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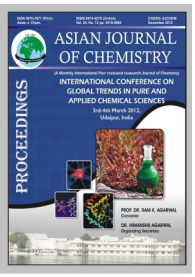

Comparative Study of Various Green Chemistry Approaches for the Efficient Synthesis of 1,4-Dihydropyridines†

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Hantzsch 1,4-dihydropyridine and its derivatives are an important class of bioactive molecules in the pharmaceutical field. The work on this project was started with the objective of synthesizing known 1,4-dihydropyridine by various green chemistry methods like microwave, solvent-free, ultrasonication and compared the results with conventional technique using different aldehydes and 1,3-dicarbonyl compounds as substituents. The twelve known 1,4-dihydropyridines were synthesized and characterized by their TLC, FT-IR and ^{1}H NMR, elemental studies. When all the data cross-examined, it was concluded that microwave, ultrasonic and solvent-free methods were efficient and less time consuming with high yield. At the same time conventional method was time consuming but scalable when compared with other methods.

Key Words: Green chemistry, 1,4-Dihydropyridine, Conventional, Microwave, Ultrasonic, Solvent-free.

INTRODUCTION

Hantzsch 1,4-dihydropyridine (1,4 DHPs) and its derivatives are the class of nitrogen containing heterocycles having 6 membered ring[1,2]. The dihydropyridines heterocyclic ring is a common feature of variety of bioactive compounds of therapeutic activities[3-6]. The classical conventional method for synthesis of 1,4-dihydropyridines involves a one-pot condensation of an aldehyde with 1,3-dicarbonyl compounds and ammonia either in acetic acid or in a refluxing alcohol for a longer time. Due to some disadvantages of low yield, long reaction times, use of large quantities of volatile organic solvent and harsh reaction condition, therefore, development of efficient and versatile methods are still required. Thus development for the new method for the preparation of Hantzsch 1,4-dihydropyridines is an active ongoing research area and there is scope for further improved yields[7-10].

In the beginning of the nineteenth century, a shift in emphasis on organic synthesis is apparent with the desire to develop environmentally benign methods to a number of biologically active molecules using non-toxic reagents, solvents and catalysts. Due to the deterioration of the environment, since 1990's, use of green protocols in the chemical reactions has become the trend setter. A microwave method is one of the green chemistry methods that induced reaction involves one pot condensation by using microwaves. Ultrasound has also increasingly been used in organic synthesis *i.e.*, sonochemistry which is becoming more and more important for a variety of synthetic organic reaction utilizing ultrasound as an energy transfer process. Similarly solvent-free method has also been exploited for the synthesis of variety of heterocyclic compounds. The work on this project was started with the objective of synthesizing known 1,4-DHP by various green chemistry methods like microwave, solvent-free, ultrasonication and compared the results with conventional technique using different aldehydes and 1,3-dicarbonyl compounds as substituents. The scheme involves Hantzsch condensation reaction of alkyl acetoacetate and aromatic aldehyde and ammonium acetate in ethanol to give 1,4-dihydropyridines.

EXPERIMENTAL

All compounds were identified by comparison of their spectral data and physical properties with those of the authentic samples. All chemicals were purchased from commercial suppliers. The melting points were determined on Veego-programmable melting point apparatus (microprocessor based) and are uncorrected. Proton (^{1}H) nuclear magnetic resonance spectra were obtained using Brucker AC-400 F, 400 MHz spectrometer and are reported in parts per million (ppm), downfield from tetramethylsilane (TMS) as internal standard. Infrared (IR) spectra were obtained with Perkin Elmer 882 spectrum and RXI, FT-IR model using potassium bromide pellets.

