Research article
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Tributyl hexadecyl phosphonium bromide as a new and efficient catalyst for the one-pot synthesis of 3,4 dihydropyrimidinones/thiones via a three component condensation reactions

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Abstract

3,4-Dihydropyrimidinones are an important class of heterocycles due to their pharmaceutical and therapeutic properties. The most efficient method for synthesis of these 3,4-dihydropyrimidinones, first reported by Biginelli, involves three component, one-pot condensation of a β-ketoester with an aldehyde and urea under strongly acidic conditions. The major drawbacks associated with this protocol, is poor to moderate yields, when using substituted aromatic and aliphatic aldehydes. Several improved methods for this protocol have been reported, can overcome the drawback of the classical protocol. This project aims investigating tributyl hexadecyl phosphoniuom bromide(TBHDPB) as a novel and efficient catalyst for synthesis of 3,4dihydropyrimidinones/thiones in milder reaction conditions. Optimization of the reaction conditions was attempted. The effect of temperature and solvent was studied. The best results were obtained in ethanol at 80 ^{o}C. The best catalytic activity of TBHDPB was optimized to be 10 mol% (0.1 mmol , 0.051g). Under optimal conditions, all reactions were completed within 45-80 min. All pure products were obtained in excellent yields (60-90%). The products were characterized by comparison of melting points and ^{1}HNMR with those prepared in accordance with the literature procedures. The remarkable advantages of the present methodology over the literatures method, including the easily and inexpensive available catalyst, simple experimental procedures, shorter reaction times, excellent yields, easy work up and purification of products by non-chromatographic methods.

Keywords: Biginelli reaction; 3,4-dihydropyrimidinone; cyclocondensation; Tributyl hexadecyl phosphonium bromide

Introduction

Multi component reactions (MCRs) are useful process and powerful tool in modern medicinal and heterocyclic chemistry. The use of MCRs for synthesis of pyrimidinones and its derivatives has attracted much interest. The original Biginelli protocol for the preparation of dihydropyrimidinones consisted of heating a mixture of the three components included β-ketoester, aldehyde and urea in ethanol containing a catalytic amount of HCl[1]. Pyrimidinones are an important class of heterocycles due to their remarkable biological activities such as antifungal [2], antibacterial [3], antihypertensive [4], anti-HIV [5] and anti-tumor proliferation effects [6]. The biological activities of some marine alkaloids isolated recently have been attributed to the presence of a dihydropyrimidinone moiety [7]. Therefore, this heterocyclic nucleus has gained great importance and several improved methodologies for the original Biginelli protocol have recently been reported in the literature [8-16]. Unfortunately, many of these methods suffer from drawbacks such as drastic conditions, expensive reagents, low yields, high temperatures, tedious work up procedure, and co-occurrence of several side reactions.

Therefore discovery of new and inexpensive catalyst for the preparation of 3,4-dihydropyrimidinones under neutral and mild conditions is of prime importance. The present work deals with a simple, effective and mild selective synthesis method utilizing tributyl hexadecyl phosphonium bromide (TBHDPB) as an efficient catalyst for condensation of aromatic aldehydes, ethyl acetoacetate, and urea or thiourea under thermal conditions. To best of our knowledge, this is the first report using TBHDPB for synthesis of dihydropyrimidinones/thiones derivatives**.**

Experimental section

Material and instrument

All Products were characterized by comparison of their physical and spectra data (mp, ^{1}HNMR and IR). Melting points was determined in open capillaries using melting point apparatus. IR spectra were recorded by perkin lmer model BXII using KBr powder technique. NMR spectra were measured in $CDCl_3$ and DMSO-d_6 on a Brucker250 MHz NMR spectrometer, using TMS as internal standard.

