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RESEARCH ARTICLE

Investigation of Various Green Chemistry Approaches for the Efficient Synthesis of Dialkyl-1, 4-dihydro-4-(substituted phenyl)-2, 6-dimethylpyridine-3, 5-dicarboxylate

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Abstract: A green chemistry methodologies were utilized for the efficient synthesis of Hantzsch 1,4-dihydropyridine derivatives by one-pot multicomponent reaction of substituted aldehydes, ethyl/methyl acetoacetate and ammonium acetate by conventional, microwave, solvent-free and ultrasonication techniques. All the compounds were characterized by TLC, FT-IR, ^{1}H NMR and elemental studies.

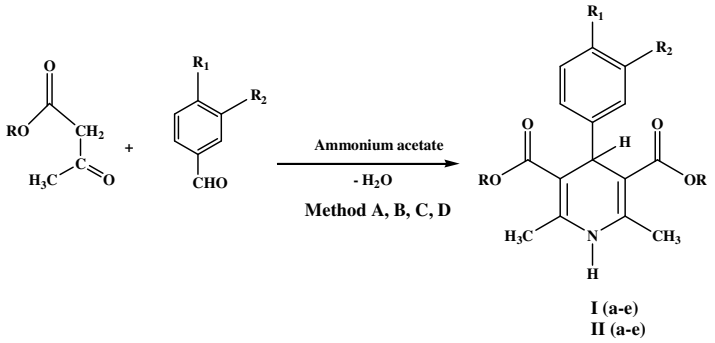
Keywords: Green chemistry, 1,4-Dihydropyridine, Conventional, Microwave, Ultrasonic, Solvent-free

Introduction

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[1]. The Pollution Prevention Act of 1990 set the stage for green chemistry. A microwave method is one of the green chemistry methods that induced reaction involves one pot condensation by using microwaves. Microwave assisted organic synthesis has become an expanding field in synthetic research because of many advantages compared to the conventional reactions which need very high temperatures. Microwave assisted reactions are "cleaner", last only very few minutes, have high yield and produce minimum waste[2-3]. Similarly, avoiding organic solvents during the reactions in organic synthesis gives clean, efficient, and economical technology. This lead to the development of solvent-free method for the synthesis of heterocyclic compounds[4-5]. Ultrasonic chemistry has received an increasing attention in recent years. Ultrasound irradiation, by virtue of cavitational collapse, is able to activate numerous organic reactions to give higher yields under short reaction time and miler condition[6-7].

One-pot multicomponent reactions (MCR's), under green chemistry approach have appeared as an imperative means for construction of diverse and complex organic molecules. MCR's have gained significant importance as a tool for the synthesis of a wide variety of useful compounds, including pharmaceuticals[8-9]. Hantzsch 1,4-dihydropyridine (1,4 DHPs) & its derivatives are the class of nitrogen containing heterocycles having 6 membered ring[10-11]. The DHPs heterocyclic ring is a common feature of variety of bioactive compounds of therapeutic activities[12-13]. The classical conventional method for synthesis of 1,4-DHPs 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 DHPs is an active ongoing research area and there is scope for further improved yields[14-19].

As a part of our continuous efforts toward the efficient synthesis of biologically active molecules[20-27], the present study focus on the synthesis of dialkyl-1, 4-dihydro-4-(substituted phenyl)-2, 6-dimethylpyridine-3, 5-dicarboxylate derivatives utilizing green chemistry techniques such as microwave, solvent-free, ultrasonication and compared the result with conventional reflux method using different aldehydes and 1,3-dicarbonyl compounds as substituents. The scheme involves Hantzsch condensation reaction of alkyl acetoacetate and substituted aromatic aldehydes and ammonium acetate to give 1, 4-dihydropyridines (Scheme 1).



Scheme 1

Experimental

All chemicals were purchased from commercial suppliers. The melting points were determined on Veego-programmable melting point apparatus (microprocessor-based) and are uncorrected. ^{1}H NMR spectra were obtained using Brucker AC-400 F, 400 MHZ spectrometer and the spectra were measured in DMSO-d_6 relative to tetramethylsilane (TMS) as internal standard and reported in parts per million (ppm). Infrared (IR) spectra were obtained with Perkin Elmer 882 Spectrum and RXI, FT-IR model using a potassium bromide pellets (in cm^{-1}). Elemental analyses for C, H, and N were performed on Thermo-flash EA-1112 CHNS-O Analyzer. Synthesis related to microwave irradiation and ultrasonication are carried out in domestic LG little chef microwave oven and fast clean ultrasonic cleaner respectively. Reactions were monitored and the homogeneity of the products was checked by TLC which were prepared with silica gel G and activated at 110 ^{o}C for 30 min. The plates were developed by exposure to iodine vapours. All chemicals

were dried and freshly prior to use according to standard procedure. All compounds were identified by comparison of their spectral data and physical properties with those of the authentic samples.

