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SYNTHESIS OF MONASTROL AND 3,4-DIHYDROPYRIMIDINE-2-(1*H*)-ONES USING $(NH_4)_2HPO_4$ AS A CATALYST

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ABSTRACT

Monastrol and 3,4-dihydropyrimidine-2-(1*H*)-ones have been synthesized via solvent free multicomponent reaction of aldehydes, urea or thiourea, 1,3-dicarbonyl compounds and 10 mol% ammonium dihydrogen orthophosphate under microwave irradiation. The protocol has key features such as catalyst used is inexpensive, environmentally benign and affords desired products readily in excellent yields by accelerating Knoevenagel, Michael and cyclization processes involved in this transformation.

Keywords: Monastrol, $(NH_4)_2HPO_4$, 3,4-dihydropyrimidine-2-(1*H*)-ones, solvent-free

INTRODUCTION

Current organic methodologies seriously focus on multi-component reactions (MCRs) as they lead to time, energy, and environment saving.[1-6] This synthetic tool is very dear to biologists and chemists also as in these days emphasis is on the efficient discoveries of new chemical entities and in this context of special significance is Biginelli reaction and Biginelli scaffold.[7-14] Ever since chemists celebrated near century of this reaction there was flood of researches in diversity improved production processes and catalysts development.[7-8,15-21] As soon as some molecular manipulations lead to discovery of Monastrol, SQ3247 and SW02 there is now again renewed interest in finding of new efficient protocol and processes.[22-26]

In this endeavor we wish to report phosphate based efficient catalysts for this important reaction and particular interest is the production of Monastrol in a single step with high yield which is being developed as a lead compound for anti-cancer activity.[13]

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. Reagent grade chemicals were purchased from commercial source and used as received. IR spectra were recorded in KBr discs on a Perkin-Elmer 24OC analyzer. ^{1}H NMR spectra were recorded on a Varian Gemini 300 (300 MHz) spectrometer using TMS as internal standard. The progress of reaction was monitored by TLC run on silica gel G (Merck). All MW reactions were performed in a Synthos 3000 microwave reactor.

Microwave irradiated synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones

A mixture of aldehyde (2 mmol), 1,3-dicarbonyl compound (2 mmol), urea (1.2 mmol) and $(NH_4)_2HPO_4$ (10 mol%) were placed in an Erlenmeyer flask and then irradiated in a Synthos 3000 microwave reactor at 80°C for the required duration (Table 1). After completion of reaction (TLC), the mixture was cooled to room temperature and poured into water (10 mL) and stirred for 5 min. The solid thus obtained was filtered and purified by recrystallization from ethanol to afford 3,4-dihydropyrimidin-2(1*H*)-ones with excellent yields.

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (4a)
IR (KBr): 3412, 3229, 1710, 1639 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.18 (s, 1H), 7.73 (s, 1H), 7.20-7.30 (m, 5H), 5.14 (s, 1H), 3.98 (q, *J* = 7.2 Hz, 2H), 2.24 (s, 3H), 1.06 (t, *J* = 7.2 Hz, 3H). Anal. Found: C, 64.67; H, 6.13; N, 10.83. $C_{14}H_{16}N_2O_3$ requires C, 64.62; H, 6.15; N, 10.77%.

4-(4-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (4e)
IR (KBr): 3420, 3242, 1708, 1645 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.20 (s, 1H), 7.76 (s, 1H), 7.40 (d, *J* = 9.0 Hz, 2H), 7.26 (d, *J* = 9.0 Hz, 2H) 5.16 (s, 1H), 3.95 (q, *J* = 7.1 Hz, 2H), 2.19 (s, 3H), 1.10 (t, *J* = 7.1 Hz, 3H). Anal. Found: C, 57.13; H, 5.09; N, 9.44. $C_{14}H_{15}ClN_2O_3$ requires C, 57.05; H, 5.13; N, 9.50%.

