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SHORT COMMUNICATION

Efficient, Environmental Friendly Green Protocol for Synthesis of Dihydropyrimidin-2-(1-H)-One / Thione by Green acids

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ABSTRACT
The main aim of the green chemistry to addresses various concerns related to minimization of hazardous chemicals and use of safer green chemicals. The Biginelli reaction is a one pot synthesis of dihydropyrimidin-2-one / thione (DHPMs) has been achieved starting from β- keto ester, urea or thiourea and aryl aldehydes in the presence of tartaric acid or citric acid as green acids. The recent environmental concerns, we developed the simple most economical, efficient and environmentally friendly green protocol for the synthesis of dihydropyrimidin-2-one / thione in very good yield (> 75 %).
Keyword**:** *dihydropyrimidin-2-one / thione, β- keto ester, Biginelli reaction, green acids, one pot synthesis.*

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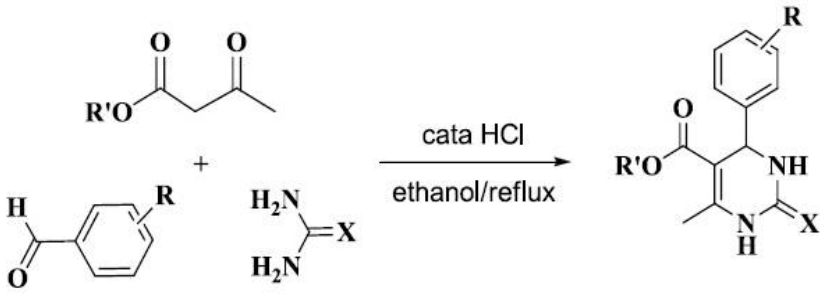
INTRODUCTION

Multi-component reactions are used for synthesis of large number of organic compounds. Multicomponent reactions have more importance in medicinal chemistry [1-5]. One of the most important Multicomponent reactions to synthesis dihydropyrimidin-2-one (DHPMs), is the Biginelli reaction which was pioneered by Pietro Biginelli in 1893 [6]. The Pietro Biginelli synthesized dihydropyrimidin-2-(1-H)-(thi)-one derivatives by using three component is aryl aldehyde, *β*- keto ester and urea or thio-urea under Bronsted acid catalysis condition. There are various reported methods to synthesized DHPM's. The dihydropyrimidin-2-one was synthesized by using green methods like solvent free and catalyst free protocol. DHPMs were synthesized by changing the mediums like conventional heating, microwave irradiation/ultrasound [7]. Recently the DHPMs have great attention in Advance synthetic organic chemistry due to its various applications in pharmaceutical industries and drug research field. The dihydropyrimidin-2-one exhibit different properties such as antibacterial [8,9], anti-inflammatory [9], antiviral [10], antitumor [11], antimalarial agent [12], hypnotics, anticonvulsant, anti-thyroid, antihistaminic agents, antibiotics [13]. The classical Biginelli reaction requires more reaction time, use of sulphuric acid or conc. HCl in presence of ethanol as solvent and yields of the desired product was low in case of substituted aromatic and aliphatic Aldehyde. Therefore, the Biginelli reaction continues to attract the organic chemist to finding more easy, most economical, efficient and environmentally friendly protocol to synthesis of dihydropyrimidin-2-(1-H)-(thi)-one.



Scheme 1: Reported

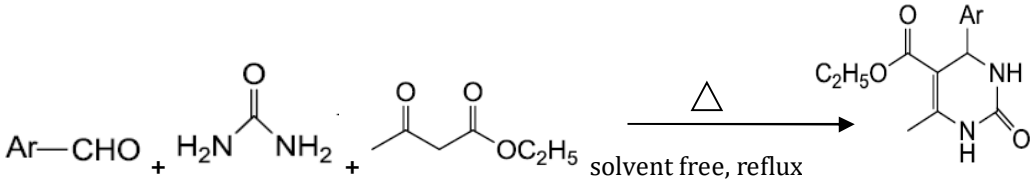
The recent environmental concerns we developed the most economical efficient and environmental friendly protocol for the synthesis of dihydropyrimidin-2-one and corresponding dihydropyrimidin-thione by using different acids such as Tartaric acid, Citric acid under catalyst free condition. In reported work, Hydrochloric acid and sulphuric acid are used. According to the Hazards Statements [14], Hydrochloric acid causes severe skin burns and eye damage (H 314) and may cause respiratory irritation (H 335). We developed green route to synthesized dihydropyrimidin-2-one/ thione by using Conc. Green acid such as Tartaric acid and Citric acid instead of Hydrochloric acid. This protocol becomes a Green approach to synthesis of dihydropyrimidin-2-one/ thione which is a key important of this work.

