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Microwave Assisted One Pot Synthesis of Substituted Dihydropyrimidine-2(1H) ones using 5-sulphosalicyclic acid as a Catalyst

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ABSTRACT

An efficient microwave assisted one pot synthesis of Dihydropyrimidine-2 (1H) from aldehydes, diketones and urea/thiourea using 5-sulphosalicylic acid as a catalyst is described, compared to classical Biginielli reaction the new method has advantage of good yield and short reaction time.

Keywords: One Pot Synthesis, Dihydropyrimidine-2 (1H) ones, 5-silphosalicylic acid

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INTRODUCTION

In recent years, dihydropyrimidine-2(1H)one derivatives have gained much interest for their biological and pharmaceuticals Properties such as HIV gp-120-CD4 inhibitors[1], calcium channel blockers[2], α-adrenergic and neuropeptide Y antagonists[3], as well as antihypertensive, antitumor, antibacterial, anti-inflammatory[4] agent. The scope of this pharmacophore has been further increased by the identification of the Monostrol as a novel as a cell-permeable lead compound for the development of the new anticancer drugs[5] bearing the dihydropyrimidones core. Thus the development of facile and environmental friendly synthetic method towards dihydropyrimidines constitute active area of investigation of in organic synthesis, the first synthetic method for the preparation of dihydropyrimidine-2(1H) ones (DHPMs) was recorded by Biginelli [6], that involves the one pot three component condensation of aldehyde, 1, 3-dicarbonyl compounds and urea or thiourea in ethanol under strongly acidic conditions producing DHPMs, albeit in low yields. In the view of the pharmaceuticals importance of these compounds many improved catalytic methods have been developed [7-11]. Although these methods have their long reaction time, harsh reaction conditions, unsatisfactory yield and use of large quantity of catalyst. Therefore improvements with respect to the above

have been continuously sought. In this paper we wish to report an efficient environment friendly procedure for the synthesis of DHPMs for aryl aldehyde using 5-sulphosalicyclic acid catalyst in microwave irradiation system.

Several catalysts like PPA, $AlCl_3$, H_3BO_3, conc., BF_3OEt, NH_4Cl, CAN, NBS, triflates of lanthanide compounds and In, Bi, Cu, along with microwave irradiation etc. have been tried[12-16] to improve yields and conditions of Biginelli reaction. However, all these several methods involving these various catalyst suffer from one or the other drawback like, expensive reagents i.e., triflates of Bi, Cu, lanthanides etc., prolonged reaction time, and strongly acidic conditions, unsatisfactory yields and tedious workup procedures (e.g. acidic alumina) for the isolation of the pure product in good yields. Catalysts like, ferric oxide nano composites is effective and give good result, but the preparation procedure of this catalyst is very difficult. This requires the development of a new catalyst for high yield and the lack of inexpensive reagent, which requires shorter reaction time and with easier workup procedure. In this paper we wish to report an efficient environment friendly procedure for the synthesis of DHPMs for aryl aldehyde using 5-sulphosalicyclic acid catalyst in microwave irradiation system.

MATERIALS AND METHODS

All reagents were purchased from Merck and Loba and used without further purification. Melting points were measured in open capillary and are uncorrected. The products were characterized by IR spectra, and ^{1}H NMR. IR spectra were recorded on SHIMADZU instrument. ^{1}H NMR was recorded on MSL-300 instrument using TMS as an internal standard. Microwave irradiation was carried out in a domestic microwave oven (LG Model MG 1742 WE, 2450 MHz).

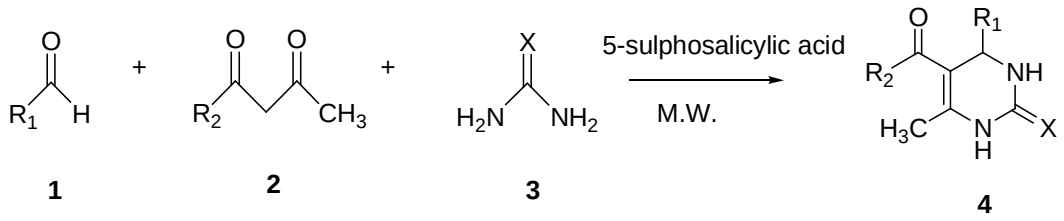
General Procedure

The mixture of an aldehyde (5mmoles), ethyl acetoacetate / acetyl acetone (6 mmoles), Urea/thiourea (10mmoles) and 5-silphosalicylic acid (0.164gm, 0.75mmol).mixed thoroughly in beaker and this reaction mixture were irradiated in microwave oven. Reaction was monitored by TLC After the completion of the reaction, the mixture was poured in water and crude product was collected as a precipitate and recrystallized by ethanol.

