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4-Sulfobenzoic Acid as an Efficient Catalyst for the Preparation of 3,4-dihydropyrimidin-2-(1H)-ones Under Solvent-free Conditions

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Abstract

In this research, one-pot three-component synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones have been developed using Biginelli reaction from the interaction between ethyl/methyl acetoacetate, aromatic aldehydes, and urea/thiourea in the presence of 4-sulfobenzoic acid as a new, effective, inexpensive, and available bronsted acid. Avoidance of toxic and dangerous solvents, easy isolation of products without the need of column chromatography, high yields, and short reaction time are some important features of the present method.

Keywords: *3,4-dihydropyrimidin-2-(1H)-one, 4-sulfobenzoic acid, one-pot, solvent-free*.

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Introduction

One of the important points in the gamut of organic synthesis is the preparation of complex compounds from simple, inexpensive, and available materials. In this regard, one-pot multicomponent reactions appeared as a prominent synthetic method for the synthesis of products with high selectivity from the condensation of three or more reactants in a single reaction flask [1-3]. On the other hand, the multicomponent reactions under solvent-free conditions are not only interest from view of environmental issues, but also present important advantages, including convenient separation of products, reducing the reaction time, increase in yields, and no need for column chromatography [4,5].

3,4-Dihydropyrimidin-2-(1*H*)-ones as N-fused heterocyclic compounds are abundant in the structure of alkaloid natural products [6,7]. Furthermore, these compounds constitute an important group of compounds with pharmaceutical properties including, antiviral [8], antibacterial, antifungal [9], anti-inflammatory [10], anticancer [11,12], and anti-hypertension [13] activities. Therefore, these compounds have found a valuable position in the drug discovery process. Some drug molecules, including pyrimidine structure are displayed in Figure 1 [14].

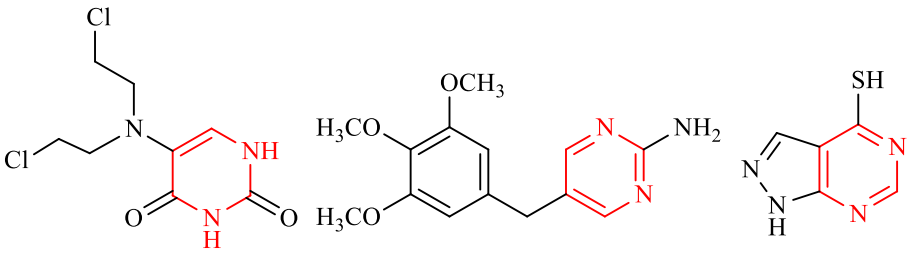
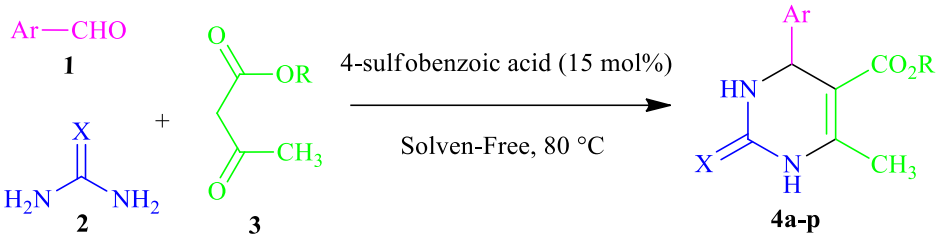


Figure 1. Some drugs containing pyrimidine structure.

Due to the foregoing biological significances of dihydropyrimidinemotifs, the synthesis of these compounds, especially using Biginelli reaction has attracted a great deal of attention. In recent years, various methods have been reported for synthesis3,4-dihydropyrimidin-2-(1*H*) -ones using catalytic systems, including Lewis and Bronsted acids such as calcium fluoride [15], β-cyclodextrine-propyl sulfonic acid [16], *p*-TSA [17], MoO_2Cl_2 [18], boric acid [19], zirconia sulfuric acid [20], Al_2O_3-$MeSO_3H$ [21], ionic liquids [22-24], GO-chitosan [25], and ultrasonic waves [26].

Development of new catalytic methods using organocatalysts or small metal-free organic molecules has attracted much attention in the field of pharmaceutical chemistry. Some advantages of these compounds are involved lack of insensitivity to humility and oxygen in the atmosphere, high selectivity and more safety due to non-toxic properties that result to be saved in energy, time, and costs as well as simplicity of operation and reduction of chemical wastes [27,28].

Accordingly, herein, we have developed a simple method for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones from the reaction of aromatic aldehydes **1**, urea/thiourea **2** and ethyl/methyl acetoacetate **3** using 4-sulfobenzoic acid as a new, inexpensive, and available organocatalyst under solvent-free conditions at 80 °C (Scheme1).