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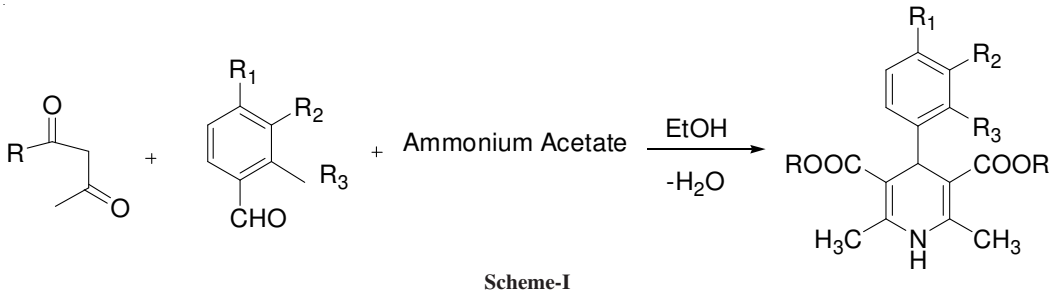


Scheme-I

Synthesis of 1,4-dihydropyridines

Method A: Conventional: 1 g Methyl acetoacetate (8 mmol) and 0.5 g of aldehyde (4.0 mmol) were taken into an RB flask and dissolved in ethanol (15 mL). To this solution 0.308 g ammonium acetate (4.0 mmol) was added with stirring and the reaction mixture was refluxed for 20.0 h. After completion of reaction (monitored by TLC), reaction mixture was cooled to room temperature and kept for stirring until appearance of crystal formation. The product thus separated was filtered and washed with ethanol. It was purified by recrystallization from ethanol to give light yellowish crystalline compound.

Method B: Microwave irradiation: 1 g Methyl acetoacetate (8.0 mmol) and 0.5 g of aldehyde (4.0 mmol) were taken into a conical flask and dissolved in minimum quantity of ethanol (10 mL). To this solution 0.308 g ammonium acetate (4 mmol) was added with stirring. A funnel covered with a watch glass was placed on conical flask. The reaction mixture was subjected to irradiation at 360 W for 8 min, with a pulse rate of 30 sec, each in a domestic LG little chef microwave oven. After completion of reaction (monitored by TLC), the solvent was removed under reduced pressure and the residue was cooled and triturated with crushed ice. The resultant product was filtered, washed with small portions of cold water and dried and purified by recrystallization from hot ethanol.

Method C: Solvent free: 1 g Methyl acetoacetate (8mmol)/ ethyl acetoacetate, 0.5 g of aldehyde (4 mmol) and 0.308 g ammonium acetate (4 mmol) added slowly with stirring. The mixture was heated on water bath at 80 ºC for 3 h. After the completion of the reaction, determined by TLC, sodium bicarbonate (20 mL, 10 %) was added to the reaction mixtures. The product was extracted with ethyl acetate and dried over sodium sulphate. The solvent was dried and product obtained was purified by recrystallization from the mixture of water and ethanol to get the desired compound.

Method D: Ultrasonication: 1 g Methyl acetoacetate (8 mmol)/ethyl acetoacetate and 0.5 g of aldehyde (4 mmol) and 0.308 g ammonium acetate (4 mmol) were taken into a beaker. The reactant mixture was dissolved in min quantity of alcohol (10 mL) and subjected to ultrasound irradiation for 12.0 min. Completion of reaction was monitored by TLC. After completion of reaction, contents were poured in crushed ice, triturated and filtered. The product was recrystallized from hot ethanol.

Spectroscopic characterization data

Dimethyl 1,4-dihydro-2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (Ia): IR(KBr, ν_{max}, cm^{-1}): 3242 (N-H), 1699 (C=O), 1649 (C=C). ^{1}H NMR (DMSO-d_6): δ 2.3 (s, 6H, 2 × CH_3)$_2$, δ 3.6 (s, 6H, 2 × $COOCH_3$), δ 4.9 (s, 1H, -CH of DHP), δ 5.9 (brs, 1H, -NH) and δ 7.2 -7.8 (m, 5H, ArH).

Dimethyl 4-(4-chlorophenyl)-1,4-dihydro-2,6-dimethyl-pyridine-3,5-dicarboxylate (Ib): IR (KBr, ν_{max}, cm^{-1}): 3336 (N-H),1699 (C=O), 1649 (C=C) and 750 (C-Cl). ^{1}H NMR (DMSO-d_6): δ 2.3 (s, 6H, 2 × CH_3), δ 3.6 (s, 6H, 2 × $COOCH_3$), δ 4.9 (s, 1H, -CH of DHP), δ 5.7 (brs, 1H, -NH of DHP) and δ 7.1-7.2 (m, 4H, ArH).

