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Design, synthesis and characterization of some new 1, 4-Dihydropyridines

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Abstract
A novel series of 4-alkyl/aryl/heteroaryl-3, 5-bis (4-chlorophenyl) carbamoyl-2, 6-dimethyl-1, 4-dihydropyridines have been synthesized by conventional and microwave irradiation methods. The synthesized compounds were purified and characterized with the help of their analytical and spectral (IR, ^{1}HMR and Mass) data. The methods employed have been compared in terms of yields, reaction times.

Keywords: calcium channel blockers, dihydropyridines, microwave synthesis

Introduction
1, 4-Dihydropyridines (DHPs) are the known class of therapeutic agents to treat angina and hypertension, as calcium channel blockers [1, 2]. Several of their derivatives are also reported to exhibit a variety of biological and pharmacological activities, viz., antitumor [3] antidiabetic [4], antioxidant [5], anti-inflammatory [6], anticoagulant and cytotoxic [7], anticonvulsant [8]. Hence, this field has-ever-growing importance resulting in the development scores of DHPs. Therefore, in continuation of our work on DHPs [9], it has been considered worthwhile to synthesize some new 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 new dihydropyridines, have been synthesized by a modified and improvised Hantzsch one-pot synthesis starting with N-(4-chlorophenyl) acetoacetamides with an appropriate aliphatic, aromatic or hetero aromatic aldehydes and ammonium acetate in conventional method and as well as rapid microwave irradiation method (Scheme-1). The synthesized DHPs were purified and characterized as 4-alkyl/aryl/heteroaryl-3, 5-bis-N-(4-chlorophenyl) carbamoyl-2, 6-dimethyl1, 4-dihydropyridines. Physical data of 1, 4-dihydropyridines are presented in Table-1.

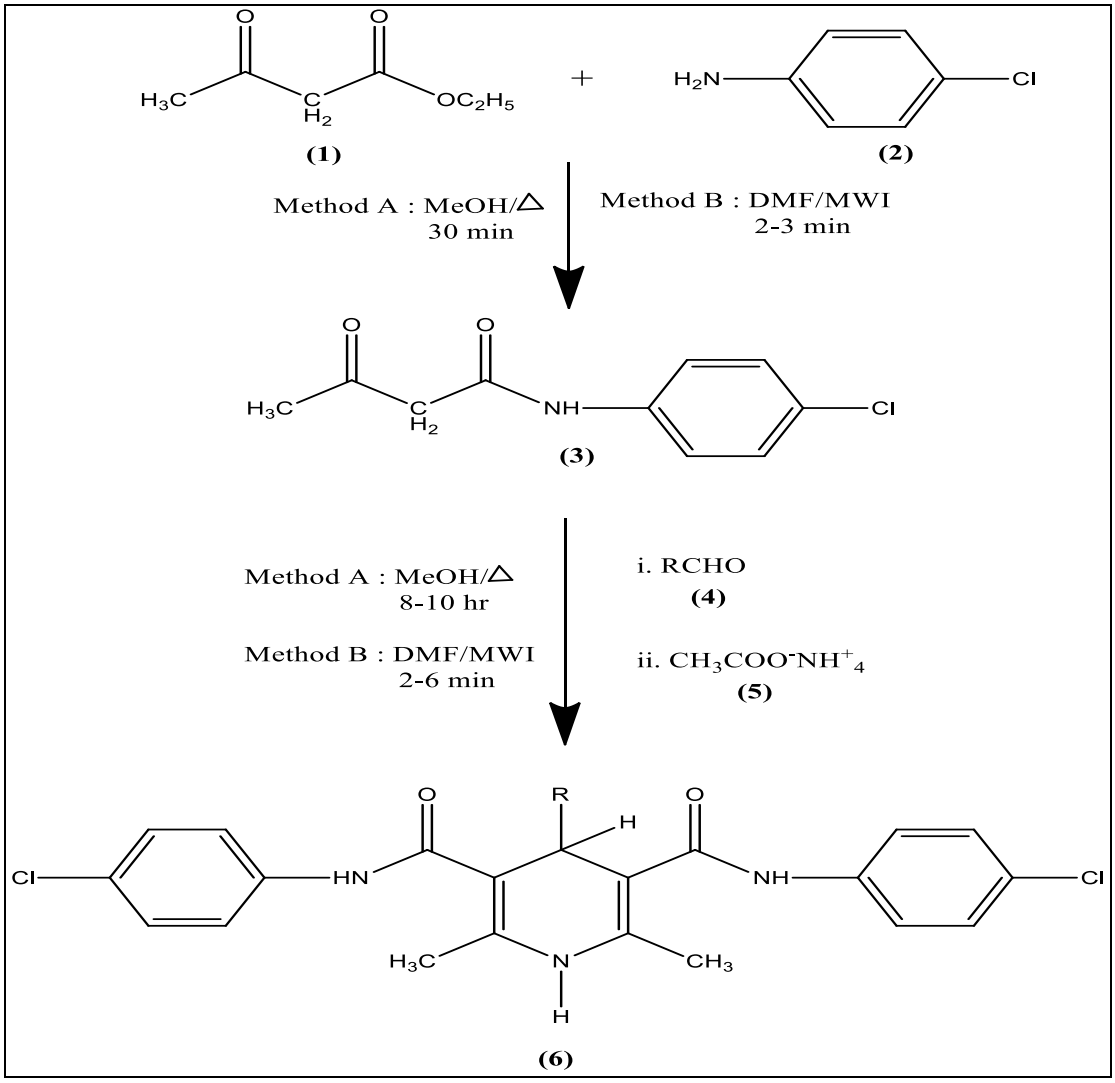
Table 1: Physical and analytical data of 4-Alkyl/aryl/heteroaryl-3, 5-bis-N-(4-chlorophenyl) carbamoyl-2, 6-dimethyl-1, 4-dihydropyridines (6a-i)