General procedure for the synthesis of 3,4-dihydropyrimidinones/thiones

In a round bottomed 50 mL flask equipped with a condenser and a magnetic stirrer, a mixture of ethyl acetoacetate (1 mmol), aldehyde (1 mmol), urea or thiourea (3 mmol) and TBHDPB (10 mol %, 0.1 mmol, 0.051g) in ethanol (10 ml) was stirred at 80^{o}C in an oil bath. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, and solvent was evaporated and precipitate was washed with cold water (2×20ml). The crude product was recrystallized from hot ethanol. The obtained products were identified by comparison of their spectral and physical data with authentic samples [17-25].

Selected Spectral Data

5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-(1H)-one (4a)

m.p.: 203-204°C; IR (KBr): 3244, 3116, 1725, 1701, 1646, 1600 cm^{-1}; ^{1}HNMR (DMSO-d_6): δ = 1.15 (t, *J*=6.9 Hz, 3H, CH_3CH_2O), 2.35(s, 3H, CH_3), 4.02 (q, *J*=6.9 Hz, 2H, CH_3CH_2O), 5.40 (s,1H, CH), 5.57 (s, 1H, NH), 7.25-7.33 (m, 5H, ArH), 7.6 (s, 1H, NH) ppm; ^{13}C NMR: δ = 14.1, 17.8, 53.9, 59.2, 99.2, 126.2, 127.2, 128.4, 144.8, 148.3, 152.1, 165.3 ppm[26].

5-(Ethoxycarbonyl)-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-(1H) one (4b) m.p.207-208°C, IR (KBr): 3243, 3110, 1705, 1648 cm^{-1}; ^{1}HNMR: δ = 1.17(t, *J*=7.2 Hz, 3H, CH_3CH_2O), 2.34 (s, 3H, CH_3), 3.79 (s, 3H, CH_3), 4.06 (q, *J*=7.2 Hz, 2H, CH_3CH_2O), 5.35 (d, 1H, CH), 5.48 (s , 1H, NH), 6.82-7.25(m, 4H, ArH), 7.49 (s, 1H, NH) ppm; ^{13}CNMR: δ= 14.50, 18.58, 55.35, 55.58, 50.30, 101.88, 114.31, 128.13, 136.53, 146.49, 154.14, 159.53, 166.10 ppm[26].

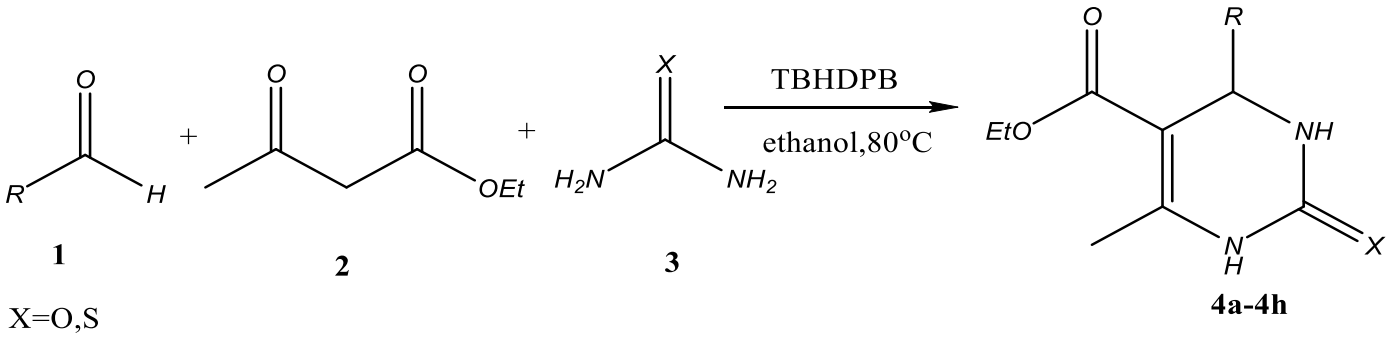
5-ethoxycarbonyl-6-methyl-4-(4-chlorophenyl)-3,4-dihydropyrimidin-(1H)one (4c)