RESULTS AND DISCOSSION

The condensation of aldehydes, diketones and urea/thiourea (carrying both electron-withdrawing and electron-donating groups in aldehydes), in presence of 5-sulphosalicylic acid **as** a catalyst under solvent free conditions yielded desired Dihydropyrimidine-2 (1H) ones derivatives in purity with good to excellent yields. As expected, satisfactory results were observed. The reaction is depicted in scheme 1 and results are summarized in Table 1. It was found that 5-sulphosalicylic acid shows better catalytic activity.

SCHEME 1



1 **2** **3** **4**

R_1= Ar.

R_2= OEt,Me

X= O, S

Spectral Data

1)5-Ethoxycarbonyl-6-methyl-4-(phenyl)-3,4-dihydropyrimidin-2(1H)-one

^{1}H NMR ($CDCl_3$) : δ 1.09 (t ,3H ,CH_3), 2.24 (s ,3H ,CH_3), 3.94 (q,2H, CH_3), 5.09 (d, 1H, CH), 9.14 (brs, 1H, NH), 7.69 (brs, 1H, NH), 7.1-7.29 (m, 5H, Ar-H) ; I.R(KBr) : 3244.38, 3122.86, 2953.12, 1726.35, 1645.33, 1467.88, 1419.66 cm^{-1}.

2)5-Ethoxycarbonyl-6-methyl-4-(4-Chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one

^{1}H NMR ($CDCl^3$) : δ 1.17 (t, 3H, CH_3), 2.83 (s, 3H, CH_3), 4.07 (q, 2H, CH_2), 5.85 (d, 1H, CH), 5.89 (s, 1H, NH), 7.21-7.28 (H, m, Ar-H), 8.14 (s, 1H, NH); I.R(KBr) : 3242.45, 3117.07, 2980.12, 1708, 1647.26 cm^{-1}.

3)5-Ethoxycarbonyl-6-methyl-4-(2-Chloro phenyl)-3,4-dihydropyrimidin-2(1H)-one

^{1}H NMR ($CDCl^3$) : δ 1.07 (t, 3H, CH_3), 2.33 (t, 3H, CH_3), 4.0 (q, 2H, CH_2), 5.78 (brs, 1H, NH), 5.87(d,1H,CH), 7.2 (d, 1H, Ar-H), 7.25 (t, 1H, Ar-H), 7.36 (t, 1H, Ar-H), 7.37 (d, 1H, Ar-H), 8.54 (brs, 1H, NH) ; I.R(KBr) : 3352.39, 3225.09, 3117.07, 2978.79, 1695.49, 1641.48, 1570.11, 1448.59cm^{-1}

4)5-Ethoxycarbonyl-6-methyl-4-(4-Methoxyphenyl)-3,4-dihydropyrimidin-2(1H)- thione

^{1}H NMR ($CDCl^3$) : δ 1.16 (t, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 4.08 (q, 2H, CH_2), 5.3 (d, 1H, CH), 6.8 (d, 2H, Ar-H), 7.18 (d, 2H, Ar-H), 7.83 (s, 1H, NH), 8.47 (s, 1H, NH) ; I.R(KBr): 3315.74, 3173.01, 2985.91, 2937.68, 1720, 1664.64, 1570.11, 1510.31, 1454.38 cm^{-1}.

5)5-Ethoxycarbonyl-6-methyl-4-(phenyl)-3,4-dihydropyrimidin-2(1H)-thione

^{1}H NMR ($CDCl_3$): δ 1.14(t, 3H, CH_3), 2.2((s ,3H ,CH_3),4.1(q,2H, CH_3), 5.3(s, 1H, NH), 6.8-7.9(m,5H,Ar-H),8.1(s,1H,NH) ; I.R(KBr):3327.32,3176.87,2983.98,1672.34,1572.04 cm^{-1}.

6) 5-Acetyl--6-methyl- 4-phenyl -3,4-dihydropyrimidin-2(1H)-one

^{1}H NMR ($CDCl_3$): δ 1.57 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 2.12 (s, 1H, NH), 2.35 (s, 1H, NH), 5.43 (d, CH, NH), 7.23-7.31 (m, 5H, Ar-H) ; I.R(KBr) : 3259.81, 2924.18, 1701.27, 1606.76, 1572.42, 1462.45 cm^{-1}

7) 5-Acetyl- 6-methyl 4-(4-methoxy phenyl) -3,4-dihydropyrimidin-2(1H)-one
^{1}H NMR ($CDCl_3$) : δ 1.24 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 5.86 (brs, 1H, NH), 8.0 (brs, 1H, NH), 5.4 (d, 1H, CH), 6.8 (d, 2H, Ar-H), 7.2 (d, 2H, Ar-H) ; I.R(KBr) : 3383.26, 3230.87, 2953.12, 1697.41, 1597.11, 1510.31cm^{-1}

8) 13-acetyl-9-methyl-11-oxo-8-oxa-10,12-diazatricyclo [7.3.1.02,7] trideca-2,4,6-triene
^{1}H NMR ($CDCl_3$) : δ 1.24 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.8 (brs, 1H, NH, D2O exch), 2.2 (brs, 1H, NH, D2O exch), 5.47 (t, 1H, CH), 4.57 (q, 1H, CH), 6.82 (d, 1H, Ar-H), 6.92 (t, 1H, Ar-H), 7.11 (d, 1H, Ar-H), 7.21 (t, 1H, Ar-H) ; I.R(KBr) : 3236.66, 3109.35, 2941.54, 1693.56, 1591.33, 1506.46 cm^{-1}.