General procedure for synthesis of 1,4-DHPs

Method A: Conventional

Methyl acetoacetate/ethyl acetoacetate (8.0 mmol) and substituted aromatic aldehyde (4.0 mmol) were taken into an RB flask and dissolved in ethanol (15 mL). To this solution 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 cold ethanol. It was purified by recrystallization from ethanol to give light yellowish crystalline compound.

Method B: Microwave irradiation

Methyl acetoacetate/ethyl acetoacetate (8.0 mmol) and substituted aromatic aldehyde (4.0 mmol) were taken into a conical flask and dissolved in minimum quantity of ethanol (10 mL). To this solution 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 appropriate time, with a pulse rate of 30 sec, each. 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

Methyl acetoacetate/ethyl acetoacetate (8.0 mmol), substituted aromatic aldehyde (4.0 mmol) and ammonium acetate (4.0 mmol) were mixed and heated on water bath at 80 ^{0}C for 3.0 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

Methyl acetoacetate/ethyl acetoacetate (8.0 mmol) and substituted aromatic aldehyde (4.0 mmol) were taken into a conical flask and dissolved in minimum quantity of ethanol (10 mL) and subjected to ultrasound irradiation for appropriate time. 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-4-(4-methyl phenyl)-2,6 dimethylpyridine-3, 5-dicarboxylate (Comp-**Ia**)*

IR (KBr, ν_{max}): 3326 cm^{-1} (N-H of DHP), 2946 cm^{-1} (Aromatic C-H), 1660 cm^{-1} (Ester C=O), 1586 cm^{-1} (Aromatic C=C), 1339 cm^{-1} (C-H) and 1228 cm^{-1} (C-N). ^{1}H NMR (DMSO-d_6): δ 2.08 (s, 3H, -CH_3), δ 2.24 (s, 6H, 2xCH_3), δ 3.53 (s, 6H, -2x-COOCH_3), δ 4.83 (s, 1H, C*H*), δ 6.92-6.94 (d, 2H, ArH_a) and δ 7.02-7.04 (d, 2H, ArH_b); Anal. calcd. for $C_{18}H_{22}NO_5$: C% 68.35, H% 6.96, N% 4.43; Found: C% 67.68, H% 7.65, N% 4.83.

*Dimethyl-1, 4-dihydro-4-(3-hydroxyphenyl)-2, 6-dimethylpyridine-3, 5-dicarboxylate (COMP-**Ib**)*

IR (KBr, ν_{max}): 3326 cm^{-1} (N-H of DHP), 3249 cm^{-1} (O-H), 3100 cm^{-1} (Aromatic C-H), 1658cm^{-1} (Ester C=O), 1487 cm^{-1} (Aromatic C=C) and 1228 cm^{-1} (C-N); ^{1}H NMR (DMSO-d_6): δ 2.29 (s, 6H, 2xCH_3), δ 3.60 (s, 6H, 2x-COOCH_3), δ 4.88 (s, 1H, -C*H* of DHP), δ 6.51- 6.97 (m, 4H, Ar*H*), δ 8.46 (s, 1H, O*H*) and δ 8.83 ppm (s, 1H, NH of DHP); Anal. calcd. for $C_{17}H_{19}NO_5$: C% 64.35, H% 5.99, N% 4.42; Found: C% 64.79, H% 5.85, N% 4.33.

*Dimethyl-1, 4-dihydro-4-(3-hydroxy-4-methoxyphenyl)-2, 6-dimethylpyridine-3, 5-dicarboxylate (COMP-**Ic**)*

IR (KBr, ν_{max}): 3570 cm^{-1} (N-H of DHP), 3330 cm^{-1} (O-H), 2953 cm^{-1} (Aromatic C-H), 1653cm^{-1} (Ester C=O), 1590 cm^{-1} (Aromatic C=C), 1340 cm^{-1} (C-N) and 1229 (Ether C-O-C); ^{1}H NMR (DMSO-d_6): δ 2.28 (s, 6H, 2xCH_3), δ 3.55 (s, 6H, 2x-COOCH_3), δ 3.76 (s, 3H, -OCH_3), δ 4.81 (s, 1H, C*H* of DHP) δ 6.59- 6.70 (m, 3H, Ar*H*).), δ 7.90 (s, 1H, O*H*) and δ 8.46 ppm (s, 1H, N*H* of DHP); Anal. calcd. for $C_{18}H_{21}NO_6$: C% 62.24, H% 6.05, N% 4.03; Found: C% 62.58, H% 6.64, N% 4.06.