MATERIAL AND METHODES

All reagents were purchased from commercial sources and used as received, unless otherwise indicated. Thin-layer chromatography (TLC) was performed on silica coated glass plate with detection by UV light.^{1}H NMR spectra were recorded with tetramethylsilane as the internal standard. ^{1}H NMR spectra were recorded at 400MHz on bruker. Chemical shift (delta) is reported in ppm downfield from Chloroform (delta = 7.26 ppm) for ^{1}H NMR. For ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s =singlet, d = doublet, t = triplet, q = quartet, m = multiplet) coupling constant (J) are given in Hz. The IR spectra were obtained on lambda scientific FTIR-7600 spectrophotometer using potassium bromide pellets. Melting points were recorded on Digital Melting Point Apparatus (Systronics EQ730).

MODIFIED PROTOCOL FOR SYNTHESIS OF DIHYDROPYRIMIDIN-2-(1-H)-ONE/THIONE:

A round bottom flask charge with mixture of aldehyde (0.02 mol), Ethylacetoacetate (0.02 mol, 2.6 gram), urea or thiourea (0.02 mol, 1.2 gram) and conc. solution of acid. The reaction mixture was then heated under reflux in oil bath for appropriate time. After completion of reaction as indicated by TLC, the reaction mixture was poured in crushed ice (30 gram) and stirred for 5 - 10 minutes. The solid separated, was filtered under suction, washed with ice cold water (50ml), and then recrystallize with ethanol to get pure product.



Reaction Scheme 2: Synthetic pathway to produce Dihydropyrimidin-2-(1-H)-one/thione.

Table 1: Comparative Study of Dihydropyrimidin-2-(1-H)-one/thione

Sr.No	Ar	X*	Citric Acid	Tartaric acid	Time (Min.)	M.P. (^{0}C)	Colour	Yield (%)
1a	C_6H_5	O	YES	-	50	206	Faint Yellow	88%
1b	C_6H_5	O	-	YES	52	204	Faint Yellow	87%
1c	C_6H_5	S	YES	-	55	198	Brown	86%
1d	C_6H_5	S	-	YES	55	200	Brown	88%
2a	(4-OH, 3-Ome) C_6H_5	O	YES	-	90-94	210	Orange	76%

2b	(4-OH, 3-Ome) C_6H_5	O	-	YES	90-94	198	Orange	78%
2c	(4-OH, 3-Ome) C_6H_5	S	YES	-	94-96	210	Dark Brown	77%
2d	(4-OH, 3-Ome) C_6H_5	S	-	YES	92-94	214	Dark Brown	76%
3a	(3-NO_2) C_6H_5	O	YES	-	45-48	218	Faint Yellow	88%
3b	(3-NO_2) C_6H_5	O	-	YES	44-48	214	Dark Yellow	84%
3c	(3-NO_2) C_6H_5	S	YES	-	46-50	222	Brown	82%
3d	(3-NO_2) C_6H_5	S	-	YES	48-50	220	Brown	84%

*** For Urea X = O & Thiourea X = S**

CHARACTERIZATIONS:

1a. Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate

IR (KBr, cm^{-1}): 3320, 3115, 2950, 1724, 1702, 1480, 1320 cm-1;

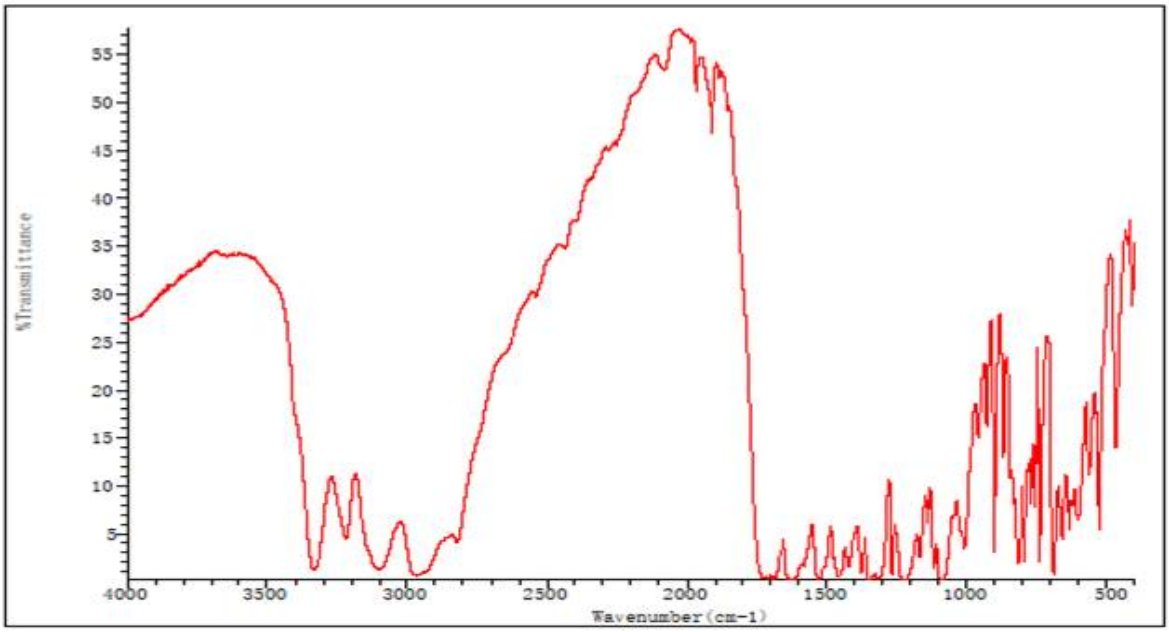


Fig 1: FTIR Spectrum

1H-NMR (400 MHz, $CDCl_3$ δ): 8.56 (s, 1H), 8.15 – 8.03 (m, 1H), 7.35 – 7.20 (m, 5H), 5.41 (d, *J* = 2.8 Hz, 1H), 4.07 (q, 2H), 2.36 (s, 3H), 1.16 (t, *J* = 7.1 Hz, 3H).

