Heterocyclic Letters
Vol. 5 | No.4|667-671| Aug-Oct| 2015
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

EFFICIENT GREEN METHODOLOGY REPORTED FOR THE BIGINELLI REACTION

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Abstract:
The 3,4-Dihydropyrimidin-2(1*H*)-ones/-thiones and their derivatives were synthesized in an excellent yields via the Biginelli reaction in the presence of catalytic amount of inexpensive, readily available and non-toxic inorganic acid in aqueous medium. The products were obtained in short reaction time without using flash chromatography.

Keywords: 3,4-Dihydropyrimidin-2(1*H*)-ones/-thiones; β-Ketoester; catalysis; green chemistry

Introduction

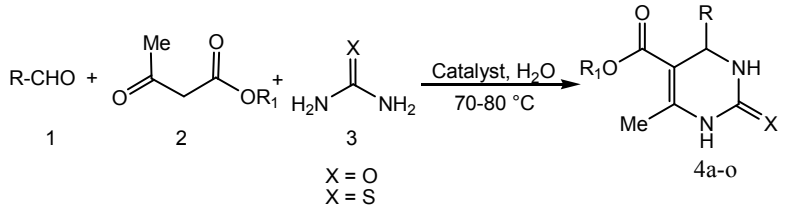
In 1893, the Italian chemist Pietro Biginelli reported cyclocondensation of ethyl acetoacetate, urea, and aryl aldehyde in the presence of an acid, furnishing 3,4-dihydropyrimidin-2(*1H*)-ones (DHPMs or Biginelli adducts) as products.[1] This approach is known as Biginelli reaction or Biginelli condensation.[2] The Biginelli reaction, a multicomponent one pot reaction (MCR), is a very attractive tool to obtain complex molecules. Compounds bearing a DHPM moiety have shown antitumor, antiviral, antibacterial, and anti-inflammatory biological activities[3,4]. Alkaloids e.g. Batzalladine found in marine sources containing a dihydropyrimidinone core, exhibit significant HIVgp-120-CD4 inhibitor activity.[5] Therefore, the synthesis of these privileged scaffolds by using convenient, green chemistry procedure is of primary concern.

The synthesis of these heterocyclic systems involves a three-component coupling of aromatic aldehyde, urea or thiourea and β-keto esters. Noteworthy modifications in the synthetic protocol were also carried out to produce DHMPs in excellent yields. Most of these procedures made use of diverse catalysts like heteropolyacids,[6] praseodymium methanesulfonate,[7] L-proline,[8] $CuCl_2$-H_2O,[9] chloroacetic acid,[10] H_2SO_4,[11] BF_3.EtOH-CuCl,[12] [Hmim]HSO_4-$NaNO_3$,[13] $LaCl_3$.$7H_2O$, HCl,[14] $CeCl_3$-$7H_2O$,[15] $InCl_3$,[16] $BiCl_3$,[17] $Cu(OTf)_2$,[18] TMSCl,[19] $SmCl_3$.$6H_2O$,[20] LiBr,[21] $InBr_3$,[22] phenyl pyruvic acid,[23] $FeCl_3$.$6H_2O$-HCl,[24] TMSI[25] and $CdCl_2$.[26] All these methodologies have some drawbacks like prolonged reaction time, tedious workup, and formation of unavoidable side products. In the light of said issues, the development of an eco-friendly reagent system is highly desirable.

In the recent year, inorganic acid has gained special attention as a catalyst in organic synthesis because of many advantages such as excellent solubility in water, non-toxic, easy to handling, inexpensive, eco-friendly nature, readily available and good reactivity as compared

to organic solvents. In the last decade, synthetically useful organic transformation using inorganic acid, as a catalyst, has been reported in the literature.[27]

The critical role of inorganic acid in organic synthesis and our earlier results,[28] inspired us to examine the catalytic scope of inorganic acid in the synthesis of 3,4-dihydropyrimidine-2-(1*H*)-ones/thiones. Herein, we report the high yield synthesis of 3,4-dihydropyrimidine-2-(1*H*)-ones/thiones by making use of inorganic acid as catalysts in aqueous medium (**Scheme 1**).



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

Results and Discussion

A inorganic acid was synthesized following a known procedure[27] with minor modification. The synthesized acid was characterized by DTA/TGA analysis and FT-IR spectral studies.

In order to optimize the product distribution at different temperature the acid was primarily screened under a variety of experimental conditions. Initially, equimolar amounts (1 mmol) of aldehyde ethyl acetoacetate or acetylacetone and urea / thiourea in aqueous medium were taken in a round-bottomed flask. The reaction mixture was stirred under reflux conditions. A catalytic amount of acid (50 mg) was added to the solution. After 1 h, TLC of the crude reaction mixture indicated the complete consumption of starting material with the formation of **4** in 80 % yield. Prolonging the reaction time did not offer any noteworthy advantage. In order to improve the yields, we performed reactions using different quantities of reagents. The best results were obtained with 1:1:1.5 ratio of aldehyde, 1,3-dicarbonyl compound and urea or thiourea with 100 mg acid catalyst at 80 °C for 30 min in aqueous medium. The acid in higher amount did not improve the result upto a greater extent. After completion of the reaction, as indicated by TLC, the reaction mixture was poured onto the crushed ice from which the 3,4-dihydropyrimidin-2(1*H*)-ones/-thiones were isolated by filtration and recrystallized using ethanol.