Dimethyl-1,4-dihydro-4-(4-hydroxyphe-nyl)-2,6-dimethyl-pyridine-3,5-dicarboxylate (Ic): IR (KBr, ν_{max}, cm^{-1}): 3329 (N-H), 1680 (C=O), 1651 (C=C). ^{1}H NMR (DMSO-d_6): δ 2.33 (s, 6H, 2 × CH_3), δ 3.64 (s, 6H, 2 × $COOCH_3$), δ 4.6 (s, 1H, -CH of DHP), δ 5.57 (brs, 1H, -OH), δ 6.6 (d, 2H, ArH), 7.1 (d, 2H, ArH).

Dimethyl-1,4-dihydro-4-(2-hydroxyphe-nyl)-2,6-dimethyl-pyridine-3,5-dicarboxylate (Id): IR (KBr, ν_{max}, cm^{-1}): 3340 (N-H), 1690 (C=O), 1645 (C=C). ^{1}H NMR (DMSO-d_6): δ 2.32 (s, 6H, 2 × CH_3), δ 3.61 (s, 6H, 2 × $COOCH_3$), δ 4.7 (s, 1H, -CH of DHP), δ 5.5 (brs, 1H, -OH), δ 6.5-7.2 (m, 4H, ArH).

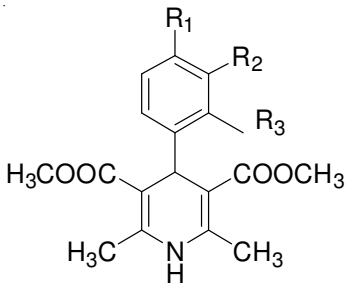
Dimethyl 1,4-dihydro-4-(4-hydroxy-3-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (Ie): IR (KBr, ν_{max}, cm^{-1}): 3354 (OH), 2952(C-H), 1649 (C=O), 1485 (C=C). ^{1}H NMR (DMSO-d_6): δ 2.33 (s, 6H, 2 × CH_3), δ 3.66 (s, 6H, 2 × $COOCH_3$), δ 3.84 (s, 3H, -OCH_3 of DHP), δ 4.9 (s, 1H, -CH of DHP), δ 5.4 (brs, 1H, -OH), δ 5.6 (brs, 1H, -NH of DHP) and δ 6.7 -6..8(m, 3H, ArH).

Dimethyl 1,4-dihydro-4-(4-dimethyl-amino)-2,6-dimethyl-pyridine-3,5-dicarboxylate (If): IR (KBr, ν_{max}, cm^{-1}): 3240 (N-H), 1694 (C=O), 1640 (C=C). ^{1}H NMR (DMSO-d_6): δ 2.2 (s, 6H, 2 × CH_3), δ 2.8 (s, 6H, 2 × $COOCH_3$), δ 3.5 (s, 6H, 2 × NCH_3), δ 4.8 (s, 1H, CH), δ 5.5 (brs, IH, NH), δ 6.5 (d, 2H, ArH), 7.0 (d, 2H, ArH).

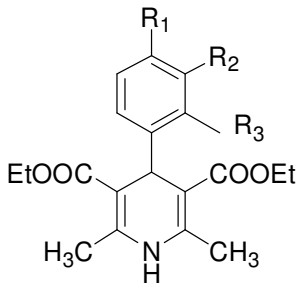
Diethyl 1,4-dihydro-2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (IIa): IR (KBr, ν_{max}, cm^{-1}): 3280 (N-H), 1659 (C=O), 1639 (C=C). ^{1}H NMR (DMSO-d_6): δ 1.2 (m, 6H, 2 × $COOCH_2CH_3$)$_2$, δ 2.3 (6H, 2 × CH_3), δ 4.0 (m, 6H, -($COOCH_2CH_3$)$_2$), δ 4.9 (s, 1H, -CH DHP), δ 5.9 (brs, 1H, -NH) and δ 7.1-7.6 (m, 4H, ArH).