m.p.: 210-213°C; IR (KBr): 3242, 3116, 1706, 1647 cm^{1}; ^{1}H NMR (DMSO-d_6): δ = 1.10 (t, *J*=6.9 Hz, 3H, CH_3CH_2O), 2.34 (s, 3H, CH_3), 4.10 (q, *J*=6.9 Hz, 2H, CH_3CH_2O), 5.37 (1H, CH), 5.56 (s, 1H, NH), 7.23-7.31 (m, 4H, ArH), 7.48 (s, 1H, NH) ppm; ^{13}C NMR: δ = 14.25, 18.72, 50.70, 53.54, 98.57, 128.10, 128.35, 131.74, 143.52, 148.90, 151.92, 165.63 ppm[26].

Results and discussion

In the present study, firstly, a mixture of benzaldehyde 1 (1mmol), ethyl acetate 2 (1mmol) and urea 3 (3mmol) was chosen as a model to provide compound 4a. Then, the reaction was performed with different amount of catalyst, solvents and temperatures to optimize the reaction conditions. It is remarkable to note that, under optimal conditions, the condensation proceeded

with a low catalyst concentration contain10 mol% (0.051 g , 0.1 mmol) of TBHDPB in ethanol , under reflux conditions at 80 °C for 45 minute and gave 90% of the desired product 4a(schem1).



X=O,S

R:C_6H_5-, MeO-C_6H_5-, 4Cl-, 3-NO_2-C_6H_5-, 4Me-C_6H_5-, 4-NO_2-C_6H_5-, MeO-C_6H_5-

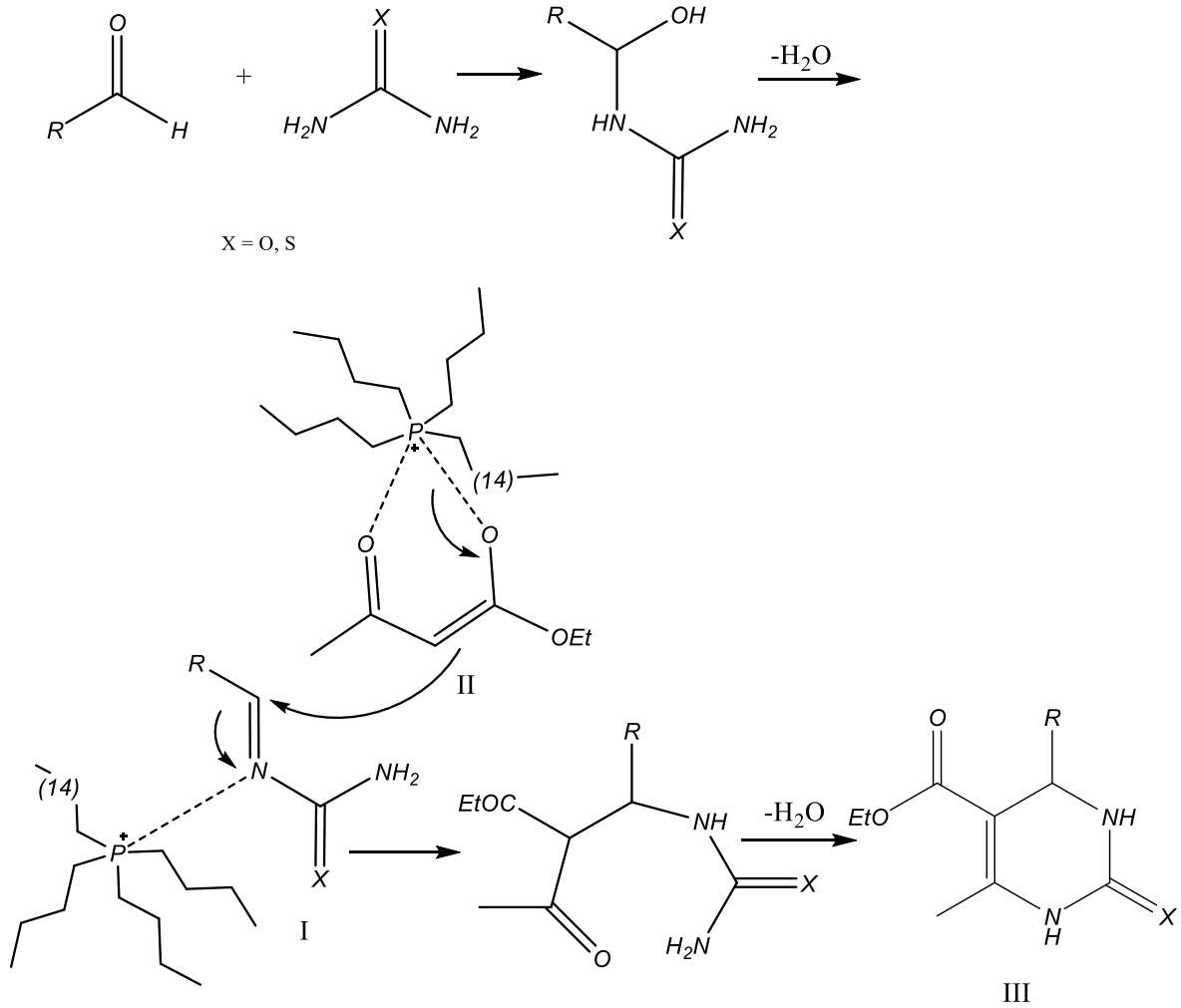
Schem1.synthesis of 3,4-dihydropyrimidinones/thiones by TBHDPB at 80 °C