*Dimethyl-1, 4-dihydro-4-(4-dimethylamino)-2, 6-dimethylpyridine-3, 5-dicarboxylate (COMP-**Id**)*

^{1}H NMR(DMSO-d_6): δ 2.2 (s, 6H, 2xCH_3), δ 2.8 (s, 6H, 2x-COOCH_3), δ 3.5 (s, 6H, -NCH_3), δ 4.8 (s, 1H, C*H* of DHP), δ 5.5(s,1H,NH of DHP), δ 6.53-6.55 (d, 2H, ArH_a) and δ 7.03-7.05 ppm (d, 2H, ArH_b).

*Dimethyl-1, 4-dihydro-4-(3-nitrophenyl)-2, 6-dimethylpyridine-3, 5-dicarboxylate (COMP-**Ie**)*

IR (KBr, ν_{max}): 3398 cm^{-1} (N-H of DHP), 3083 cm^{-1} (Aromatic C-H), 1668 cm^{-1} (Ester C=O), 1482 cm^{-1} (Aromatic C=C), 1269 cm^{-1} (R-NO_2) and 1208 cm^{-1} (C-N); ^{1}H NMR (DMSO-d_6): δ 2.27 (s, 6H, 2xCH_3), δ 3.54 (s, 6H, 2x-COOCH_3), δ 4.97 (s, 1H, C*H* of DHP), δ 7.37 - 7.796 (m, 4H, Ar*H*)) and δ 8.77ppm (s, 1H, N*H* of DHP).

*Diethyl-1, 4-dihydro-4-(4-methylphenyl)-2, 6-dimethylpyridine-3, 5-dicarboxylate (COMP-**IIa**)*

IR (KBr, ν_{max}): 3322 cm^{-1} (N-H of DHP), 2979 cm^{-1} (Aromatic C-H), 1694 cm^{-1} (Ester C=O), 1610 cm^{-1} (Aromatic C=C) and 1365 cm^{-1} (C-N); ^{1}H NMR (DMSO-d_6): δ 1.05 (s, 6H, 2x-$COOCH_2CH_3$), δ 2.09 (s, 3H, -CH_3), δ 2.11(s, 6H, 2x-CH_3), δ 3.91 (m, 4H, 2x-$COOCH_2CH_3$), δ 4.78 (s, 1H, C*H* of DHP), δ 6.07 (s, 1H, N*H* of DHP) , δ 6.82 -6.84 (d, 2H, ArH_a) and δ 6.99 -7.01 ppm (d, 2H, ArH_b).

*Diethyl-1, 4-dihydro-4-(3-hydroxyphenyl)-2, 6-dimethylpyridine-3, 5-dicarboxylate (COMP-**IIb**)*

IR (KBr, ν_{max}): 3351 cm^{-1} (N-H of DHP), 3308 cm^{-1} (O-H), 2978 cm^{-1} (Aromatic C-H), 1650 cm^{-1} (Ester C=O), 1594 cm^{-1} (Aromatic C=C) and 1217 cm^{-1} (C-N); ^{1}H NMR (DMSO-d_6): δ 1.22 (t, 6H, 2x -$COOCH_2CH_3$), δ 2.29 (s, 6H, 2x-CH_3), δ 4.05 (m, 4H, 2x$COOCH_2CH_3$), δ 4.89 (s, 1H, OH), δ 6.54 -6.98 (m, 4H, Ar*H*) and δ 8.18 ppm (s, 1H, N*H* of DHP); Anal. calcd. for $C_{19}H_{23}NO_5$: C% 66.08, H% 6.66, N% 4.05; Found C% 66.99, H% 6.36, N% 4.59.

*Diethyl-1, 4-dihydro-4-(3-hydroxy-4-methoxyphenyl)-2, 6-dimethylpyridine-3, 5-dicarboxylate (Comp-**IIc**)*

IR (KBr, ν_{max}): 3398 cm^{-1} (N-H of DHP), 3315 cm^{-1} (O-H), 2992 cm^{-1} (Aromatic C-H), 1669 cm^{-1} (Ester C=O), 1483 cm^{-1} (Aromatic C=C), 1270 cm^{-1} (C-N) and 1208 cm^{-1} (Ether C-O-C); ^{1}H NMR (DMSO-d_6): δ 1.23 (s, 6H, 2x-$COOCH_2CH_3$), δ 2.30 (s, 6H, 2x-CH_3), δ 3.8 (s, 3H, -OCH_3), δ 4.05 (m, 4H, -$COOCH_2CH_3$) δ 4.90 (s, 1H, C*H* of DHP), δ 5.53 (s, 1H, O*H*), δ 5.69 (s, 1H, N*H* of DHP) and δ 6.67 -6.84 ppm(m, 3H, Ar*H*); Anal. calcd. for $C_{20}H_{25}NO_6$: C% 64, H% 6.66, N% 3.75; Found: C% 63.39, H% 6.46, N% 3.58.