Compound Code	R	Mol. Formula	Mol. Wt	Method-A (% yield)	Method-B (% yield)	m.p (°C)
6a	H	$C_{21}H_{19}N_3O_2Cl_2$	416	54	78	168-170
6b	CH_3	$C_{22}H_{21}N_3O_2Cl_2$	429	46	69	124-126
6c	C_6H_5	$C_{27}H_{23}N_3O_2Cl_2$	491	52	78	186-188
6d	4-NO_2 C_6H_4	$C_{27}H_{22}N_4O_4Cl_2$	536	56	84	162-164
6e	4-$CH_3C_6H_4$	$C_{28}H_{25}N_3O_2Cl_2$	505	49	76	194-196
6f	4-OHC_6H_4	$C_{27}H_{23}N_3O_3Cl_2$	507	42	72	202-204
6g	3,4,5-$(OCH3)_3$ C_6H_2	$C_{30}H_{29}N_3O_5Cl_2$	581	58	68	186-188
6h	2_Furyl	$C_{25}H_{21}N_3O_3Cl_2$	481	42	72	240-242
6i	2-Pyridyl	$C_{26}H_{22}N_4O_2Cl_2$	492	54	80	221-223

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.

Chemistry



Scheme-I

General Procedure for the synthesis of 4-alkyl/aryl/heteroaryl-3, 5-bis-N-(4-chloro- phenyl) carbamoyl-2,6-dimethyl-1,4-dihydropyridines

A. Synthesis of N-(4-chlorophenyl) acetoacetamide

a. Conventional method

Ethyl acetoacetate (1; 0.025 mole) and 4-chloroaniline (2; 0.025 mole) were taken into a round bottomed flask and dissolved in methanol (10 ml) and added catalytic amount of potassium ter-butoxide. The reaction mixture was heated under reflux for 30 min, on a hot water bath. After completion of the reaction, monitored by TLC, the resultant product was triturated with ice cold water, filtered, washed with cold water and dried. It was purified by recrystallization from aqueous ethanol to get a pure crystalline solid.

b. Microwave irradiation method

An equimolar (0.025 mole each) mixture of ethyl acetoacetate and 4-chloroaniline were taken into a beaker and dissolved in dimethyl formamide (10ml). Add catalytic amount of potassium ter-butoxide while shaking thoroughly. A funnel was hanged in the beaker and covered with a watch glass. The reaction mixture was subjected to the microwave irradiation at 480 watts for 2 min in microwave oven at a pulse rate of 30 Sec, each. The resultant product was triturated with crushed ice, filtered, washed with cold water and dried. The product was further purified by recrystallization from aqueous ethanol to get a pure colourless, crystalline solid.