9) 5-Acetyl- 6-methyl 4- phenyl -3,4-dihydropyrimidin-2(1H)-thione
^{1}H NMR ($CDCl_3$) : δ 1.65 (brs, 1H, NH), 2.14 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 5.45 (d, 1H, NH), 7.24-7.38 (m, 5H, Ar-H), 7.62 (brs, 1H, NH) ; I.R(KBr) : 3294.53, 3198.08, 2994.50, 1610.61, 1572.04, 1452.45 cm^{-1}.

10) 5-Ethoxycarbonyl-6-methyl-4-(2-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-thione
^{1}H NMR ($CDCl_3$) : δ 1.13 (t, 3H, CH_3), 2.53 (s, 3H, CH_3), 4.05 (q, 2H, CH_2), 5.02 (d, 1H, CH), 7.23 (s, 1H, NH), 7.35-7.49 (m, 5H, Ar-H & NH), 7.96 (brs, 1H, NH) ; I.R(KBr) :3379.40, 3304.17, 3066.92, 2933.83, 1683.91, 1645.33, 1591.33, 1533.46 cm^{-1}.

Table 1: Data for the synthesis of Dihydropyrimidine-2 (1H) ones in the presence 5-silphosalicylic acid of catalyst in microwave oven power 350 W

Entry	R_1	R_2	X	Time(minutes)	Yield (%)	M.P(obs/lit)°C
1	C_6H_5	OEt	O	2.0	78	205 /204[7c]
2	4-(Cl)- C_6H_4	OEt	O	1.5	72	217 /216-217[14c]
3	2-(Cl)- C_6H_4	OEt	O	2.3	61	215-216/215-218[17]
4	4-(CH_3O)- C_6H_4	OEt	S	3.3	75	150 /150-152[16]
5	C_6H_5	OEt	S	2.3	65	208-209/(208-209)[17]
6	C_6H_5	Me	O	1.45	70	243 /242-244[17]
7	4-(CH_3O)- C_6H_4	Me	O	2.30	68	166 /166-168[16]
8	2-(OH)- C_6H_4	Me	O	2.45	65	202 / 200-202[19]
9	C_6H_5	Me	S	1.45	62	221 /220-222[16]
10	2-NO_2- C_6H_4	OEt	S	4.3	57	229-230(228-230)[18]
11	4-(CH_3O)- C_6H_4	OEt	O	3.30	78	149-150/(150-152)[19]
12	2-(Cl)- C_6H_4	OEt	S	4.0	70	205-206[21]

11)5-Ethoxycarbonyl-6-methyl-4-(4-Methoxyphenyl)-3,4-dihydropyrimidin-2(1H)- one
^{1}H NMR ($CDCl_3$) : δ 1.2 (t, 3H, CH_3), 2.3 (s, 3H, CH_3), 3.7(s, 3H, CH_3), 4.1 (q, 2H, CH_2), 5.3 (d, 1H, CH), 5.7 (brs, 1H, NH),6.8 (d, 2H, Ar-H), 7.3 (d, 2H, Ar-H) ,8.1(brs,1H,NH) ;I.R(KBr) :3242.45,3107.43,2982.05,2910.68,2835.45,1707.06, 1647.26,1510.31,1448.59,1386.86,1224.84,1091.75.

12)5-Ethoxycarbonyl-6-methyl-4-(2-Chlorophenyl)-3,4-dihydropyrimidin-2(1H)-thione
^{1}HNMR($CDCl_3$):δ:7.30(m,5H,C_6H_5),7.07(s,1H,NH),6.50(d,,1H,CH),6.24(dd,.4Hz,1H,CH),5.35(s,1H, NH),5.01(s,1H,CH),4.20(s,2H,CH_2),2.32(s, 3H, CH_3),1.21(t, 3H, CH_3); I.R(KBr) : 3240, 3109, 2976, 1703, 1653, 1460, 1226, 1093, 783

CONCLUSION

In conclusion, a simple, quick and efficient method for the synthesis of Dihydropyrimidine-2 (1H) ones using 5-sulphosalicylic acid as catalyst was developed. The important advantage of the present protocol is the ability to tolerate variations in all the components of the reaction. This is one of the quickest and simple alternative giving moderates to good yield towards the synthesis of Dihydropyrimidine-2 (1H) ones.

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