*Diethyl-1, 4-dihydro-4-(4-dimethylamino)-2, 6-dimethylpyridine-3, 5-dicarboxylate (COMP-**IId**)*

IR (KBr, ν_{max}): 3303 cm^{-1} (N-H of DHP), 3197 cm^{-1} (Aromatic C-H), 1604 cm^{-1} (Ester C=O), 1579 cm^{-1} (Aromatic C=C) and 1212 cm^{-1} (C-N); ^{1}H NMR(DMSO-d_6): δ 1.24 (s, 6H, 2x-$COOCH_2CH_3$), δ 2.31(s, 6H, 2x-CH_3), δ 2.89 (s, 6H, -$N(CH_3)_2$, δ 4.10 (m, 4H, 2x-$COOCH_2CH_3$), δ 4.90 (s, 1H, C*H* of DHP), δ 6.10 (s, 1H, N*H* of DHP), δ 6.61 - 6.63 (d, 2H, ArH_a) and δ 7.15-7.17 ppm (d, 2H, ArH_b); Anal. calcd. for $C_{19}H_{24}N_2O_4$: C% 66.27, H% 6.98, N% 8.13; Found: C% 67.25, H% 7.24, N% 8.24.

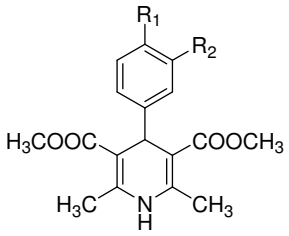
*Diethyl-1, 4-dihydro-4-(3-nitrophenyl)-2, 6-dimethylpyridine-3, 5-dicarboxylate (COMP-**IIe**)*

IR (KBr, ν_{max}): 3330 cm^{-1} (N-H of DHP), 2955 cm^{-1} (Aromatic C-H),1653 cm^{-1} (Ester C=O), 1528cm^{-1} (R-NO_2), 1482 cm^{-1} (Aromatic C=C) and 1229 cm^{-1} (C-N).^{1}H NMR (DMSO-d_6): δ 1.20 (t, 6H, 2x$COOCH_2CH_3$), δ 2.32 (s, 6H, 2x-CH_3), δ 4.0 (m, 4H, 2x-$COOCH_2CH_3$), δ 5.09 (s, 1H, C*H* of DHP), δ 6.59 (s, 1H, N*H* of DHP) and δ 7.28 - 8.12 ppm (m, 4H, Ar*H*); Anal. calcd. for $C_{19}H_{23}N_2O_7$: C% 60.8, H% 6.14, N% 7.46; Found: C% 61.37, H% 6.03, N% 6.97.

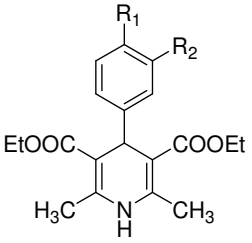
Results and Discussion

The 1,4-dihydropyridines have attracted the interest of many medicinal chemists and because of their privileged structure, many modifications have been carried out in the last decade.

To the date, much research has been directed towards the clean technologies for the 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 in less time when compared to conventional, solvent free and ultrasonication method (Table 1). At the same time conventional method was time consuming but scalable when compared with other methods.



I(a-e)



II(a-e)

Table 1. Percentage yield and time taken by compounds from various methods

Compd.	R_1,R_2	M.P, ^oC	Conventional		Microwave		Solvent-free		Ultrasonication	
			Yield, %	Time, h	Yield, %	Time, min	Yield, %	Time, h	Yield, %	Time, min
Ia	R_1-CH_3, R_2-H	177-179	62	23	85	8	57	2.5	60	12
Ib	R_1-H, R_2-OH	168-170	58	25	76	10	53	3	56	12
Ic	R_1-OCH_3, R_2-OH	169-170	66	26	73	14	58	3	60	18
Id	R_1-$N(CH_3)_2$, R_2-H	158-160	69	21	75	16	56	3	62	17
Ie	R_1-H, R_2-NO_2	160-162	70	23	87	14	60	3	63	16
IIa	R_1-CH_3, R_2-H	120-122	66	22	75	14	59	2.5	61	18
IIb	R_1-H, R_2-OH	182-184.5	60	28	75	12	55	3	57	12
IIc	R_1-OCH_3, R_2-OH	169-170	57	27	71	15	54	3.5	55	12
IId	R_1-$N(CH_3)_2$ R_2-H	156-158	63	23	70	13	59	3	59	18
IIe	R_1-H, R_2-NO_2	168-170	70	24	88	10	65	3	68	14

[*] *All products are known and their physical and spectral data were compared with authentic samples*[14,15]

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