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MICROWAVE-ASSISTED SYNTHESIS AND CHARACTERIZATION OF 1,4-DIHYDROPYRIDINES

N. Venu Madhav[1], A. Srinivas Nayak*[2] and Chinna Eswaraiah[3]

[1]St'Peters Institute of Pharmaceutical Sciences, Warangal, India.
[2]University College of Pharmaceutical Sciences, Satavahana, University, Karimnagar, India.
[3]Anurag Pharmacy College, Kodad, Nalgonda, India.

***Corresponding Author: A. Srinivas Nayak**
University College of Pharmaceutical Sciences, Satavahana, University, Karimnagar, India.

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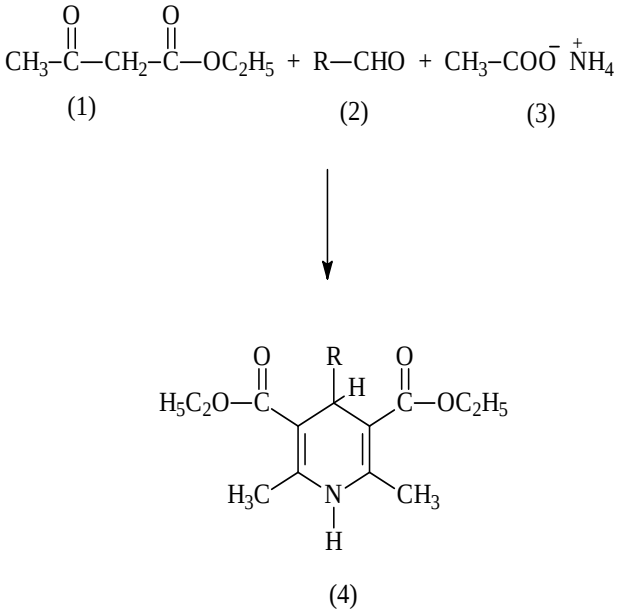
ABSTRACT
1,4-Dihydropyridines are well known for their potential biological activity. An efficient microwave assisted synthesis of 1,4-dihydropyridines have been involved aromatic/aliphatic/ hetero aromatic aldehyde, ethyl acetoacetate and ammonium acetate. When compared to conventional, microwave assisted synthesis is easy, simple, eco-friendly and the reactions are rapid and improved yields and it tolerates variety of substituent's. The newly synthesized 1,4-dihydropyridines have been purified and characterized by their spectral (IR, ^{1}H NMR and Mass) data.

KEYWORDS: Hantzsch reaction, 1,4-Dihydropyridines, Microwave assisted synthesis, Eco-friendly, Calcium channel blockers.

INTRODUCTION

1,4-Dihydropyridines[1] (DHPs) belongs to the class of nitrogen containing heterocycles having a six member ring. They have been used as calcium channel blocking agents and valuable drugs for heart diseases with useful effects on angina, hypertension[2] They have been also used as antitubecular[3], analgesic[4], antitumor[5], vasodilator[6], bronchodilator[7] and anti-inflammatory agent[8] and in biological systems, particularly in NADH led biological oxidation-reduction[9] Hence, Owing to their significant biological activity, this field has-ever-growing importance resulting in the development of DHPs. Therefore, in continuation of our work on DHPs[10], it has been considered worthwhile to synthesize some DHPs by two different procedures, i.e., conventional method and microwave irradiation (MWI) methods for comparison, to characterize the new DHPs by their analytical and spectral (IR, ^{1}H NMR and Mass) data. The classical method and microwave assisted method of synthesis of DHPs involves mixing of an aromatic or aliphatic aldehyde with ethyl acetoacetate and ammonium acetate in alcohol (Scheme-I).



Scheme-I
R = Alkyl/Aryl/Heteryl

The synthesized DHPs were purified and characterized as 4-alkyl/aryl/substituted aryl/heteryl-3,5-dicarboethoxy -2, 6-dimethyl-1,4-dihydropyridines. In microwave assisted method, the reaction time was considerably reduced (4 min only) with increased percentage yields

(70-90%) when compared with the conventional method. Physical data of 1,4-dihydropyridines are presented in Table-I.

MATERIALS AND METHODS

The conventional and microwave assisted experimental procedures are given as general methods. The melting points were determined in open capillaries using Toshnwal melting point apparatus. Infra-red spectra of the compounds were recorded in KBr pellet using Shimadzu FTIR-8700 spectrometer, ^{1}H NMR spectra on omega-500 MHz spectrometer using TMS as internal standard and mass spectra by the direct inlet method on VG micromass 7070 H spectrometer operating at 70 ev.

General Procedure for the Synthesis of 1,4-dihydropyridines

Conventional Method

A mixture of ethyl acetoacetatae (1; 0.05 M), aliphatic, aromatic, or hetero aromatic aldehyde (2; 0.025M) and ammonium acetatae were taken into a RB flask and dissolved in alcohol (25 ml) by shaking. The reaction mixture was heated at 80^0 C under reflux with constant stirring for appropriate time till the reaction completed, (monitored by TLC). The alcohol was removed to a possible extent by distillation and the residue was cooled and triturated with crushed ice. The product was filtered, washed with small portion of cold water and dried. It was purified by recrystallization from hot alcohol or column chromatography over silica gel using hexane: ethyl acetate (9:1) as eluent.

