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O-SULFANILIC ACID AS A NEW CATALYST FOR BIGINELLI TYPE COMPOUNDS UNDER SOLVENT-FREE CONDITIONS

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Abstract :
Biginelli derivatives (3,4-Dihydropyrimidin-2(1H)-ones/thiones) were synthesized by three component cyclocondensation of ethylacetoacetate, arylaldehydes, urea and thiourea under solvent-free conditions and using *o*-Sulfanilic acid as catalyst. The protocol is featured by high yields, easy workup, short reaction time and solvent-free conditions.

Keywords: *o*-Sulfanilic acid; Dihydropyrimidinones; Dihydropyrimidinthiones; Solvent-free.

Introduction:

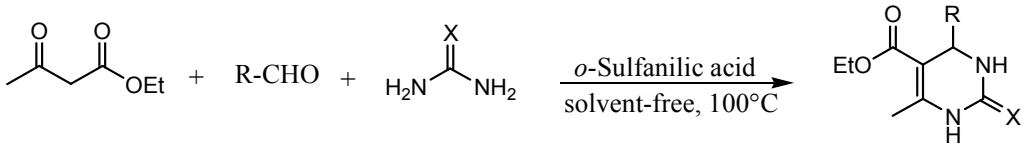
In 1893, Biginelli[1] synthesized for the first time the so called 3,4-Dihydropyrimidin-2(1H)-ones compounds by reacting together in one-pot using ethylacetoacetate with aromatic aldehydes and urea. This type of reaction belongs to the category of MRC (Multi-Component Reactions) which have an increasing importance in pharmaceuticals. These Biginelli compounds have attracted much more attention of organic chemists because of their pharmacological and biological properties such as antibacterial[2], antifungal[3]antiviral [4],anticancer[5], anti-inflammatory[6], antitumor[7], antihypertensive[8], calcium channel inhibitor[9], antioxidant[10].

Many synthetic protocols have been used to improve the preparation of Biginelli derivatives (DHMP'S) by using different types of catalysts such as $CdCl_2$[11], NH_4Cl[12], HCOOH [13], HCl/EtOH[14], $TaBr_5$[15], L-ascorbic acid [16], $ZrCl_4$[17], $Fe(OTs)_3$[18], CaF_2[19], $NaIO_4$[20], $Fe(OTf)_3$[21], $Y(NO_3)_3.6H_2O$[22], $LaCl_3/ClCH_2COOH$[23], $AlCl_3.6H_2O$[24], *p*-TsOH [25],$HmimHSO_4$-$NaNO_3$[26], $ClSO_3H$ [27],SiO_2.TTC[28],$LaCl_3$-GRAPHITE[29],$H_4PMo_{11}VO_{40}$[30],$Bi(NO_3)_3$[31],Nebivolol nanoparticles[32], $CaBr_2$[33],$InBr_3$[34],$FeCl_3.6H_2O$/TMSBr[35], Granite or quartz[36],Mg/Fe hydrotalcite[37], DBSA [38],$NaHSO_4$-Red Sea Sand[39], Cl_3CCOOH [40],lime juice[41], Melamine trisulfonic acid[42],as well as the use of ultrasound and microwave irradiation[43].

Most of the presented catalysed reaction conditions suffer from the use of expensive reagents, long reaction times, toxic solvents, strong acidic conditions and low yields.

In this work, we report our results for the synthesis of some DHPM's by one-pot three component cyclocondensation reaction of ethylacetoacetate, aromatic aldehyde and urea using *o*-Sulfanilic acid as a catalyst under solvent-free conditions.

Therefore, the search for more efficient procedures to prepare DHMP's is still being of big interest. Many catalysts have been used to develop this type of reactions under mild conditions. Some catalysts like *p*-aminobenzene sulfonic acid [44], N-alkylated sulfamic acid [45], sulfamic acid or silica sulfiric acid [46] have been utilized to synthesise these DHMP's. For this, we found it worth evaluating the effectiveness to use *o*-Sulfanilic acid as catalyst in Biginelli type reaction.



X = O,S 1 2 3 (a-l)

Scheme1 Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones/thiones

Results and discussion

To investigate the reaction conditions, the reaction of benzaldehyde, ethylacetoacetate and urea was used as a model reaction. The amount of the catalyst affects mainly the efficiency of the reaction. We note that no product was obtained even after 60 min which indicates that the use of the catalyst is necessary for the reaction. Our reactions were carried out under solvent-free conditions. The results (**table1**) show that the use of 20% of catalyst referring to benzaldehyde at 100°C is the most efficient and the yield obtained was 91% with a 1:1:2:0.2 of benzaldehyde, ethylacetoacetate, urea and *o*-Sulfanilic acid for 15 min under solvent-free conditions (**scheme1**).

Table1: Reaction of benzaldehyde, ethyl acetoacetate and urea (1:1:2) under solvent-free

Entry	Cat. (mol%)	Time (min)	Temperature (°C)	Yield (%)
1	10	30	80	72
2	20	26	80	80
3	30	22	80	89
4	**20**	**15**	**100**	**91**

Cat: *o*-Sulfanilic acid

In a typical way, different aromatic aldehydes carrying electron-withdrawing or electron-donating substituents have been used to produce the corresponding 3,4-Dihydropyrimidin-2(1H)-ones in good yields (table2). The use of thiourea instead of urea gave the corresponding thiones derivatives of 3,4-dihydropyrimidinones in good yields. In this method we use low cost reagents affording different Biginelli products in high yields and short times.

Table 2: *o*-Sulfanilic acid catalyzed synthesis of 3,4-dihydropyrimidin-2(1H)-ones/-thiones under solvent-free at 100 °C.