Adapting the above two procedures N-(4-chlorophenyl) acetoacetamide was prepared, purified by recrystallization and characterized.

B. Synthesis of 4-Alkyl/aryl/heteryl-3, 5-bis-N (4-chlorophenyl) carbamoyl-2,6-di- methyl-1,4-dihydropyridines

a. Conventional method

N-(4-Chlorophenyl) acetoacetamide (3; 0.01 mole) and an appropriate aliphatic or aromatic or hetero aromatic aldehyde (4; 0.005 mole) were taken into a RB flask and dissolved in methanol (15 ml) by shaking. To this solution, ammonium acetate (5; 0.01 mole) was added while shaking and the reaction mixture was heated under reflux for 8 to 10 hr on a hot water-bath. Alcohol was removed to a possible extent by distillation under reduced pressure and the residue was cooled. The product was filtered, washed with small portions of distilled water and dried. It was purified by recrystallization from hot alcohol.

b. Microwave irradiation method

N-(4-Chlorophenyl) acetoacetamide (3; 0.01 mole) was taken into a beaker and dissolved in dimethyl formamide (10 ml). An appropriate aliphatic, aromatic or hetero aromatic aldehyde (4; 0.005 mole) was added to the above solution while shaking followed by the addition of ammonium acetate (5; 0.01 mole). The reaction mixture was irradiated in a microwave oven at 480 watts for 2-6 min. The mixture was cooled and poured onto crushed ice (100g), while stirring. The resultant product was filtered, washed with cold water and dried. It was purified by recrystallization from alcohol.

Adapting the above two procedures the following nine (9) different 4-alkyl/aryl/heteroaryl-3, 5-bis-N (4-chlorophenyl) carbamoyl-2, 6-dimethyl-1, 4-dihydropyridines (6a-i) were synthesized and characterized.

Spectral characterization data of N-(4-chlorophenyl) acetoacetamide (3)

IR (KBr, Cm^{-1}) υ: 3346 (-NH, carbamoyl), 3028 (C-H, aromatic) 2836 (C-H, aliphatic), 1642 (C=O, ketone), 1608 (C=C, aromatic) and 1102 (C-Cl, aromatic).

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 2.38 (s, 3H, -CH_3CO), 3.60 (s, 2H, -COCH_2), 9.64 (s, 1H, D_2O exchangeable, -CONH) and 6.98 to 7.40 (m, 4H, Ar-H of aromatic).

Mass spectrum of the compound exhibited its molecular ion (M^+) at m/z 211.

Spectral characterization data of 4-Phenyl-3,5-bis-N-(4-chlorophenyl)carbamoyl-1,4-dihydro-2,6-dimethylpyridine (6c).

IR (KBr, Cm^{-1}) υ: 3160 (-NH, carbomoyl), 3326 (-NH, DHP) 3052 (C-H, aromatic), 2986 (C-H, aliphatic), 1674 (-C=O, carbamoyl), 1630 (C=C, aromatic) and 1087 (C-Cl, aromatic).

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 2.40 (s, 6H, -CH_3 at C_2 & C_6 of DHP), 4.90 (s, 1H, -NH of DHP), 5.22 (s, 1H, -CH at C_4 of DHP), and 6.94 to 7.62 (m, 13H, Ar-H at C_3, C_4 & C_5 of DHP) 8.30 (d, 2H, D_2O exchangeable, -CONH at C_3 & C_5 of DHP).

Mass spectrum: of the compound exhibited its molecular ion (M^+) at m/z 490.

Results and Discussion

4-Alkyl/aryl/heteroaryl-3,5-bis-N-(4-chlorophenyl) carbamoyl-2,6-dimethyl1, 4dihydro- pyridines (6a-i) 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.

Conclusions

The present work was intended for the synthesis and characterization of some new dihydropyridines by conventional and MWI methods. The methods are easy simple, eco-friendly and the reactions are rapid and high yielding. The area of the synthesis of dihydropyridine ring continues to grow, and the organic chemistry will provide more and better methods for the synthesis of this interesting heterocycle, allowing the discovery of new drug candidates more active, more specific and safer.

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