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Research Article

MICROWAVE ASSISTED SYNTHESIS OF 4-SUBSTITUTED-1, 2, 3, 4-TETRAHYDROPYRIMIDINE DERIVATIVES

NIHARIKA I SINGH*, SANDIP S KSHIRSAGAR[1], HEMLATA M NIMJE[2], PRAFUL S CHAUDHARI[3], JAYENDRASING P BAYAS[4], RAJESH J OSWAL[5]

JSPM'S Charak College of pharmacy and research, Pune-Nagar Road, Wagholi, Pune 412207, India Email: sanpals24@rediffmail.com

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ABSTRACT

A simple and efficient method has been developed for the synthesis of various 1, 2, 3, 4-tetrahydropyrimidine derivatives prepared from urea and substituted aldehydes using microwave irradiation technique. The series of Ethyl1- (2-hydrazino-2-oxoethyl)-6-methyl-2-oxo -4 – phenyl - 1, 2, 3, 4 – tetrahydropyrimidine – 5 -carboxylate synthesized, confirmed by analytical and spectral data and evaluated for their *calcium channel inhibition using nifedipine as a analog*.

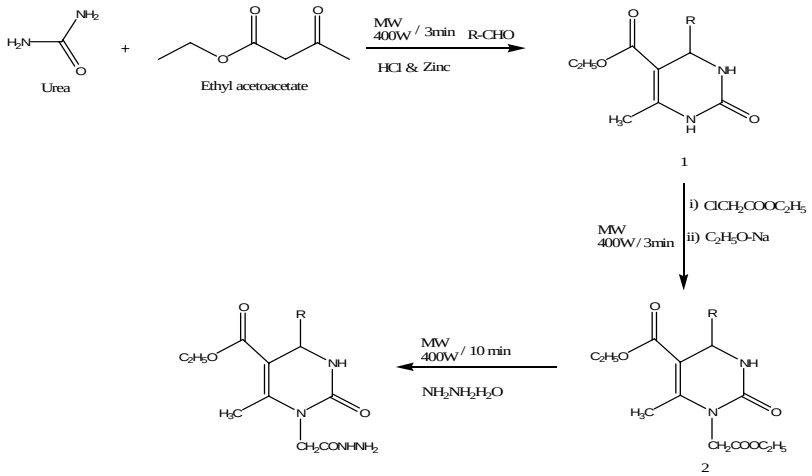
Keywords: Microwave synthesis, Biginelli reaction, DHPM

INTRODUCTION

The use of microwave irradiation in organic synthesis has become increasingly popular within the pharmaceutical and academic arenas, because it is a new enabling technology for drug discovery and development. By taking advantage of this efficient source of energy, compound libraries for lead generation and optimization can be assembled in a fraction of time required by classical thermal methods. In the past decade, dihydropyrimidine derivatives have exhibited important pharmacological properties, as the integral backbone of several calcium channel blocker, antihypertensive agents, alpha-la-antagonists and neuropeptide Y (NPY) antagonist. One of the most potent drug synthesized was 4-subsituted-1,2,3,4-tetrahydropyrimidine derivative, which has been found to be potent anti-hypertensive, calcium channel antagonist that is comparable with standard drug Nifedipine. A classical root to obtain 4-subsituted-1,2,3,4-tetrahydropyrimidine derivatives is by reaction of aldehyde, ethyl acetoacetate and urea along with refluxing with ethanol, hydrazine hydrate (for 24 hours) following Biginelli reaction was carried out. However, in generality of the methods is limited and mostly required long time and hence, considering the importance of dihydropyrimidine moiety as pharmacophoric scaffold, therefore we applied the application of microwave irradiation to the reaction; thus, it has accelerated the rate and yield of product. And, thus using the Biginelli reaction, we carried out the following synthesis 4-subsituted-1,2,3,4-tetrahydropyrimidine derivatives.

MATERIALS AND METHODS

The microwave assisted synthesis were carried out using a Synthos 300 monomode oven monitored manually and temperature maintained at a constant value (140˚C) within the power modulation of 1400 W. Stirring was provided manually in intervals. While reactions were performed in open glass vessels within a ramp time of 10 sec to 2 min. All reagents were obtained from Merk Chemicals Limited. Solvents used were of analytical grade and, when necessary, were purified and dried by standard methods.



SCHEME 1:

EXPERIMENTAL PART

Synthesis of [4-Substituted Phenyl 5-Ethoxy Carbonyl-6-Methyl]-3,4-Dihydropyrimidine -2 (1H) -one [i]

To a mixture of urea (0.1mole), substituted aldehydes (0.1mole) and ethylacetoacetate (0.1mole) in ethanol, 4 drops of concentrated hydrochloric acid was added and was refluxed under microwave for 3min.at 840 power.

