Microwave-induced Perchloric Acid Catalyzed Novel Solvent-free Synthesis of 4-Aryl-3,4-dihydropyrimidones *Via* Biginelli Condensation

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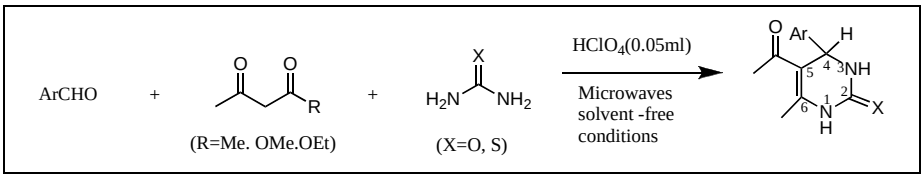

We report here domestic microwave-induced perchloric acid-catalyzed solvent-free synthesis of various 4-aryl-3,4-dihydropyrimidones for the first time. In all the cases the yields are excellent and the mechanism follows a simple Biginelli condensation to produce the dihydropyrimidones in a few seconds. This procedure has been successfully employed to synthesize the mitotic kinesin EG5 inhibitor Monastrol (Figure I).

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INTRODUCTION

Microwave-assisted synthesis has been investigated extensively using organic solvents in open vessels. High-boiling microwave-absorbing solvents have shown a great promise for this purpose. But, the use of solvents has limited the advantages in relation to product isolation. On this basis, designing of solvent-free reaction in microwave oven would be ideal. The protection of the environment is a major requirement in our overcrowded world of increasing demands. One of the very promising approaches to this effect is the employment of solvent-free techniques in Organic Synthesis [1]. The effects of microwave-induced reaction under solvent-free conditions have several advantages. This method would be economical, convenient and simple. Herein we report an expeditious solvent-free Biginelli condensation method for the synthesis of 4-aryl-3,4-dihydropyrimidones with catalytic amounts of perchloric acid in a domestic microwave oven including that of the mitotic kinesin EG5 inhibitor Monastrol.

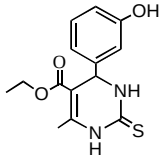


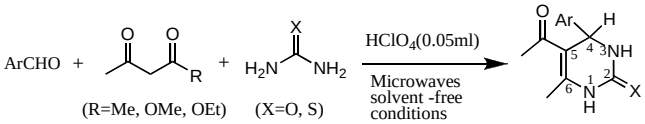
Figure-I
Monastrol

(entry 29, Table)

RESULTS AND DISCUSSION

The dihydropyrimidone nucleus exhibits wide potentiality as calcium channel blockers, antihypertensive agents, alpha-1a-antagonists [2] and neuropeptide Y (NPY) antagonists [3]. Therefore, new method for the synthesis of the dihydropyrimidone nucleus is important. The first synthesis was carried out by Biginelli in low yield (20-50%) [4] following a condensation reaction of ethylacetoacetate with aldehydes and urea in presence of strong mineral acid. Subsequently, other improved procedures have been reported [5], but they suffer serious drawbacks. Strong Lewis acids [6,7,8] or costly lanthanide compounds [9] in the presence of use of toxic organic solvents are used in some of the recent results. On this basis, a high yielding, cost effective, rapid synthesis of the dihydropyrimidone nucleus is necessary. The simplicity of the procedure can be enhanced using the application of "Microwave induced Organic Reaction Enhancement" (MORE) [10] techniques. For example, the reaction of benzaldehyde, acetylacetone and urea required almost 10 hours for completion in an oil bath at 100 °C. In a detailed study, we prepared several dihydropyrimidones in excellent yield and within minutes using catalytic amounts of perchloric acid (0.05 ml) in a domestic microwave oven in the absence of any solvents. Higher quantity of perchloric acid led to charring of the reaction mixture. The use of microwave oven resulted in not only higher reaction rates, but also the formation of cleaner products. The crude reaction products solidified as soon as they were taken out of the microwave oven. A medium power level was used (10-20% of a 1200 watt microwave oven system). The reaction was very rapid and completed

Scheme I



within 4-5 minutes. Several products were synthesized in gram scale. This method was applied to β-keto esters and β-diketones and a variety of substituted aryl aldehydes.

microwave oven (Scheme-I). This method is very general and tolerates different types of functional groups. Considering the simplicity and environ-

Table

Perchloric Acid catalysed "solvent free" synthesis of 4-aryl-3,4-dihydropyrimidones in the microwave oven.

