounds is of current interest.

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 of dihydropyrimidinones.

Several methods improved the procedure using phosphorus pentoxide-methanesulfonic acid[4], potassium *ter*-butoxide (*t*-BuOK)[5], ammonium dihydrogen phosphate[6], silica-gel[7], mesoporous molecular sieve MCM- 41[8], cyanuric chloride[9,10], nano-BF_3 ·SiO_2 silica gel supported polyphosphoric acid[11], zirconium(IV) chloride[12], and indium(III) bromide[13] as catalysts. More recently Lewis acids like $BiCl_3$, $Bi(OTf)_3$, $InCl_3$, $LiClO_4$, $ZrCl_4$, $La(OTf)_3$, $NiCl_2.6H_2O$, $FeCl_3.6H_2O$ and ionic liquids[14] have been employed for this transformation.

At the same time, use of heavy metals as catalyst will be subjected to the contamination of dhydropyrimidinones, which is extremely important when concerning about synthesizing

active pharmaceutical ingredients. Thus, despite all these improvements made by several groups, the research for better promoter still continues to be desirable especially in terms of cost-effectiveness, readily or commercial availability and environmentally benign solvent-free procedures.

In a continuation of our earlier efforts to develop new synthetic routes for carbon-carbon[15] and carbon-heteroatom bond formation, herein we disclose an efficient synthetic method for the formation of 3,4-dihydropyrimidinones using PTSA (p-Toluenesulfonic acid) as an organopromoter. Over the past few years the use of PTSA as a catalyst has received considerable attention in different areas of organic synthesis[16]. Especially it makes reaction convenient, cost effective and environmentally benign.

The objective of this study was to design and synthesize new 3,4- diydropyrimidinones containing heterocyclic and aromatic nucleus.

Experimental

Chemicals and solvents required were from Merck and SD fine meck. ^{1}H NMR spectra were recorded in ppm on Bruker Avance at 400 MHz. IR spectra were recorded in KBr on Perkin-Elmer FTIR spectrophotometer. Mass spectra were recorded on VG 7070H micromass mass spectrometer. The melting points were taken in open capillary and are uncorrected.

*General procedure for the synthesis of dihydropyrimidinones (**4a-l**)*

A mixture of aldehyde (1 mmol), ethyl acetoacetate (2 mmol) and urea (2 mmol) were heated under reflux by using PTSA (60 mg) in ethanol (10 mL) for 45-60 min. The reaction mass was allowed to cool to room temperature and poured on ice cold water. Thus obtained solid mass was filtered, washed with water and purified by acetic acid / 70% ethanol. The progress of the reaction was monitored by thin layer chromatography on Merck plates (silica gel 60F-254).

Spectral analysis of compounds

*Ethyl 4-(2-chloroquinolin-3-yl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate **(4a)***

^{1}H NMR (DMSO- d_6)**:** δ 11.80 (s, N_1- H), 9.15 (s, N_3-H), 6.8-7.7 (m, 5H, Ar-H), 5.35 (s, C4-H), 3.99 (q, OCH_2CH_3, J= 7.2 Hz), 2.37 (s, 3H, C_6-CH_3), 1.08 (t, OCH_2CH_3, 3H, J= 7.2 Hz). **IR** (KBr cm^{-1}): 3400 (N_1-H Str.), 3215 (N_3-H), 1720 (-C=O ester), 1660 (-C=O). **MS (EI)**: 345 (100%), 347, (33%). Analysis calcd for $C_{17}H_{16}ClN_3O_3$: C, 59.05; H, 4.66; N, 12.15; Found C, 59.00; H, 4.60; N 12.18.

*Ethyl 4-(2-chloro, 6-methylquinolin-3-yl)-1, 2, 3, 4-tetrahydro-6-methyl-2-oxopyrimidine 5-carboxylate **(4b)***

^{1}H NMR (DMSO- d_6)**:** δ 11.81 (s, N_1- H), 9.17 (s, N_3-H), 6.8-7.5 (m, 4H, Ar-H), 5.37 (s, C4-H), 3.99 (q, OCH_2CH_3, J= 7.2 Hz), 2.37 (s, 3H, C_6-CH_3), 2.52 (s, 6-CH_3), 1.08 (t, OCH_2CH_3, 3H, J= 7.2 Hz). **IR** (KBr cm^{-1}): 3402 (N_1-H Str.), 3217 (N_3-H), 1718 (-C=O ester), 1661 (-C=O). **MS (EI)**: 359 (100%), 361, (33%). Analysis calcd for $C_{18}H_{18}ClN_3O_3$: C, 60.09; H, 5.01; N, 11.68; Found C,60.00; H, 5.00; N 11.60.