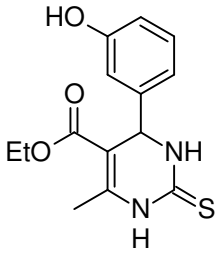
4-(3-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one, (4g)
IR (KBr): 3416, 3230, 1706, 1642 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.02 (s, 1H), 7.50 (s, 1H) 7.16-7.35 (m, 4H), 5.20 (s, 1H), 4.02 (q, *J* = 7.2 Hz, 2H), 2.29 (s, 3H), 1.12 (t, *J* = 7.2 Hz, 3H). Anal. Found: C, 57.16; H, 5.15; N, 9.39. $C_{14}H_{15}ClN_2O_3$ requires C, 57.05; H, 5.13; N, 9.50%.

5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (4h)
IR (KBr): 3415, 3236, 1715, 1675 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.28 (s, 1H), 8.26 (d, *J* = 8.7 Hz, 2H), 7.80 (s, 1H), 7.70 (d, *J* = 8.7 Hz, 2H) 5.26 (s, 1H), 3.93 (q, *J* = 7.0 Hz, 2H), 2.25 (s, 3H), 1.09 (t, *J* = 7.0 Hz, 3H). Anal. Found: C, 55.14; H, 4.95; N, 13.69. $C_{14}H_{15}N_3O_5$ requires C, 55.08; H, 4.92; N, 13.77%.

5-Ethoxycarbonyl-6-methyl-4-(2-thienyl)-3,4-dihydropyrimidin-2(1H)-thione (4j)
IR (KBr): 3423, 3243, 1651, 1555 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.39 (s, 1H), 9.67 (s, 1H), 7.41 (d, *J* = 4.2 Hz, 1H), 7.00-6.85 (m, 2H), 5.39 (s, 1H), 4.06 (q, *J* = 6.8 Hz, 2H), 2.29 (s, 1H), 1.16 (t, *J* = 6.8 Hz, 3H). Anal. Found: C, 51.14; H, 4.89; N, 9.83. $C_{12}H_{14}N_2O_2S_2$ requires C, 51.02; H, 5.00; N, 9.93%.

5-Acetyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (4l)
IR (KBr): 3415, 3232, 1700, 1598 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.15 (s, 1H), 7.67 (s, 1H), 7.21 (d, *J* = 8.3 Hz, 2H), 6.82 (d, *J* = 8.3 Hz, 2H) 5.16 (s, 1H), 3.67 (s, 3H), 2.22 (s, 3H), 2.10 (s, 3H). Anal. Found: C, 64.77; H, 6.06; N, 10.65. $C_{14}H_{16}N_2O_3$ requires C, 64.62; H, 6.15; N, 10.77%.

5-Ethoxycarbonyl-6-methyl-4-(isopropyl)-3,4-dihydropyrimidin-2(1H)-one (4o)
IR (KBr): 3416, 3239, 1704, 1651 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.67 (s, 1H), 6.38 (s, 1H), 4.28 (s, 1H), 4.12 (q, *J* = 7.3 Hz, 2H), 2.27 (s, 3H), 1.80 (m, 1H) 1.26 (t, *J* = 7.1 Hz, 3H);), 0.94 (d, *J* = 6.5 Hz, 3H),), 0.85 (d, *J* = 6.5 Hz, 3H). Anal. Found: C, 60.98; H, 5.72; N, 10.08. $C_{14}H_{16}N_3O_4$ requires C, 60.87; H, 5.80; N, 10.14%.



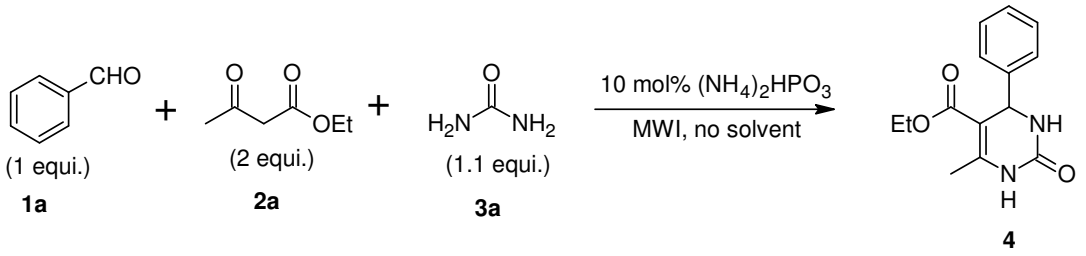
Monastrol
4d: Yield=95%
Fig.-1: Structure of Monastrol