The 3,4-dihydropyrimidin-2(1*H*)-ones/-thiones were synthesized by multicomponent one pot cyclocondensation of aldehyde, β keto esters and urea/thiourea catalyzed by acid in good to excellent yields (Table 2). The mixture was stirring at 80 °C temperature for appropriate time given in table 2 and the product was isolated by filtration. However, 5-10 % product formation was observed in absence of acid at prolong reaction time. The structures of compounds (4a-4n) were confirmed by ^{1}H NMR and ^{13}C NMR spectroscopic data.

The results obtained with inorganic acid prompted us to further investigate the effect of solvents on Biginelli reactions. Water was found to be the best solvent, followed by ethanol, methanol, DMSO, and acetonitrile. Initially, acetonitrile, a solvent commonly used in Biginelli reactions, provided poor yields. Tetrahydrofuran and hexane are not suitable solvents for the Biginelli reaction. Water accelerates the rate of reaction due to its polar and protic nature (**Table 1**).

Table 1: Effect of solvent on the synthesis of 3,4-dihydropyrimidine-2(1H)-ones[a]

Entry	Solvent	Temp (°C)	Yield[b]
1	Water	80	92
2	C_2H_5OH	70	80
3	CH_3OH	40	60
4	CH_3CN	75	40
5	$CHCl_3$	60	35
6	DMSO	120	70
7	THF	55	20
8	Hexane	55	20
9	-	100	20

[a]Reaction condition: benzaldehyde (1 mmol), ethylacetoacetate (1 mmol), urea (1.5 mmol) acid (100 mg), solvent: 5 mL, time: 30 min, temp.: 80 °C. [b]Isolated yield.

The results shown in Table 1 indicate that the water is the most efficient reaction medium for inorganic acid. With respect to the appealing results obtained from the catalyst and solvent screening, we framed the general protocol for the synthesis of 3,4-dihydropyrimidine- 2(1*H*)-one/thione by treating several aromatic aldehydes and β-keto esters with urea or thiourea using inorganic acid in aqueous medium (**Table 2**).

Table 2: Synthesis of 3,4-dihydropyrimidine-2-one/thione in water[a]

Entry	Compound	R	R_1	X	Time (min)	Yield[b] (%)
1	4a	C_6H_5	C_2H_5	O	30	92
2	4b	4-$CH_3C_6H_4$	C_2H_5	O	30	86
3	4c	2-$NO_2C_6H_4$	C_2H_5	O	40	82
4	4d	4-OHC_6H_4	C_2H_5	O	40	84
5	4e	4-$COOHC_6H_4$	C_2H_5	O	30	94
6	4f	4-$OCH_3C_6H_4$	C_2H_5	O	30	86
7	4g	4-$C(CH_3)_3C_6H_4$	C_2H_5	O	30	89
8	4h	C_6H_5	C_2H_5	S	40	94
9	4i	4-$CH_3C_6H_4$	C_2H_5	S	40	90
0	4j	2-$NO_2C_6H_4$	C_2H_5	S	30	89
11	4k	4-OHC_6H_4	CH_3	O	30	90
12	4l	4-$COOHC_6H_4$	CH_3	S	40	99
13	4m	4-$OCH_3C_6H_4$	CH_3	O	30	92
14	4n	4-$C(CH_3)_3C_6H_4$	CH_3	O	30	96
15	4o	3-$NO_2C_6H_4$	C_2H_5	O	30	80

[a]All products were characterized by FT-IR, ^{1}H NMR and their melting points in comparison with that of previous literatures temp.: 80 °C; [b]Isolated yield

This method not only preserved the simplicity of Biginelli's one-pot condensation but also remarkably improved the yields (>99%) of dihydropyrimidinones in short reaction time (30-40 min) as compared to the longer reaction time reported for other catalysts after the addition of low catalyst concentration.

In general, the reaction works best with aromatic aldehydes. These can be substituted in the *o-, m-* or *p* position with either electron-withdrawing or donating groups. Good yields are usually obtained with *p*-substituted aromatic aldehydes carrying electron-withdrawing

substituents. For *o*-substituted benzaldehydes having bulky substituents, yields can be significantly lower.

Conclusion

We have developed a convenient, and clean protocol for the synthesis of 3,4-dihydropyrimidine-2(1*H*)-ones/thiones (DHPMs).The high yield, operational simplicity, easy availability and low cost of the reagents makes the procedure scientifically more attractive as compared to existing procedures.

Acknowledgments

The authors are thankful to the University Grant Commission (UGC) and the Department of Science and Technology (DST), New Delhi, for the financial assistance.

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Received on May 23, 2015.