The reaction mixture was poured into ice water (100 ml) with stirring and left overnight at room temperature. Filtered and residue was dried at room temperature, recrystallized from ethanol.

IR: 1648 cm^{-1} (amide C=O); 1703cm^{-1} (C=O ester); 3244cm^{-1} (NH) 1H NMR Spectral Data of compound: δ ppm, $CDCl_3$,1.15(t, 3H, CH_3 ester); 2.25 (s, 3H, dihydropyridyl CH_3); 4.05 (q, 2H, CH_2 ester); 6.8(s, 1H, dihydropyridyl-CH); 7.2-7.3 (m, 4H, Ar H) 7.4 (s, 1H, 3 NH); 8.9 (s, 1H, 1 NH). Mass (FAB):237(M+, 12%), 189(Base peak 100%).

Ethyl(2–Ethoxy–2-Oxoethyl)–6–Methyl–2–oxo–4–Phenyl–1,2,3,4 - Tetrahydropyrimidine – 5- Carboxylate [ii]

The compound 1 (0.1mol) was dissolved in a solution prepared by reacting Na (0.1mol) with 200ml of absolute ethanol. The solution was refluxed with stirring and ethyl chloroacetate (0.1mol) was added in three portions over a period of 0.5 hr. After heating under reflux for 16 hr, the reaction mixture was filtered while hot to remove precipitated sodium chloride; the solvent was removed on a rotary vaccum evaporator. The crude product was collected and recrystallized from ethanol.

IR : (KBr) 1648 cm^{-1}(CONH), 1701 cm^{-1}(C=O of ring carbonyl), 1725 cm^{-1}(C=O ester), 2978 cm^{-1}(aromatic proton stretching), 3116 cm^{-1}(CONH), 3245 cm^{-1}(NH stretching), ^{1}H NMR:δ ppm $CDCl_3$, 1.1(t,6H,CH_3), 2.45(s,3H,CH_3), 4.13(s,3H,CH_3), 4.2(q,4H,CH_2), 4.45(d,2H,CH_2), 5.2(s,1H,dihydropyridyl-CH), 7.3-7.4(m,10 H Ar), 7.9(S,1H,NH). Mass (FAB): 265 (M+, 12%), 178 (Base peak 100%).

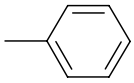
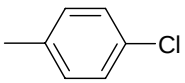
Ethyl 1-(2-Hydrazino-2-Oxoethyl)-6-Methyl-2-oxo-4-Phenyl-1, 2, 3, 4-Tetrahydropyrimidine-5-Carboxylate [iii]

A mixture of the appropriate compound (1) (0.1mol), hydrazine hydrate (8 drops), and 10ml of 95% ethanol was refluxed under microwave for 3min at 840 power. The solvent was removed by evaporating the compound at the room temperature and the residue was poured into cold water. The solid that formed was collected, washed with ice-cold water, and recrystallized from ethanol.

IR: (KBr) 1608cm^{-1}(amideC=O), 1647 cm^{-1}(ester C=O), 1706 cm^{-1}(carbohydrazide C=O), 3238 cm^{-}(-NH) 1H NMR δ ppm, $CDCl_3$, 1.14 (t, 3H, CH3 of C_2H_5), 1.5 (s,3H, dihydropyridyl CH_3), 4.04 (q,2H,CH_2 of $C2H_5$) 5.4 (s, 2H, NH_2); 5.6 (d, 1H, NH); 7.22-7.3 (m, 4H, Ar H), 7.8 (s, 1H, 1 NH) Mass (FAB):251(M+,9%), 186(Base peak 100%)

Elemental analysis**:** C,57.82 ; H,6.07; N, 16.86; O, 19.26;

Table 1

SL. NO	R	% YIELD	M.P. ºC	MOL. FORMULA
a]		89	207	$C_{19}H_{24}N_3O_4$
b]		75	210	$C_{18}H_{22}ClN_3O_4$

RESULTS AND DISCUSSION

Antibacterial activity: Synthesis and antimicrobial activity of compound 3a-3b was tested against bacteria, the tested compounds 3a-3b showed promising antibacterial activity against gram positive (Staphylococcus aureus) and both are showed potent activity against gram negative (E.coli), compared to standard drugs procaine penicillin and streptomycin respectively.

Table 2: Zone of Inhibition (in mm)

Sr. No	Compound	Staphylococcus aureus (+ve)		Escherichia coli (-ve)	
		50µg/ml	100µg/ml	50µg/ml	100µg/ml
1	Procaine penicillin	20	22	-	-
2	Streptomycin	-	-	17	23
3	3a	08	11	09	13
4	3b	07	11	13	17

CONCLUSION

Synthesis of substituted-1,2,3,4-tetrahydropyrimidine derivatives using microwave irradiation technique found efficient and time saving. Synthesis was done successfully and compounds 3a-3b showed promising antibacterial activity against gram positive and gram negative bacteria.

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