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Efficient P_2O_5 Catalyzed Microwave Assisted One Pot Synthesis of Substituted Dihydropyrimidine-2(1*H*)-ones

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Phosphorus pentaoxide catalyzed and microwave enhanced three component Biginelli reaction of aldehyde, 1,3-dicarbonyl compounds and urea or thiourea under reflux microwave conditions to afford dihydropyrimidin-2-(1*H*)-ones in excellent yield is described. The improved procedure is fairly simple, facile and environment friendly.

Key Words: One pot synthesis, Dihydropyrimidines, Microwave irradiation, P_2O_5.

INTRODUCTION

In recent years, dihydropyrimidine-2-(1*H*)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, antitumour, antibacterial, antiinflamatory[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-(1*H*)-ones 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 dihydropyrimidine-2-(1*H*)-ones, albeit in low yields. In the view of the pharmaceuticals importance of these compounds many improved catalytic methods have been developed[7-10]. Although these methods have theirlong 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, an efficient environment friendly procedure for the synthesis of dihydropyrimidine-2-(1*H*)-ones for aryl aldehyde using P_2O_5 catalyst in microwave irradiation system is reported.

Several catalysts like PPA, $AlCl_3$, H_3BO_3, conc. HCl, BF_3OEt, NH_4Cl, CAN, NBS, triflates of lanthanide compounds and In, Bi, Cu, along with microwave irradiation *etc.* have been tried[11-13] to improve yields and conditions of Biginelli reaction. However,

all these methods involving 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 nanocomposites 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.

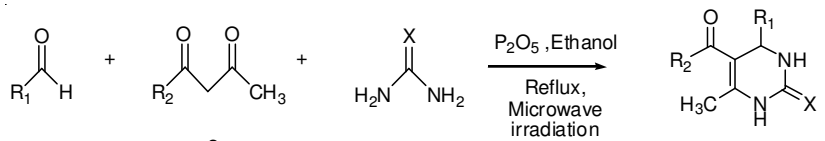
EXPERIMENTAL

All melting points were measured in open capillaries and are uncorrected. Silica gel used for TLC was 200-300 mesh with Binder. IR spectra were recorded on a Shimadzu instruments. Proton magnetic resonance spectra were recorded on a Varion T-60, FT 80 A MSL-300 instrument. All spectra were recorded in $CDCl_3$ and chemical shifts are reported in parts per million (ppm) down field from tetramethyl silane (TMS) as the internal standard.

For microwave assisted organic reactions, modified microwave with reflux condenser was used. The technical specifications are as follows:

Power input: Voltage: 220-240 volts; Current: 8 amps (max); Frequency: 50 Hz; Type: Single phase 3 wire grounded; Cooling method: Forced air; Power output: 10 levels (variable) (1 to H = 700 Watts).

General procedure: The mixture of an aldehyde (10 mmol), acetyl acetone/ethyl acetoacetate (10 mmol), urea/thiourea (30 mmol) and phosphorus pentoxide (0.5 g, 3.54 mmol) were mixed thoroughly with ethanol as solvent (20 mL) in a round bottom flask and this reaction mixture was refluxed in microwave with constant stirring. The completion of the reaction was monitored by TLC and the mixture was poured in water, after stirring the desired dihydropyridines separated as a precipitate in almost quantitative yield (**Scheme-I**). The physical characteristics of the synthesized dihydropyrimidine-2-(1*H*)-ones using P_2O_5 catalyst in microwave irradiation are given in Table-1.



Scheme-I

Spectral studies

4a: ^{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); IR (KBr, cm^{-1}): 3244, 3122, 2953, 1726, 1645, 1467, 1419.

TABLE-1
DATA FOR THE SYNTHESIS OF DIHYROPYRIMIDINES IN THE PRESENCE OF P_2O_5 CATALYST IN MICROWAVE IRRADIATION

Entry	No.	R_1	R_2	X	Time (min)	Yield (%)	m.p. (obs/lit) ºC
1	**4a**	C_6H_5	OEt	O	3.0	93	205 /204[7c]
2	**4b**	4-(Cl)-C_6H_4	OEt	O	5.0	94	217 /216-217[14c]
3	**4c**	2-(Cl)-C_6H_4	OEt	O	6.0	90	215 /215-218[14]
4	**4d**	4-(CH_3O)-C_6H_4	OEt	S	6.0	90	150 /150-152[15]
5	**4e**	2-(NO_2)-C_6H_4	OEt	S	9.0	80	230 / 230[16]
6	**4f**	C_6H_5	Me	O	3.5	94	243 /242-244[14b]
7	**4g**	4-(CH_3O)-C_6H_4	Me	O	4.0	91	166 /166-168[15]
8	**4h**	C_6H_5	Me	S	6.0	92	221 /220-222[15]
9	**5a**	2-(OH)- C_6H_4	Me	O	5.0	97	202 / 200-202[17]
10	**5b**	2-(OH)-C_6H_4	Me	S	6.5	94	181

4b: ^{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); IR (KBr, cm^{-1}): 3242, 3117, 2980, 1647, 1647.