Scheme1. Synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one derivatives.

Experimental

General

Melting points and IR spectra of all compounds were measured with an Electrothermal 9100 apparatus and a JASCO FTIR 460 Plus spectrometer, respectively. The ^{1}H and ^{13}C NMR spectra were obtained on Bruker DRX-300 Avance instruments with DMSO-d6 as a solvent. Mass spectra were obtained on an Agilent Technology (HP) spectrometer operating at an ionization potential of 70 eV. All reagents and solvents obtained from Fluka and Merck were used without further purification.

General procedure for the synthesis of 3,4-dihydropyrimidin-2-(1H)-ones

The mixture of different aromatic aldehydes (1.0 mmol), urea/thiourea (1.5 mmol), ethyl/methyl acetoacetate (1.0 mmol), and 4-sulfobenzoic acid (15 mol %) was stirred under solvent-free conditions at 80° C. Progress of the reaction was monitored by thin layer chromatography (TLC). Then, the reaction mixture was cooled down to the room temperature. The solid precipitate was filtered off and washed with water. Water was evaporated to obtain 4-sulfobenzoic acid. Finally, the crude products were recrystallized from ethanol to give the pure products **4a–p**.

Characterization data of selected compounds

*Ethyl 6-methyl-2-oxo-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4e**):*

White solid; m.p: 204-206°C; IR (KBr): 3245 (N–H), 3117 (N–H), 2980 (CH), 2932 (CH), 1722 (CO_2), 1704 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d6, 300 MHz): δ1.21 (3H, t, J = 6.9 Hz, CH_3CH_2), 2.25

(3H, s, CH_3), 2.27 (3H, s, CH_3), 3.99 (2H, q, *J* = 6.9 Hz, CH_2O), 5.12 (1H, d, *J* = 3.3 Hz, CH), 7.13 (4H, s, ArH), 7.70 and 9.17 (2H, 2s, 2NH).

Ethyl 4-(4-(dimethylamino)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate ***(4j)****:*

White solid; m.p: 248-251°C; IR (KBr): 3244 (N–H), 3115 (N–H), 2977 (CH), 2931 (CH), 1720 (CO_2), 1703 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d6, 300 MHz): δ 1.13 (3H, t, *J* = 7.2 Hz, CH_3CH_2), 2.25 (3H, s, CH_3), 2.86 (6H, s, $2CH_3$), 4 (2H, q, *J* = 4.2 Hz, CH_2O), 5.06 (1H, d, *J* = 3 Hz, CH), 6.67 (2H, d, *J* = 8.7 Hz, ArH), 7.6 (2H, d, *J* = 8.7 Hz, ArH), 7.61 and 9.11 (2H, 2s, 2NH).

Ethyl 4-(4-hydroxy-3-methoxy-5-nitrophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate ***(4o)****:*

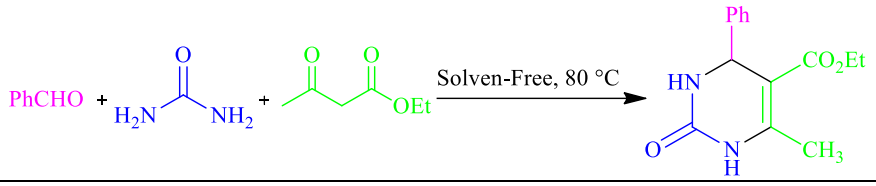
Yellow solid;m.p:214-218°C; ^{1}H NMR (DMSO-d6, 300 MHz): δ1.13 (3H, t, *J* = 7.2 Hz, CH_3CH_2), 2.26 (3H, s, CH_3), 3.8 (3H, s, CH_3) 4.04 (2H, m, CH_2O), 5.12 (1H, d, *J* = 2.7 Hz, CH), 7.17 (1H, s, ArH), 7.26 (1H, s, ArH), 7.83 and 9.31 (2H, 2s, 2NH), 10.43 (1H, s, OH). ^{13}C-NMR (DMSO-d6, 75.6 MHz): δ 14.5, 18.3, 53.6, 56.9, 57.1, 59.8, 98.8, 113.3, 115.0, 135.8, 137.0, 142.4, 149.5, 149.9, 152.4, 160.1, 165.6, 190.8. MS m/z (%): 134.1 (100), 274.2 (82), 282.2 (36), 304.3 (63),352 (M+1, 8).