*Ethyl 4-(2-chloro, 7-methylquinolin-3-yl)-1, 2, 3, 4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate **(4c)***

^{1}H NMR (DMSO- d_6): δ 11.80 (s,N_1- H), 9.16 (s, N_3-H), 6.7-7.57 (m, 4H, Ar-H), 5.36 (s, C4-H), 3.98 (q, OCH_2CH_3, J= 7.2 Hz), 2.37 (s, 3H, C_6-CH_3), 2.50 (s, 7-CH_3), 1.08 (t, OCH_2CH_3, 3H, J= 7.4 Hz). **IR** (KBr cm^{-1}): 3401 (N_1-H Str.), 3215 (N_3-H), 1716 (-C=O

ester), 1660 (-C=O). **MS (EI)**: 359 (100%), 361, (33%). Analysis calcd for $C_{18}H_{18}ClN_3O_3$: C, 60.00; H, 5.00; N, 11.50; Found C, 60.05; H, 5.05; N 11.60.

*Ethyl 1, 2, 3, 4-tetrahydro-4-(2-methoxyquinolin-3-yl)-6-methyl-2-oxopyrimidine-5-carboxylate**(4e)***

^{1}H NMR (DMSO- d_6) : δ 11.70 (s, N_1- H), 9.16 (s, N_3-H), 6.7-7.57 (m, 4H, Ar-H), 5.34 (s, C4-H), 3.96 (q, OCH_2CH_3, J= 7.3 Hz), 3.75 (s, 3H, OCH_3), 2.34 (s, 3H, C_6-CH_3), 2.50 (s, 7-CH_3), 1.09 (t, OCH_2CH_3, 3H, J= 7.3 Hz.). **IR** (KBr cm^{-1}) **:** 3400 (N_1-H Str.), 3215 (N_3-H), 1718 (-C=O ester), 1660 (-C=O), 1125 (C-O-C). **MS (EI)**: 341(100%). Analysis calcd for $C_{18}H_{19}N_3O_4$: C, 63.33; H, 5.61; N, 12.31; Found C, 63.00; H, 5.55; N 12.25.

*Ethyl 1, 2, 3, 4-tetrahydro-6-methyl-2-oxo-4-(pyridine-2-yl)pyrimidine-5-carboxylate **(4f)***

^{1}H NMR (DMSO- d_6): δ 9.09 (s, N_1- H), 8.49 (s, N_3-H), 7.1-7.70 (m, 4H, Ar-H), 5.26 (s, C4-H), 3.99 (q, OCH_2CH_3, J= 7.2 Hz), 2.25 (s, 3H, C_6-CH_3), 1.11 (t, OCH_2CH_3, 3H, J= 7.2 Hz). **IR** (KBr cm^{-1})**:** 3229 (N_1-H Str.), 3113 (N_3-H), 1711 (-C=O ester), 1672 (-C=O). **MS (EI)**: 261 (100%). Analysis calcd for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08; Found C, 59.60; H, 5.65 ; N 16.00.

*Ethyl 1, 2, 3, 4-tetrahydro-6-methyl-4-(naphthalene-2-yl)-2-oxopyrimidine-5-carboxylate **(4g)***

^{1}H NMR (DMSO- d_6): δ 9.14 (s, N_1- H), 7.80 (s, N_3-H), 7.30-7.70 (m, 7H, Ar-H), 5.68 (s, C4-H), 3.94 (q, OCH_2CH_3, J= 7.3 Hz), 2.30 (s, 3H, C_6-CH_3), 1.06 (t, OCH_2CH_3, 3H, J= 7.3 Hz). **IR** (KBr cm^{-1}): 3220 (N_1-H Str.), 3113 (N_3-H), 1716 (-C=O ester), 1674 (-C=O). **MS (EI)**: 310 (100%). Analysis calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.09; Found C, 69.68; H, 5.87; N 9.11.

*Ethyl 1, 2, 3, 4-tetrahydro-4-(3,4,5-trimethoxyphenyl)-6-methyl-2-oxopyrimidine-5-carboxylate **(4h)***

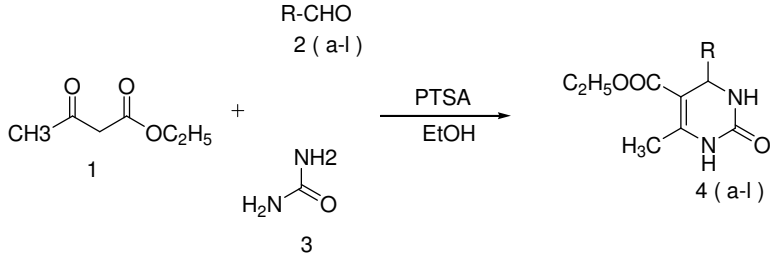
^{1}H NMR (DMSO- d_6): δ 8.53 (s, N_1- H), 7.28 (s, N_3-H), 6.53 (s, 1H, Ar-H), 6.07(s, 1H, Ar-H), 5.36 (s, C_4-H), 4.11 (q, 2H, OCH_2CH_3, J= 7.2 Hz), 2.34 (s, 3H, C_6-CH_3), 3.8 (s, 9H, OCH_3), 1.10 (t, OCH_2CH_3, 3H, J= 7.2 Hz). **IR** (KBr cm^{-1}) : 3232 (N_1-H Str.), 3104 (N_3-H), 1712 (-C=O ester), 1654 (-C=O), 1127 (C-O-C). **MS (EI)**: 350 (100%). Analysis calcd for $C_{17}H_{22}N_2O_6$: C, 58.28; H, 6.33; N, 8.00; Found C, 58.21; H, 6.35; N 8.02.