4c: ^{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); IR (KBr, cm^{-1}) δ: 3352, 3225, 3117, 2978, 1695, 1641, 1570, 1448.

4d: ^{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); IR (KBr, cm^{-1}): 3315, 3173, 2985, 2937, 1720, 1664, 1570, 1510, 1454.

4e: ^{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); IR (KBr, cm^{-1}): 3379, 3304, 3066, 2933, 1683, 1645, 1591, 1533.

4f: ^{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); IR (KBr, cm^{-1}): 3259, 2924, 1701, 1606, 1572, 1462.

4g: ^{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); IR (KBr, cm^{-1}): 3383, 3230, 2953, 1697, 1597, 1510.

4h: ^{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); IR (KBr, cm^{-1}): 3294, 3198, 2994, 1610, 1572, 1452.

5a: ^{1}H NMR ($CDCl_3$) δ: 1.24 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.8 (brs, 1H, NH, D_2O exch), 2.2 (brs, 1H, NH, D_2O 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); IR (KBr, cm^{-1}): 3236, 3109, 2941, 1693, 1591, 1506.

5b: ^{1}H NMR ($CDCl_3$) δ: 1.8 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), 3.2 (s, 1H, CH), 4.64 (q, 1H, CH), 1.65 (brs, 1H, NH, D_2O exch), 7.58 (brs, 1H, NH, D_2O exch), 6.82 (d, 1H, Ar-H), 6.9 (t, 1H, Ar-H), 7.15 (d, 1H, Ar-H), 7.3 (t, 1H, Ar-H); IR (KBr, cm^{-1}): 3227, 3146, 2956, 1714, 1564, 1512, 1622.

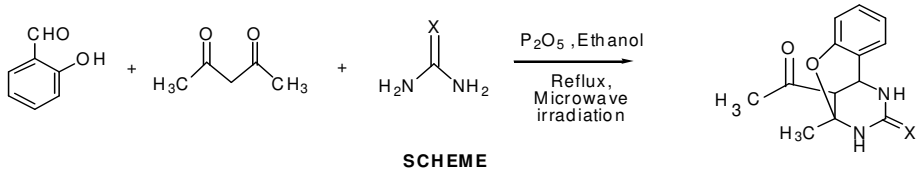
RESULTS AND DISCUSSION

Biginelli reaction gives good result and fulfills the requirement in presence of P_2O_5 as catalyst. In Biginelli reaction water molecule formed during the progress of the reaction, which is absorbed by the P_2O_5 and gets converted into phosphoric acid. This increases the acidic condition of the reaction mixture and due to which the rate of the reaction is enhanced, which leads to shorter reaction time.

Various changes were made in the reactants to observe the reactivity of the reaction like, apart from various kinds of aromatic aldehydes, ethyl acetoacetate and acetylacetone acts as 1,3-dicarbonyl compound and urea and thiourea was taken.

Reaction mixture constitutes of aldehyde (10 mmol), 1,3-dicarbonyl compound (10 mmol), urea/thiourea (30 mmol) with P_2O_5 (0.5 g, 3.54 mmol), ethanol was taken as solvent. This was taken in a round bottom flask and refluxed under microwave irradiation. After the reaction completion the reaction mixture was poured in the water in which the product precipitates out as a white solid in quantitative yield.

There was a variation from the **Scheme-I** and epoxide formation takes place when the salicyaldehyde was treated with urea/thiourea. This happened only in case of acetylacetone and the product was confirmed by ^{1}H NMR (D_2O exchange) and IR (**Scheme-II**). Variation in the quantity of P_2O_5 showed an interesting trend in the quantity of dihydropyrimidines. The variation is listed in the table.



SCHEME

X=O,S. 5

Entry	Weight of catalyst (mg)	Reaction time (min)	Yield of product (%)
1	100	9.0	55
2	250	6.5	75
3	500	3.0	93

Conclusion

In conclusion, a simple, quick and efficient method for the synthesis of Biginelli dihydropyrimidines using phosphorus pentoxide under microwave irradiation is 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, economical and simple alternatives giving almost quantitative yield towards the synthesis of 3,4-dihydropyrimidines.

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