Entry	Ar	R	X	Time (seconds)	Power (watt)	Yield (%)	References
1	Ph	Me	O	30	120	94	5, 7
2	Ph	OMe	O	120	240	92	6, 7
3	Ph	OEt	O	120	240	95	6, 7
4	Ph	Me	S	140	120	90	7
5	Ph	OEt	S	180	120	93	7, 12
6	Ph	OMe	S	180	120	89	13
7	4 OH-3OMe-C_6H_3	OEt	O	60	240	87	14
8	4 OH-3OMe-C_6H_3	Me	O	30	120	93	15
9	4 OH-3OMe-C_6H_3	OMe	O	60	240	95	16
10	2Cl- C_6H_4	Me	S	180	240	90	
11	4OMe-C_6H_4	OEt	O	180	120	92	8, 17
12	4OMe-C_6H_4	OMe	O	240	120	82	8, 17
13	4OMe-C_6H_4	Me	O	180	120	90	8
14	4OMe-C_6H_4	OEt	S	30	120	85	17, 18
15	3NO_2-C_6H_4	OEt	O	300	240	91	14, 19
16	3NO_2-C_6H_4	OMe	O	300	240	94	17
17	3NO_2-C_6H_4	Me	O	120	120	94	20
18	3NO_2-C_6H_4	OEt	S	210	240	82	17
19	4OH-C_6H_4	OMe	O	300	240	93	7, 21
20	4OH-C_6H_4	OEt	O	180	240	92	6, 7
21	4OH-C_6H_4	Me	O	30	240	92	22
22	4OH-C_6H_4	OEt	S	110	120	83	23
23	4Cl-C_6H_4	OMe	O	240	600	88	6, 7, 8,17
24	4Cl-C_6H_4	OEt	O	180	600	84	6, 7, 8,17
25	4Cl-C_6H_4	Me	O	150	240	86	22
26	4NMe_2-C_6H_4	OEt	O	90	240	83	14
27	4NMe_2-C_6H_4	OMe	O	120	240	90	16
28	3OH-C_6H_4	OEt	O	180	240	93	7
29	3OH-C_6H_4	OEt	S	300	600	92	24
30	furanyl	OEt	O	50	120	84	21
31	4NO_2-C_6H_4	Me	O	180	240	85	17
32	4NO_2-C_6H_4	OMe	O	300	600	89	8, 17
33	4NO_2-C_6H_4	OEt	O	180	720	87	8, 17
34	4OH-3OMe-C_6H_3	OMe	S	30	240	90	25

Nitro, chloro, hydroxy, methoxy, and N,N-dimethyl-amino groups on the aryl nucleus posed no problem. Both urea and thiourea were equally effective in this reaction (table). Although we have not investigated the mechanism of the reaction, it may follow a path proposed by Folkers and Johnson [11]. Perchloric acid may stabilize the initially formed acylimine intermediate. Subsequently, the β-diketone or the β-keto ester (enolate) may add to the acylimine intermediate. A cyclization and dehydration route may follow to produce the dihydropyrimidone.

CONCLUSION

In conclusion, in this paper a catalytic amount of perchloric acid has been used very effectively for the first time for a solvent-free high yielding rapid synthesis of 4-aryl, 3,4-dihydropyrimidones including that of Monastrol in a one-pot operation in a domestic mentally benign process, this method may find useful application in the near future.

EXPERIMENTAL

Typical Experimental Procedure. 4 mmol of aldehyde, 5mmol of β-diketone or β-keto ester, 6 mmol of urea or thiourea and 0.05 ml of perchloric acid were mixed thoroughly. The mixture was taken in a 50 ml Erlenmeyer flask, placed in an alumina bath inside a microwave oven (BPL Sanyo, BMO-700T, 2450 MHz, 1200 W) and irradiated at a specified power level for the specified time period (Table). The crude mass was removed from the oven, poured into crushed ice, stirred for several minutes and filtered. The solid residue was washed with cold water several times and crystallized from hot ethanol.

The products were characterized by mp, IR, ^{1}H NMR and ^{13}C NMR data. The compounds were also compared with respect to authentic compound available in literature. The melting point,

spectral and analytical data of the new compound (entry 10 in the Table) is presented below:

5-Acetyl-4-(2-Chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine (entry10). (yellow crystalline solid) mp: 186-188°C (ethanol), ir (potassium bromide): 3315, 3187, 1611, 1454, 1327, 1198 and 760cm^{-1}; ^{1}H NMR (300MHz, DMSO-d_6): δ 10.34(s, 1H, NH), 9.62 (s, 1H, NH), 7.40-7.48 (m, 1H, aromatic C_3-H), 7.29-7.36 (m 2H, aromatic C_4-H and C_5-H), 7.23-7.27 (m, 1H, aromatic C_6-H), 5.69 (d, 1H, J=3.60Hz, C_4-H), 2.37 (s, 3H, -$COCH_3$), 2.11 (s, 3H, C_6-CH_3); ^{13}C NMR (DMSO-d_6): δ 195.04, 174.40, 145.32, 140.16, 132.33, 130.19, 130.14, 129.54, 128.37, 110.18, 52.07, 30.72, 18.63. Anal. Calcd. for $C_{13}H_{13}N_2OSCl$: C, 55.61; H, 4.67; N 9.98. Found: C, 55.50; H, 4.70; N, 9.95.

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