Diethyl 4-(4-chlorophenyl)-1, 4-dihydro-2,6-dimethyl-pyridine-3,5-dicarboxylate (IIb): IR (KBr, ν_{max}, cm^{-1}): 3356 (N-H), 1696 (C=O),1649 (C=C), 743 (C-Cl). ^{1}H NMR(DMSO-d_6): δ 1.2 (m, 6H, 2 × $COOCH_2CH_3$)$_2$, δ 2.3 (6H, 2 × CH_3), δ 4.0 (m, 6H, -($COOCH_2CH_3$)$_2$), δ 4.9 (s, 1H, -CH DHP), δ 5.9 (brs, 1H, -NH) and δ 7.2-7.3 (m, 4H, ArH).

Diethyl-1, 4-dihydro-4(4-hydroxyphenyl)-2,6-dimethyl-pyridine-3,5-dicarboxylate (IIc): IR (KBr, ν_{max}, cm^{-1}): 3346 (N-H), 1662 (C=O) and 1591 (C=C). ^{1}H NMR (DMSO-d_6): δ 1.2 (m, 6H, 2 × $COOCH_2CH_3$)$_2$, δ 2.3 (6H, 2 × CH_3), δ 4.0 (m, 6H, -($COOCH_2CH_3$)$_2$), δ 4.9 (s, 1H, -CH DHP), δ 6.63 (d, 2H, ArH), 7.23 (d, 2H, ArH), δ 7.8 (brs, 1H, -NH of DHP) and δ 8.5 (brs, 1H, C_6H_4-OH).



I(a-f)



II(a-f)

TABLE-1
PERCENTAGE YIELD AND TIME TAKEN BY COMPOUNDS FROM VARIOUS METHODS

Product*	R_1,R_2, R_3	m.p. (°C)	Method A		Method B		Method C		Method D	
			Yield (%)	Time (h)	Yield (%)	Time (min)	Yield (%)	Time (h)	Yield (%)	Time (min)
Ia	R_1-H, R_2-H, R_3-H	176-178	68	20	78	8	57	3	62	12
Ib	R_1-Cl, R_2-H, R_3-H	164-168	72	22r	76	10	53	2.5	63	12
Ic	R_1-OH, R_2-H, R_3-H	220-224	66	23	76	14	58	3	67	18
Id	R_1-H, R_2-H, R_3-OH	188-190	68	23	77	14	57	3	61	14
Ie	R_1-OH, R_2-OCH_3, R_3-H	198-204	66	22	75	14	59	2.5	63	16
If	R_1-$N(CH_3)_2$,R_2-H, R_3-H	154-159	69	21	72	15	54	3	62	18
IIa	R_1-H, R_2-H, R_3-H	154-158	70	12	78	8	59	3	65	12
IIb	R_1-Cl, R_2-H, R_3-H	146-148	72	12	76	6	59	2.5	65	12
IIc	R_1-OH, R_2-H, R_3-H	220-224	66	17	76	14	55	3	65	18
IId	R_1-H, R_2-H, R_3-OH	198-204	65	18	72	14	58	2.5	63	14
IIe	R_1-OH, R_2-OCH_3, R_3-H	160-164	62	17	77	14	58	2.5	66	16
IIf	R_1-$N(CH_3)_2$,R_2-H, R_3-H	150-153	67	22	70	16	53	3	61	18

*All products are known and their physical and spectral data of them were compared with authentic samples[11].
Method A: Conventional; Method B: Microwave irradiation; Method C: Solvent free; Method D: Ultrasonication.

Diethyl-1,4-dihydro-4(2-hydroxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (IId): IR (KBr,ν_{max}, cm^{-1}): 3346 (N-H), 1662 (C=O) and 1591 (C=C). ^{1}H NMR (DMSO-d_6): δ 1.2 (m, 6H, 2 × $COOCH_2CH_3)_2$, δ 2.3 (6H, 2 × CH_3), δ 4.0 (m, 6H, -($COOCH_2CH_3)_2$), δ 4.9 (s, 1H, -CH DHP), δ 6.6-7.0 (m, 4H, ArH), δ 7.4 (brs, 1H, -NH of DHP) and δ 8.3 (brs, 1H, C_6H_4-OH).