RESULTS AND DISCUSSION

In a general experimental procedure, benzaldehyde (10 mmol) **1a** and 1,3-dicarbonyl compound (20 mmol) **2a**, urea (12 mmol) **3a** and $(NH_4)_2HPO_4$ (10 mol %) were irradiated under microwave (Synthos

3000 microwave reactor) for 60 sec. to afford 3,4-dihydropyrimidine **4a** (Scheme-1) in 98 % yield (Table-1, entry 1), without the formation any side product viz. pyridine. Similarly, other aldehydes **1b-1j** were reacted with 1,3-dicarbonyl **2a-b**, and (thio)urea **3a-b** under microwave irradiation (MWI) using $(NH_4)_2HPO_4$ (10 mol %) without using any solvent system (Scheme -2) to afford end product in high yields 90-95 % (Table-1, entry 2-15). In continuation to this investigation, condensation of 3-hydroxy benzaldehyde **1c** with thiourea **3b** and ethyl acetoacetate **2a** under identical reaction condition afforded Monastrol **4d** (Figure- 1) with excellent yield (95%) in 80 seconds reaction time (Table-1, entry 4).

For this investigation, firstly the above reaction was examined in different solvents (Table-2). The excellent yields in shorter reaction time, obtained in solvent free reaction condition (Table-2, entry 1). However, the same reaction in presence of solvents did not give satisfactory results even in longer reaction time (Table-2, entry 2-8) as comparable to no solvent (Table-2, entry 1).



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

Table -1: $(NH_4)_2HPO_4$ catalyzed synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones

Entry	Product[a]	R^1	R^2	X	Reaction time (sec.)[b]	Yield (%)[b,c]	m.p. (^oC)[d]
1	4a	1a	2a	O	60	98	201-202 (202-03)
2	4b	1a	2a	S	65	96	209-210 (208-210)
3	4c	1b	2a	O	70	94	199-200 (199-201)
4	4d	1c	2a	S	80	95	179-181 (179-180)
5	4e	1e	2a	O	60	98	211-212 (210-212)
6	4f	1e	2a	S	60	96	193-195 (192-195)
7	4g	1d	2a	O	80	95	191-193 (192-193)
8	4h	1f	2a	O	90	92	208-209 (207-210)
9	4i	1h	2a	O	85	90	204-206 (204-205)
10	4j	1g	2a	S	80	91	214-215 (215-217)
11	4k	1a	2b	O	70	95	210-211 (209-212)
12	4l	1b	2b	O	80	94	190-192 (191-93)
13	4m	1f	2b	O	90	94	235-237 (235-38)
14	4n	1j	2a	O	85	91	156-157 (156-58)
15	4o	1i	2a	O	80	91	194-195 (194-95)

[a] All product were characterized by m.p. and spectral (IR, ^1H NMR) data. [b] A: reaction carried out under microwave irradiation in solvent free condition. [c] Yields refers to pure isolated products. [d] Value in parenthesis indicates lit. m.p.[9,27]

Therefore, by employing the optimized conditions benzaldehyde (1 mmol), ethylacetoacetate (2 mmol), urea (1.2 mmol) and $(NH_4)_2HPO_4$ (10 mol %), without solvent for the synthesis of 3,4-dihydropyrimidine, provide variously substituted Knoevenagel-Michael followed by cyclization products **4b-o** in excellent yields.