Promoted by this success, the remaining products of scheme (1) were obtained under these optimized conditions. The results are summarized in Table (1)

Table1. TBHDPB catalyzed synthesis of 3,4-dihydrppyrimidinones/thiones 4a-4h in ethanol at 80°C

Entry	R	X	Time(min)	Yield	Mp (°C)	Product
1	C_6H_5-	O	45	90	203-204	4a
2	MeO-C_6H_5-	O	50	75	207-208	4b
3	4Cl-C_6H_5-	O	60	90	210-213	4c
4	3-NO_2-C_6H_5-	O	60	85	227-229	4d
5	4Me-C_6H_5-	O	60	88	211-213	4e
6	4-NO_2-C_6H_5-	O	60	90	207-208	4f
7	C_6H_5-	S	80	60	202-204	4g
8	MeO-C_6H_5-	S	80	65	151-153	4h

According to the mechanism suggested by kap[27], we propose a plausible mechanism for the TBHDPB-catalyzed Biginelli reaction as shown in schem(2).



Scheme (2) :A plausible mechanism for the formation of 3,4-dihydropyrimidinones/thiones

The aldehyde may react with urea/thiourea to form an acyl imine intermediate **I**, which is activated by TBHDPB. Subsequent nucleophilic addition of the activated 1,3-dicarbonyl compound **II** followed by cyclization and dehydration affords the desired product **III**.

Conclusion

In this research, the compound TBHDPB has been employed as a novel and efficient catalyst for the one-pot multicomponent synthesis of 3,4-dihydropyrimidinones in good yield from aryl aldehyde, ethyl acetoacetate, and urea or thiourea. All the reactions were carried out in ethanol at reflux conditions while using 10 mol % the catalyst TBHDPB. This synthetic methodology offers several advantages such as a cheap, environmentally friendly, easy to handle and non-toxic reagent, simple experimental, work-up procedures, and mild reaction conditions. It could be recommended to the advantageous of optimum conversion in specific temperature this

catalyst could permanently use in Biginelli reaction. Due to the salient advantages of this compound as a catalyst, it can be used in multi-component synthesis reactions of other heterocycles, in other processes, and to produce some compounds on an industrial scale.

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