Compounds	R	X	Time (min)	Yield (%)	mp(°C, found)	mp(°C,lit) [ref]
3a	C_6H_5	O	15	91	204-206	206-208 [47]

3b	2-ClC_6H_4	O	18	87	215-217	216-218	[48]
3c	4-BrC_6H_4	O	20	89	213-215	212-214	[40]
3d	2-$NO_2C_6H_4$	O	21	79	203-205	205-207	[48]
3e	4-$OCH_3C_6H_4$	O	22	88	200-202	203-205	[47]
3f	2-OHC_6H_4	O	18	89	201-203	199-201	[49]
3g	4-$CH_3C_6H_4$	O	23	90	210-212	213-215	[40]
3h	$CH=CHC_6H_5$	O	23	87	223-225	225-227	[40]
3i	C_6H_5	S	25	89	205-207	208-210	[49]
3j	2-ClC_6H_4	S	28	85	215-217	216-218	[50]
3k	4-$OCH_3C_6H_4$	S	26	84	148-150	150-152	[47]
3l	2-OHC_6H_4	S	24	87	218-220	220-222	[49]

Experimental section

All the chemicals were purchased from MERCK and used as received. Melting points of the synthesized products compounds were measured using Kofler melting point apparatus and are uncorrected. The purity of the compounds was confirmed by TLC using silica gel plates with ethyl acetoacetate and petroleum ether (1:1) as eluent. IR spectra were obtained on a Shimadzu Spectrometer IR-435 using KBR disk. The ^{1}HNMR were recorded on Brucker 300 MHz in DMSO-*d*6/$CDCL_3$.

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

Aromatic aldehyde (1mmol), ethylacetoacetate (1mmol), Urea or thiourea (2mmol), and *o*-Sulfanilic acid (20mol%) were taken in a round bottom flask and contents were heated on oil bath at 100°C for the indicated time in table. the progress of reactions was monitored by TLC. After completion of the reaction, a solid was obtained and the mixture was cooled to room temperature. The product so formed was separated by filtration and recrystallized using ethanol.

Selected Physical and Spectral Data

***Ethyl 6-methyl-2-oxo-4-(2-chlorophenyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate*(3b):**
m.p. 215–217°C; IR (KBr) ν = 3353, 3235, 3117, 2978, 1697, 1644 cm^{-1}; ^{1}H NMR (DMSO-*d*6, 300 MHz): δ 9.28 (s, 1H, NH), 7.71 (s, 1H, NH), 7.22–7.46 (m, 4H , Ar), 5.62 (d, *J*=2.68, 1H, CH), 3.91 (q, *J*= 7.05 Hz, 2H, CH_2), 2.30 (s, 3H, CH_3), 1.01 (t, *J*= 7.1 Hz, 3H, CH_3).

***Ethyl 6-methyl-2-oxo-4-(4-bromophenyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate*(3c):**
m.p. 213–215°C; IR (KBr) ν = 3429, 3260, 3130, 2980, 1700, 1647, 1458 cm^{-1}; ^{1}H NMR (DMSO-*d*6, 300 MHz): δ 9.33 (s, 1H, NH), 7.80 (s, H, NH), 7.53 (d, *J*= 8.40 Hz, 2H, Ar), 7.20 (d, *J*= 8.41 Hz, 2H, Ar), 5.14 (d, *J*= 3 .15 Hz, 1H, CH), 3.98 (q, *J*= 7.08 Hz, 2H, CH_2), 2.23 (s, 3H, CH_3), 1 .09 (t, *J*= 7.1 Hz, 3H, CH_3).

***Ethyl 6-methyl-4-(2-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate*(3d):**
m.p. 203–205°C; IR (KBr): 3240, 3100, 1710, 1650 cm^{-1}; ^{1}H NMR (DMSO-*d*6, 300 MHz): δ 9.37 (s, 1H, NH), 7.66 (s, 1H, NH), 7.45–7.96 (m, 4H , Ar), 5.80 (d, *J* = 2.68, 1H, CH), 3.87 (q, *J* = 7.05 Hz, 2H, CH_2), 2.29 (s, 3H, CH_3), 0.96 (t, *J* = 7.1 Hz, 3H, CH_3).

***Ethyl 4-(2-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate*(3j):**
m.p. 215-217°C; IR (KBr) v = 3450, 3140, 2860, 1655, 1620, 1720, 1275 cm^{-1}; ^1H NMR (DMSO-*d*6, 300 MHz): δ 9.12 (s, 1H, NH), 7.69 (s, 1H, NH), 6.69–7.29 (m, 4H , Ar), 4.61 (d, J = 2.68, 1H, CH), 4.16 (q, J = 7.05 Hz, 2H, CH_2), 1.89 (s, 3H, CH_3), 1.18 (t, J = 7.1 Hz, 3H, CH_3).
***Ethyl 4-(2-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate*(3l):**
m.p. 218-220°C; IR (KBr) v = 3280–3080, 1722, 1600, 1501 cm^{-1}; ^1H NMR (DMSO-*d*6, 300 MHz): δ 8.39 (s, 1H, OH), 10.10 (s, 1H, NH), 9.53 (s, 1H, NH), 6.71–7.06 (m, 4H , Ar), 5.09 (d, J = 2.68, 1H, CH), 3.96 (q, J = 7.05 Hz, 2H, CH_2), 2.18 (s, 3H, CH_3), 1.18 (t, J = 7.1 Hz, 3H, CH_3).

Conclusion:

In conclusion, we have explored the use of *o*-Sulfanilic acid as catalyst for the synthesis of 3,4-Dihydropyrimidin-2(1H)-ones and their corresponding thiones. Their preparation has been performed at 100°C under solvent free conditions. This protocol presents the advantages of high yields, easy workup, short reaction time and solvent-free conditions.

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