Ethyl 4-(2,4-dimethoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate ***(4p)****:*White solid;m.p:210-212°C; ^{1}H NMR (DMSO-d6, 300 MHz): δ 1.06 (3H, t, *J* = 6.9 Hz, CH3CH2), 2.28 (3H, s, CH_3), 3.74 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.9 (2H, m, CH_2O), 5.42 (1H, d, *J* = 3 Hz, CH), 6.4 (1H, m, ArH), 6.5 (1H, d, *J* = 2.4 Hz, ArH), 6.9 (1H, d, *J* = 8.4 Hz, ArH), 7.22 and 9.1 (2H, 2s, 2NH); ^{13}C-NMR (DMSO-d6, 75.6 MHz): δ 14.5, 18.1, 48.9, 55.625, 55.8, 59.4, 98.3, 98.8, 104.8, 124.6, 128.2, 149.0, 152.7, 158.0, 160.3, 165.8. MS m/z (%): 134.1 (16), 274.2 (100), 304.2 (25), 318.3 (18), 321.2 (M+1, 34).

Results and discussion

To achieve optimal conditions, the reaction of benzaldehyde, ethyl acetoacetate, and urea was chosen as the model reaction and the effect of temperature and amount of catalyst was examined under solvent-free conditions. First, the effect of amount of catalyst was envisaged and the results were summarized in Table 1. The best result obtained in the presence of 15 % mol of 4-sulfobenzoic acid (Table 1, entry 3). Furthermore, in the absence of the catalyst, desirable product was not observed (Table 1, entry 1).

Table 1. Optimizing the amount of catalyst in the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one .

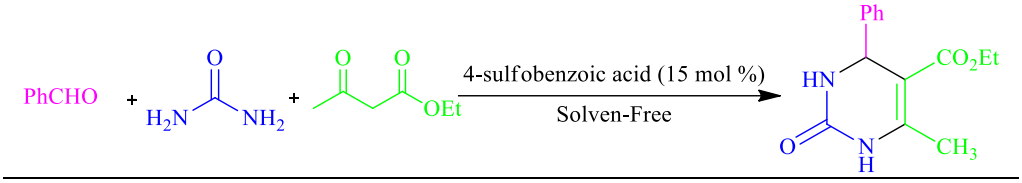


Entry	Catalyst (mol%)	Time(min)	Yield (%)[a]
1	-	540	-
2	10	15	79
3	**15**	**9**	**94**
4	20	9	92
5	25	7	86

[a] The yield of the isolated product

Next, the effect of different temperatures on the model reaction was investigated (Table 2) and the results were summarized in Table 2. It was found that 80 °C is an efficient temperature (Table 2, Entry 4).

Table 2. Optimizing the temperature for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones in the presence of 15mol% of the catalyst.



Entry	Temperature (°C)	Time(min)	Yield (%)[a]
1	r.t [b]	120	-
2	40	60	59
3	60	30	71
4	**80**	**9**	**94**
5	100	8	95

[a] The yield of the isolated product
[b] room temprature

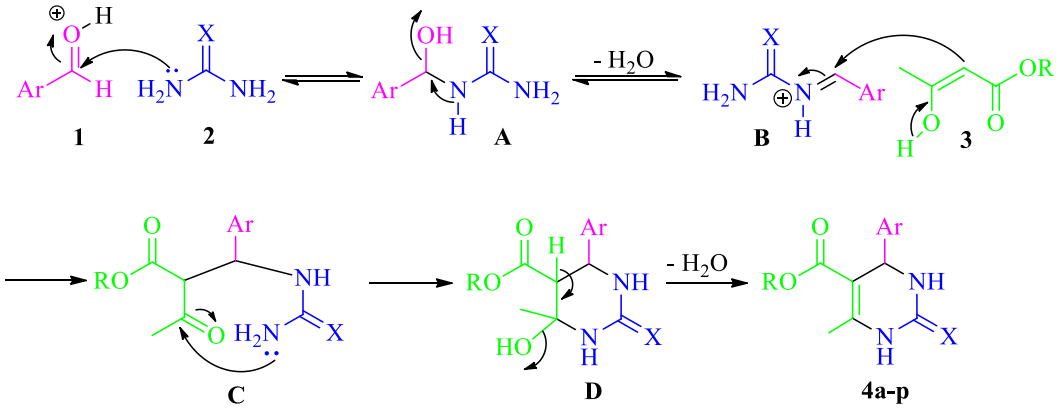
After determining the optimal conditions, to evaluate the range of this strategy, a set of different aromatic aldehydes including electron-donating and electron-withdrawing groups, urea or thiourea, and ethyl or methyl acetoacetate was applied to form 3,4-dihydropyrimidin-2-(1*H*)-one derivatives. As shown in Table 3, the substitution of the aldehyde group has any significant effect on the progress of the reaction.

Table 3. Preparation of 3,4-dihydropyrimidin-2-(1*H*)-ones.

