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One Pot Microwave Assisted Synthesis and Biological Activities of 1, 4-Dihydropyridines

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ABSTRACT

One pot microwave assisted synthesis of 1,4-Dihydropyridine derivatives have been synthesized from ethyl aetoacetate, various aldehydes and ammonium acetate The derivatives have been purified and characterized by spectral analysis. Synthesized 1,4-dihydropyridines were screened for their antimicrobial activities. All the synthesized compounds have been exhibited moderate to good antimicrobial activities.

Keywords: 1,4-Dihydropyridines, Microwave assisted synthesis, Characterization, Antimicrobial activity.

I. INTRODUCTION

The synthesis of 1, 4-Dihydropyridines (DHPs) was first reported Arthur Hantzsch [1]. These have important pharmacological and biological activities, such as antihypertensive, anti-anginal and as calcium channel blocker for cardiovascular disease [2]. Several of their derivatives have been reported to exhibit a variety of biological and pharmacological activities, viz., anti tubercular [3] anticancer [4], anticonvulsant [5], antiulcer [6], antioxidant [7], anti microbial [8] and anti-inflammatory [9]. Microwave irradiation method of this reaction allows the synthesis of dihydropyridine derivatives by condensation of an aliphatic or aromatic aldehyde with two equivalents of ethylaceto acetate in the presence of ammonium acetate [10]. The synthesized products have been purified by recrystallization or column chromatography and characterized by their analytical and spectral (IR, ^{1}H NMR and Mass) data. Microwave assisted synthesis have proved that the reactions are easy, simple, rapid, eco-friendly and products are obtained in higher yields. The compounds evaluated for their biological activities and exhibited moderate to good antimicrobial activities.

II. MATERIALS AND METHODS

1,4-Dihydropyridine derivatives have been synthesized by a three component reaction of ethylaceto acetate (1), aromatic or aliphatic aldehydes (2) and ammonium acetate (3) by MWI methods as presented in **Scheme-I.** The products obtained in each of such reactions were purified and characterized by IR, ^{1}HNMR and mass data. The physical data of 1,4-dihydropyridines are presented in **Table-1.**

Experimental procedures are given as general methods. A domestic Samsung microwave oven was used for microwave irradiation synthesis. All melting points were determined in open capillaries using Toshnwal melting point apparatus. Infra-red spectra of the compounds were recorded in KBr pellet using Bruker FTIR 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.

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General Procedure for the Synthesis of 4-aryl/ heteroaryl-3,5-dicarboethoxy-2,6-dimethyl-1,4-dihydropyridines

In a beaker take a mixture of ethylaceto acetate (2.25 ml) and an appropriate aliphatic or aromatic aldehyde (1 ml) in 20 ml of methanol. Then add ammonium acetate (2 g) while stirring. A funnel was hanged in the beaker and covered with a watch glass. The reaction mixture was subjected to the microwave irradiation at 180 W for 2-6 min, with a pulse rate of 20 sec, each in a domestic Samsung microwave oven. After completion of the reaction the solvent was removed by distillation and residue was cooled and triturated with crushed ice. The resultant product was filtered, washed with small portions of cold water and dried. It was purified by recrystallization from aqueous ethanol.

Spectral characterization data of the 1,4-dihydropyridines (4c)

IR (KBr, Cm^{-1}) υ: 3342 (-NH), 3028 (Ar-H) 2972 (C-H of CH_3), 1736 (C=O, ester), 1524 (C=C, aromatic).

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 1.38 (t, 6H of -$OCH_2C\underline{H}_3$ at C_3&C_5 of DHP), 2.24 (s, 6H of –$C\underline{H}_3$ at C_2&C_6 of DHP), 3.72 (s, 3H, of –OCH_3), 4.12 (q, 4H of -$OC\underline{H}_2CH_3$ at C_3&C_5 of DHP), 4.74 (s, 1H of-C<u>H</u> of DHP), 8.26 (s, 1H of –N<u>H</u> of DHP ring), and 6.98-7.14 (dd,4H of –$C_6\underline{H}_5$ at C_4 of DHP).

Mass spectrum of the compound exhibited its molecular ion (M^+) at m/z 359.

Thus based on the spectral data the compound has been characterized as 4-(3-Methoxy phenyl)-3,5-dicarboethoxy-2,6-dimethyl-1,4-dihydropyridine (4c).

Antimicrobial activity

The dihydropyridine derivatives were screened for their antibacterial activity by cup plate method against Staphylococus aureus and Klebsiella pneumonia and antifungal activit against candida albicans. Ampicilline sodium and Nystatin were taken as standard drugs to compare the results with dihydropyridine. The results of bacterial zones of inhibition values (mm) are given in **Table 2.**

III. RESULTS AND DISCUSSION

The 1,4-dihydropyridine derivatives (4a-4e) have been synthesized from a three component reaction of ethylaceto acetate (1), aromatic or aliphatic aldehydes (2) and ammonium acetate (3) by one pot MWI method. A significant increase in yields with shorter reaction times has been recorded in the MWI method. All the synthesized products have been evaluated for their antimicrobial activity. Among the series, the compounds **4e** and **4d** exhibited better anti bacterial activity against Staphylococus aureus and Klebsiella pneumonia. Remaining compounds showed mild to moderate antibacterial activity. Compound **4d** exhibited good antifungal activity against candida albicans whereas remaining compounds showed moderate activity.

IV. CONCLUSIONS

A series of 1,4-dihydropyridines have been synthesized as per scheme-1 and characterized by IR, ^{1}HNMR and mass data. Microwave assisted synthesis is easy, simple, economical eco-friendly and their reactions are rapid and improved yields. The dihydropyridine derivatives have been synthesized with excellent yields. All the synthesized compounds have been screened for their antimicrobial activity. Moreover the derivatives substituted with heterocyclic and halogen substituted aromatics at 4 position of dihydropyridine exhibited good antimicrobial activity.

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Table1. Physical and analytical data of 4-aryl/heteroaryl-3,5-dicarboethoxy-2,6-dimethyl 1,4-dihydropyridines (4a-4e)

Compound Code	R	Mol.Formula	Mol.Wt	% yield	m.p (°C)
4a	C_6H_5	$C_{19}H_{23}N_1O_4$	329	72	154-156
4b	3-NO_2 C_6H_4	$C_{19}H_{22}N_2O_6$	374	93	196-198
4c	3-$OCH_3C_6H_4$	$C_{20}H_{25}N_1O_5$	359	86	188-190
4d	3-Cl C_6H_4	$C_{19}H_{22}N_1O_4Cl$	363	83	220-222
4e	2-Pyridyl	$C_{18}H_{22}N_2O_4$	330	79	196-198

Table 2: Antimicrobial activity of 4-aryl/heteroaryl-3,5-dicarboethoxy-2,6-dimethyl 1,4-dihydropyridines (4a-4e)

Compound Code	Antibacterial		Antifungal
	Staphylococus aureus (Grame+Ve)	*Klebsiella pneumoniae* (Grame-Ve)	*Candida albicans*
4a	09	08	08
4b	12	10	10
4c	11	10	09
4d	14	11	13
4e	16	12	12
Ampicilline sodium (10µg)	18	19	-
Nystatin (10µg)	-	-	18

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