Microwave Irradiation Method

A mixture of ethyl acetoacetate (1; 0.05M), an appropriate aliphatic, aromatic or hetero aromatic aldehyde (2; 0.025M) and ammonium acetate were placed into a beaker and dissolved in 5 ml of ethanol. The reaction mixture was heated under MW irradiation at 480 W (Samsung Microwave oven) for appropriate time. After the reaction was completed, monitored by TLC, the reaction mixture was poured into ice-water; the obtained precipitate was filtered and crystallized from ethanol-water.

By following the above procedures, compound (4a-4j) were synthesized, purified and characterised. Table 1.

Spectral characterization data of the compound (4b)

IR (KBr, Cm^{-1}) ν: 3340 (-NH of DHP), 3068 (C-H, aromatic) 2985 (C-H of aliphatic), 1659 (C=O, of CO_2 Et), and 1591 (C=C, aromatic).

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 1.26 (6H, of -$CH_2C\underline{H}_3$ at C_3&C_5 of DHP), 2.24 (6H of –$C\underline{H}_3$ at C_2&C_6 of DHP), 4.12 (4H of -$C\underline{H}_2CH_3$ at C_3&C_5 of DHP), 4.98 (1H of-C<u>H</u> of DHP), 5.62 (1H of –N<u>H</u> at C_4 of DHP), and 0.96 (3H of –$C\underline{H}_3$ at C_4 of DHP).

Mass spectrum: Recorded its heaviest ion at m/z 267, which is in agreement with the mass (mol.wt.) of its assigned structure.

Thus based on the spectral data the compound has been characterized as 4-(methyl)-3,5-dicarboethoxy-2,6-dimethyl-1,4-dihydropyridine(**4b**; R= CH_3).

Spectral characterization data of the compound (4)

IR (KBr, Cm^{-1}) ν: 3350 (-NH of DHP), 2958 (C-H of aromatic), 1664 (C=O, of CO_2Et), 1484 (C=C, aromatic).

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 1.32 (6H, of -$CH_2C\underline{H}_3$ at C_3&C_5 of DHP), 2.38 (6H of –$C\underline{H}_3$ at C_2&C_6 of DHP), 4.09 (4H of -$C\underline{H}_2CH_3$ at C_3&C_5 of DHP), 5.06 (1H of-C<u>H</u> of DHP), 5.70 (1H of –N<u>H</u> at C_4 of DHP), and 7.20 to 7.38 (4H of Ar-<u>H</u> of aromatic at C_4 of DHP).

Mass spectrum: Recorded its heaviest ion at m/z 375, which is in agreement with the mass (mol.wt.) of its assigned structure.

Thus based on the spectral data the compound has been characterized as 4-(4-nitrophenyl)-3,5-dicarboethoxy-2,6-dimethyl-1,4-dihydropyridine (4; R= C_6H_4-NO_2-4).

RESULTS AND DISCUSSION

4-Alkyl/aryl/heteryl-3,5-dicarboethoxy-2,6-dimethyl1,4-dihydropyridines (yield 70-95%) could be successfully synthesized by a modified Hantzsch method. Among the two different experimental methods adopted: (a) Conventional method and (b) MWI method, a significant increase in yields with a shorter reaction times have been recorded in the later (MWI) method, when compared with conventional methods which involves longer reaction times under refluxing conditions with moderate yields.

Table 1: Physical and analytical data of 4-alkyl/aryl/heteryl-3,5-dicarboethoxy-2,6-dimethyl-1,4-dihydropyridines.

S. No	Compound Code	R	Mol.Formula	Mol.Weight	% yield Method-A	% yield Method-B	m.p(°C)
1	4a	H	C13H19NO4	253	80	95	176 -178
2	4a	CH3	C14H21NO4	267	78	86	120-122
3	4b	C_2H_5				85	
4	4c	C_3H_7	$C_{16}H_{25}N_1O_4$	295	47	90	122-124
5	4d	C_4H_9	$C_{17}H_{27}N_1O_4$	309	39	72	92-94
6	4e	C6H5	$C_{19}H_{23}N_1O_4$	329	52	93	150-152
7	4f	4-NO2 C6H4	$C_{19}H_{22}N_2O_6$	374	54	92	130-132
8	4g	4-OCH3C6H4	$C_{20}H_{25}N_1O_5$	359	41	86	148-150
9	4h	4-CH3C6H4	$C_{20}H_{25}N_1O_4$	343	53	89	140-142
10	4i	4-ClC6H4	$C_{19}H_{22}N_1O_4Cl$	363	59	85	144-146
11	4j	3,4,5-(OCH3)3 C6H2	C22H29NO7	419	76	79	140-142
12	4k	2_Furyl	C17H21NO5	319	63	72	160-162
13	4l	2-Pyridil	C18H22N2O4	330	69	82	196-198

CONCLUSION

A convenient and efficient process for the synthesis of 1,4-DHPs through solvent-free and catalyst-free microwave induced three component coupling of aldehydes, ethyl acetoacetate and ammonium acetate has been developed. The present method offers very attractive features such as reduced reaction times, higher yields and with no catalyst, when compared with any conventional method as well as with other catalysts, which will have wide scope in organic synthesis. The simple procedure combined with easy workup of the reaction mixture makes this method economic, benign and a waste-free chemical process for the synthesis of 1,4-DHPs of biological and medicinal importance.

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