Entry	Ar	R	X	Product	Time(min)	Yiled (%)	Melting points	
							Found	Reported [Ref]
1	H	C_2H_5	O	**4a**	9	94	202-203	203-205 [29]
2	4-OCH_3	C_2H_5	O	**4b**	11	89	199-201	200 -202 [29]
3	4-NO_2	C_2H_5	O	**4c**	5	94	205-207	206-207 [29]
4	4-F	C_2H_5	O	**4d**	12	93	184-186	186-188 [30]
5	4-CH_3	C_2H_5	O	**4e**	8	91	204-206	204-205 [31]
6	2-Cl	C_2H_5	O	**4f**	5	93	217-219	215-216 [32]
7	4-OH	C_2H_5	O	**4g**	20	94	227-229	225-228 [29]
8	H	C_2H_5	S	**4h**	15	84	206-208	208-209 [33]
9	3-OCH_3	C_2H_5	O	**4i**	7	93	210-212	207-208 [32]
10	4-$N(CH_3)_2$	C_2H_5	O	**4j**	8	94	248-251	255-257 [33]
11	4-Br	C_2H_5	O	**4k**	5	92	213-215	216-218 [34]
12	3-NO_2	C_2H_5	O	**4l**	13	91	226-228	225-227 [30]
13	4-Cl	C_2H_5	O	**4m**	12	90	206-208	207-210 [30]
14	4-OH	CH_3	O	**4n**	8	93	245-247	245-246 [31]
15	4-OH-3-OCH_3-5-NO_2	C_2H_5	O	**4o**	8	89	214-218	This work
16	2,4-di-OCH_3	C_2H_5	O	**4p**	13	94	210-212	This work

[a] The yield of the isolated product

The proposed mechanism for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones in the presence of 4-sulfobenzoic acid has been demonstrated in Scheme 2. First, aldehyde transports to an active electrophileby the proton from 4-sulfobenzoic acid, which is attacked by the nucleophile (urea or thiourea) to create intermediate **A** (N-Asiliminum). This intermediate undergoes the removal of water and intermediate **B** (Iminium) is produced, which acts as the electrophile in enhancing the nucleophile of enol β- ketoester to give intermediate **C**. Finally, intermediate **C** undergoes intramolecular cycloaddition with the elimination of one H_2O molecule to afford 3,4-dihydropyrimidin-2-(1*H*)-ones **4a-p**.



Scheme 2. The proposed mechanism for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones.

In order to demonstrate the elegant properties of our research, we have compared our result achieved from the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones with the known data from the other literature. As shown in Table 4, no use of any transition metal catalysts, high yields of products, short reaction time, no use of any hazardous solvent and utilizing 4-sulfobenzoic acid as new, economical, and commercially available catalyst makes this route as a useful strategy for the synthesis of this library of compounds.

Table 4. Comparison of the results afforded for the model reactionin the presence of tannic 4-sulfobenzoic acid with some that obtained via other catalysts.

Entry	Catalyst	Time	Reaction conditions	Yield (%)	Reported[Ref]
1	Calcium fluoride	2h	EtOH/Reflux	98	[15]
2	β-CD-PSA	20 min	Solvent-free/80 °C	91	[16]
3	MoO_2Cl_2	1h	EtOH/Reflux	95	[18]
4	$[Et_3N–SO_3H]HSO_4$	40 min	Solvent free/70 °C	98	[22]
5	GO-chitosan	10 min	Solvent free/110 °C	86	[25]
6	Amberlyst-70	3h	H_2O/90 °C	81	[35]
7	$Ce(C_{12}H_{25}SO_3)_3$	8h	EtOH/80 °C	93	[36]
8	Carbon-SO_3H	4h	CH_3CN/80° C	90	[37]
9	SBNPSA	3-4h	EtOH/Reflux	95	[38]
10	Sulfated polyborate	20 min	Solvent free/100 °C	94	[39]
11	Sulfated silica tungsten acid	15 min	Solvent free/70 °C	94	[40]
12	Dendrimer-PWA^n	10 min	Ultrasonic/EtOH/50 °C	97	[41]
13	GO-PO_3H_2	4 min	Microwave (70 W)	4	[42]
14	4-sulfobenzoic acid	9 min	Solvent free/80 °C	94	This work

The reusability of 4-sulfobenzoic acid was examined in the synthesis of **4a** as an example. It was observed that the yield of product reduced in the 3rd and 4th runs.

Conclusion

In summary, we reported an efficient strategy for the synthesis of 3,4-dihydropyrimidin-2-(1*H*) -ones using Biginelli reaction in the presence of 4-sulfobenzoic acid as a catalyst under solvent-free conditions. 4-Sulfobenzoic acid as an inexpensive, available, and effective catalyst facilitated one-pot three-component condensation of aldehydes, urea/thiourea, and ethyl/methyl acetoacetate. High yield of products, short reaction time, simplicity of operation and comfortable purification are the outstanding advantages of this methodology.

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