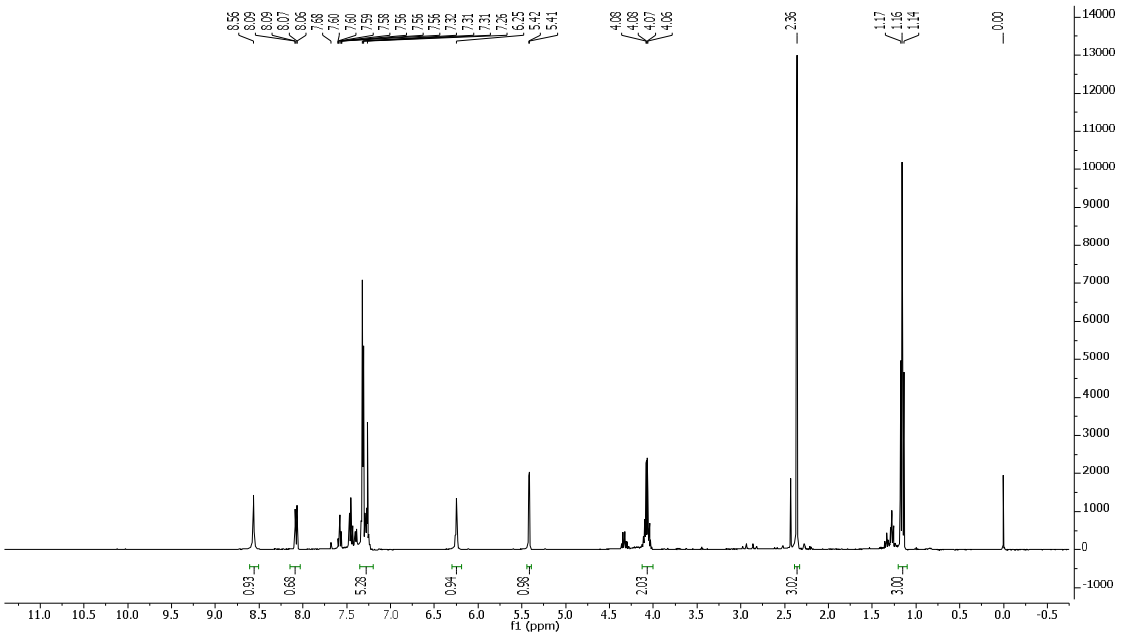


Fig 2:1H NMR Spectrum

1d. Ethyl 6-methyl-2-thio-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate

IR (KBr, cm^{-1}): 3230, 2980, 2920, 1715, 1535, 1090, 1030 cm-1.

1H-NMR (400 MHz, $CDCl_3$ δ): 8.5 (s, 1H), 8.20-8.12 (s, 1H), 7.40 – 7.22 (m, 5H), 5.41 (d, 1H), 4.09 (q, 2H), 2.46 (s, 3H), 1.20 (t, 3H).

RESULT AND DISCUSSION

This is a modified protocol for synthesis of Dihydropyrimidin-2-(1-H)-one/thione. The key point of this reaction is the use of citric acid and tartaric acid as a green acid. In this protocol there is also another important change in reaction procedure such as aldehyde, *β*- keto ester, urea or thiourea and green acids are reflux in oil bath. This procedure requires very less reaction time as compared to reported work. In reported work there is use of hydrochloric acid, various catalysts and solvent which is hazardous to environment as well as living organisms.

In table 1, there are three different aldehydes **(-Ar)** are used such as simple benzaldehyde (1a-1d), 4-hydroxy-3-methoxy benzaldehyde (2a-2d) and 3- nitro benzaldehyde (3a-3d). These protocols are studied with urea or thiourea and green acids in reflux condition. The green acids, citric acid and tartaric acid give satisfactory result. The results indicate that, reactions 2a-2d requires more time for completion as well as its yield is less, this happens due to electron donating groups 'OH' and 'Ome' are attached to ring while reactions 3a-3d completed with less time with very good yield as compared to reactions 2a-2d because electron withdrawing 'nitro' group present at meta position. The reaction 1a-1d also show good yield in less reaction time as compared to reactions 2a-2d. The product Dihydropyrimidin-2-(1-H)-one/thione were confirmed based on TLC, Melting point, FTIR, ^{1}H-NMR data.

CONCLUSION

In conclusion, we developed the easy, most economical, efficient green protocol and observed that the reactions underwent very smoothly to furnish the Dihydropyrimidin-2-(1-H)-one/thione product with very good yield in short reaction time.

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