*Ethyl 4-(3-bromophenyl)-1, 2, 3, 4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate **(4i)***

^{1}H NMR (DMSO- d_6): δ 9.15 (s, N_1- H), 7.81 (s, N_3-H), 7.35-7.52 (m, 4H, Ar-H), 5.70 (s, C4-H), 3.95 (q, OCH_2CH_3, J= 7.3 Hz), 2.30 (s, 3H, C_6-CH_3), 1.05 (t, OCH_2CH_3, 3H, J= 7.3 Hz). **IR** (KBr cm^{-1})**:** 3225 (N_1-H Str.), 3110 (N_3-H), 1710 (-C=O ester), 1670 (-C=O), 843 (C-Br str.). **MS (EI)**: 338 (100%), 340 (98%). Analysis calcd for $C_{14}H_{15}BrN_2O_3$: C, 49.57; H, 4.46; N, 8.26; Found C, 49.50; H, 4.40; N 8.20.

Results and Discussion

As shown in Scheme 1, the one pot reaction of aldehyde (0.01 M) with urea (0.02 M) and ethyl acetoacetate (0.02 M) in the presence of PTSA (p-toluenesulfonic acid) as catalyst in ethanol as solvent furnished substituted 3, 4-dihydropyrimidinone in 95-100% yield within 1 h. We propose a mechanism similar to that of Kappe for the Biginelli reaction[16].



Scheme 1

For optimization of reaction condition, various trial reactions were conducted with a combination of **1, 2(a-l)** and **3** by using different concentrations of PTSA which is summarized in Table 1.

Table 1. Effect of PTSA concentration on reaction

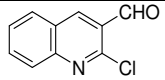
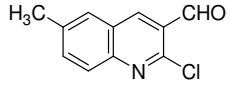
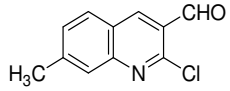
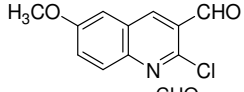
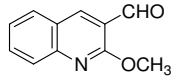
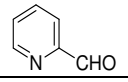
Entry	PTSA %	Yield %
1.	20	50-55
2.	25	80-85
3.	30	95-100

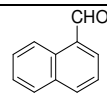
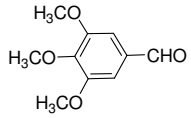
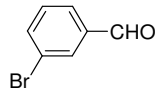
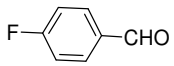
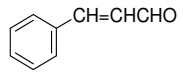
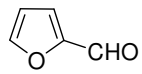
Notably, 30% PTSA concentration gave the best results. Hence all dihydropyrimidinones **4(a-l)** were synthesized by using the same concentration.

It is observed that reaction proceeds fastly for heterocyclic aldehydes within short reaction time (30-40 minutes). As reaction is highly selective no other side products are formed in the reaction. The progress of the reaction was monitored by TLC.

As can be seen from data in Table 2, in all cases studied the three component reaction with both aromatic and heterocyclic aldehydes carrying different substituents proceeded smoothly giving the corresponding dihydropyrimidinones in high yield.

Table 2. Synthesis of dihydropyrimidinones (DHPMs) catalyzed by PTSA

Entry	R	Reaction Time	Yield %	M.P.^{o}C	
				Found	Reported
4a		30-40 min	95	329	-
4b		30-40 min	97	>330	-
4c		30-40 min	96	>330	-
4d		30-40 min	97	172-175	-
4e		30-40 min	95	245	-
4f		1 h	95	210-212	-

4g		40-45 min	96	261-264	-
4h		30-40 min.	97	190	-
4i		1 h	96	203-204	-
4j		1 h	95	185	190-192[9]
4k		1 h	95	230-232	229-239[9]
4l		1 h	95	205	211-213[9]

Conclusion

We have reported a simple method for the synthesis 3,4-dihydripyrimidin-2(1*H*)-ones promoted by PTSA provided an efficient, eco-friendly, commercially available and economic promoter. Excellent yields are obtained than the already reported 3,4-dihydripyrimidin-2(1*H*)-ones by PTSA[15].

Acknowledgement

Authors are thankful to SAIF, Chandigarh for providing spectral facilities.

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