Table -2: Condensation of benzaldehyde, ethyl acetoacetate and urea in different solvents[a]

Entry	Solvent	Time (sec)	Yield (%)[b]
1	No solvent	60	98

2	H_2O	85	90
3	THF	90	91
4	MeOH	70	92
5	DMF	55	93
6	PEG-400	70	95
7	EtOH	60	96
8	MeCN	75	91

[a]Reaction conditions: benzaldehyde (1 mmol), ethyl acetoacetate (2 mmol), urea (1.2 mmol), $(NH_4)_2HPO_4$ (10 mol %), solvent (5 mL), irradiated in MW. [b]Isolated yield

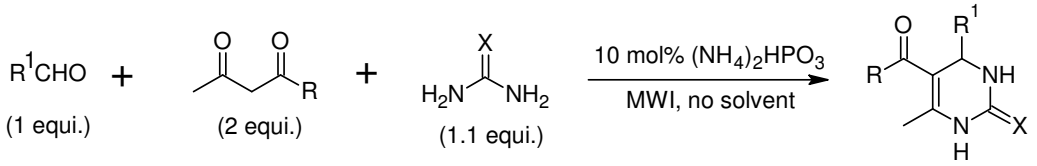
To study the effect of catalyst, we carried out a set of reactions of benzaldehyde **1a** ethyl acetoacetate **2a** and urea **3a** by varying amount of catalysts and keeping other reaction conditions constant (**Table 3**). Obtained results with large amount of catalyst did not show significant influence on the rate of reaction as well as yield.

Table -3: Condensation of 1a with 2a and urea employing different amount of catalyst[a]

Entry	$(NH_4)_2HPO_4$ (mol%)	Time (sec.)	Yield[b]
1	5	60	95
2	10	60	98
3	15	60	92
4	20	60	92
5	30	60	92

[a]Reaction conditions: benzaldehyde (1 mmol), ethyl acetoacetate (2 mmol), urea (1.2 mmol) and catalysts, without solvent under MWI. [b]Isolated yield.

Various aromatic **1a-f**, aliphatic **1i-j** and heterocyclic aldehydes **1g-h** have been employed in this reaction successfully which is testimony to the large scope of this catalyst system. Acetylacetone **2b** was also used with similar success to provide the corresponding 3,4-dihydropyrimidin-2-(1*H*)-ones (Table -1, entries 13, 14, 15). When urea **3a** was replaced with thiourea **3b** the corresponding 3,4-dihydropyrimidin-2-(1*H*)-thiones **4a-o** were obtained with comparable results. Thus, variations in all three components have been accommodated very comfortably.



1a-j **2a):** R=OEt; **2b):** R=Me **3a)** X = O; **3b)** X = S **4 a-o**

1a: R^1=C_6H_5, **1b:** R^1=4-CH_3O-C_6H_4, **1c:** R^1=3-OH-C_6H_4,
1d: R^1=3-Cl-C_6H_4, **1e:** R^1=4-Cl-C_6H_4, **1f:** R^1=4-NO_2-C_6H_4,
1g: R^1=2-C-S-(CH)3-, **1h:** R^1=2-C-O-$(CH)_3$-, **1i:** R^1=-$CH(CH_3)_2$,
1j: R_1=-$(CH_2)_3CH_3$.

Scheme-2: $(NH_4)_2HPO_4$ catalyzed synthesis of 3,4-dihydropyrimidine-2-(1*H*)-ones

This condensation process is fairly general and several functionalities like methoxy **1b**, hydroxyl **1c**, chloro **1d-e**, and nitro **1f** survived during the course of reaction and of special interest is the production of Monastrol **4d** in a single step with excellent yield. Acid sensitive aldehyde such as furfural **1h** also worked well without the formation of any side product. The reaction proved to be very reproducible and could be carried out in a domestic microwave oven as well as in designed Synthos 3000 microwave reactor.

CONCLUSION

In summary, we have generated a simple, rapid, convenient, environmentally benign and effective method for the condensation of aldehydes with aliphatic as well as heterocyclic in the absence of any toxic, volatile and corrosive catalysts or organic solvents. However, the beauty of this method is its milder reaction condition, reduced reaction time, excellent yields, microwave heating (an alternate and green source of energy) also recyclable, biodegradable and mild nature of $(NH_4)_2HPO_4$. These Knoevenagel-Michael products have wide scope in synthesis of biologically active heterocyclic compounds. In addition to this, it involved mild reaction conditions and simple work up. The present study describes the first ever use and catalytic activity of $(NH_4)_2HPO_4$ in the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones.

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