Diethyl 1,4-dihydro-4-(4-hydroxy-3-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (IIe): IR (KBr, ν_{max}, cm^{-1}): 3350 (OH), 2984 (C-H), 1681 (C=O) and 1488 (C=C). ^{1}H NMR (DMSO-d_6): ^{1}H NMR (DMSO-d_6): δ 1.2 (m, 6H, 2 × $COOCH_2CH_3$), δ 2.3 (m, 6H, 2 × CH_3), δ 3.8 (s, 3H, -OCH_3), δ 4.0 (m, 4H, ($COOCH_2CH_3)_2$), δ 4.9 (s, 1H, -CH of DHP), δ 5.4 (brs, 1H, -NH of DHP), δ 5.6 (brs, 1H, C_6H_4-OH of DHP) and δ 6.7-7.2 (m, 3H, ArH).

Diethyl 1,4-dihydro-4-(4-dimethylamino)-2,6-dimethylpyridine-3,5-dicarboxylate (IIf): IR (KBr, ν_{max}, cm^{-1}): 3240 (N-H), 1609 (C=O), 1629 (C=C). ^{1}H NMR (DMSO-d_6) : δ 1.2 (m, 6H, 2 × $COOCH_2CH_3)_2$, δ 2.3 (s, 6H, 2× CH_3), δ 3.5 (s, 6H, 2 × NCH_3), δ 4.0 (m, 6H, -($COOCH_2CH_3)_2$), δ 4.9 (s, 1H, -CH DHP), δ 6.62 (d, 2H, ArH), 7.32 (d, 2H, ArH), δ 7.82 (brs, 1H, -NH of DHP) and δ 8.4 (brs, 1H, C_6H_4-OH).

RESULTS AND DISCUSSION

To the date, much research has been directed towards the novel synthesis of 1,4-dihydropyridine compounds. The work on this project was started with the objective of synthesizing some known 1,4-DHP by various green chemistry methods and then compare the results with conventional method of synthesis. Among the four methods studied, the microwave has shown high yield, sharp melting points and pure compounds in crystalline form as compared to conventional, solvent free and ultrasonic method (Table-1). At the same time conventional method was time consuming but scalable when compared with other methods.

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REFERENCES

1. A.M. Gasco, G. Ermondi, R. Fruttero and A. Gasco, *Eur. J. Med. Chem.*, **31**, 3 (1996).
2. S.R. Pattan, S.S. Purohit, V.P. Rasal, S. Mallya, S.C. Marihal, A.B. Khade and M.S. Paschapur, *Indian J. Chem.*, **47B**, 626 (2008).
3. D.M. Stout and A.I. Meyers, *Chem. Rev.*, **82**, 223 (1982).
4. R. Fosshein, *J. Med. Chem.*, **29**, 305 (1996).
5. H.A. Abbas, W.A. El-Sayed and N.M. Fathy, *Eur. J. Med. Chem.*, **45**, 973 (2010).
6. T. Godfraid, R. Miller and M. Wibo, *Pharmacol. Rev.*, **38**, 321 (1986).
7. M. Anniyappan, D. Muralidharan, P.T. Perumal, *Synth. Commun.*, **32**, 659 (2002).
8. J.S. Yadav, B.V.S. Reddy and P.T. Reddy, *Synth. Commun.*, **31**, 425 (2001).
9. A.S. Nayak, G. Achaiah and V.M. Reddy, *Indian J. Heterocycl. Chem.*, **19**, 193 (2009).
10. N.R. Chatterjee, D.C. Sharma, Y.D. Choudhary and A.D. Deshpande, *Indian J. Heterocycl. Chem.*, **16**, 293 (2007).
11. S.A. Nayak and V.M. Reddy, *Indian J. Heterocycl. Chem.*, **18**, 413 (2009).