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Synthesis of Diethyl 4-(Phenyl-substituted)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylates Catalyzed by $CoCl_2$/K-10 Montmorillonite in Water and Their Antimicrobial Activity[1]

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Abstract—A simple and efficient method of one pot synthesis of 1,4-dihydropyridine by three components reaction of aromatic aldehydes with 1,3-dicarbonyl compound, ammonium acetate and catalytic amount of $CoCl_2$ based on the Hantszch reaction is developed. The process is catalysis by an inexpensive catalyst in water medium, gives high yield of products and involves no volatile organic solvents. Some synthesized compounds demonstrated antimicrobial activity.

Keywords: antimicrobial activity, $CoCl_2$ catalyst, 1,4-dihydropyridine, Hantszch reaction, K-10 montmorillonite

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INTRODUCTION

Dihydropyridyl compounds attract close attention due to various applications in medicine and specific properties determined by several reactive centers combined in their molecules [1, 2]. Dihydropyridine derivatives, including nifedipine, nitrendipine and nimodipine [3, 4], are calcium channel blockers. A number of dihydropyridines are potential drugs for treatment of congestive heart failure [5, 6] and demonstrate properties of neuroprotective [7], antihypertensive, antibacterial, and anticancer agents [8, 9].

RESULTS AND DISCUSSION

We report herein water-mediated method of synthesis of Hantzsch dihydropyridines bearing various substituents (Table 1) using $CoCl_2$/K-10 Montmorillonite as the catalyst (Scheme 1). A number of aryl and heteroaryl aldehydes smoothly underwent rapid multicomponent condensation to accomplish several substituted functionally important Hantzsch dihydropyridines in high yield and purity.

Different solvents, including dimethylformamide, chloroform, tetrahydrofuran, acetonitrile, ethanol, and water were tested in the process. Water was determined to be the most efficient media for the reaction.

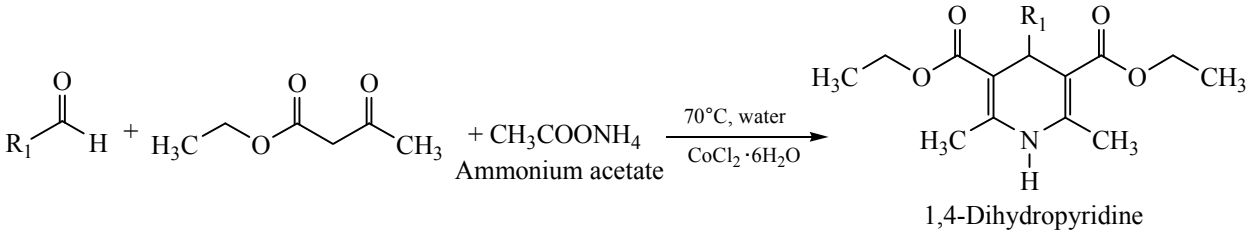
Aryl aldehydes with electron-donating and electron-withdrawing substituents at various positions produced the corresponding products without affecting the substituents and the substitution pattern. α,β-Unsaturated aryl aldehydes (cinnamaldehyde) underwent rapid conversion without polymerization and other side reactions.

Table 1. Physical characteristics of the synthesized compounds

Comp. no.	R	Formula	*M*, mg	Time, min
1a	C_4H_3O	$C_{17}H_{21}NO_5$	319.35	65
1b	C_6H_4OH	$C_{19}H_{23}N0_5$	345.38	95
1c	$C_6H_4NO_2$	$C_{19}H_{22}N_2O_6$	374.38	60
1d	C_7H_7O	$C_{20}H_{25}NO_5$	359.41	85
1e	C_8H_7	$C_{21}H_{26}NO_4$	343.41	105
1f	C_5H_4N	$C_{18}H_{22}N_2O_4$	330.37	70
1g	$C_6H_4NO_2$	$C_{19}H_{22}N_2O_6$	374.39	75
1h	C_4H_3O	$C_{17}H_{21}NO_5$	319.35	70
1i	C_6H_4Br	$C_{19}H_{22}BrNO_4$	408.29	65
1j	C_6H_4Br	$C_{19}H_{22}BrNO_4$	408.29	60

[1] The text was submitted by the authors in English.

Scheme 1. Synthesis of 1,4-dihydropyridine derivatives.



$CoCl_2$ in combination with K-10 Montmorillonite clay acted as efficient catalysts in the synthesis of title compounds from acid sensitive aldehydes (Table 2).

Application of $CoCl_2$ as a catalyst reduced time required for the reaction to complete and led to high yields of the process. Influence of concentration of $CoCl_2$ catalyst was studied (Table 3). Concentration of 2 mol % was determined to be the optimum one.

Antibacterial screening. The compounds **1a–1j** were tested for their *in vitro* antibacterial activity against *Pseudomonas aeruginosa* (MTCC-2435), *Streptococcus epidermidis* and *Staphylococcus aureus* (MTCC-96) by the disc diffusion method using Muller–Hinton agar (Hi-Media) medium and ciprofloxacin tablet (250 mg) as the standard. The compounds **1a–1j** were tested at concentrations of 50, 100, 200, and 300 μg/mL in DMSO. The minimum inhibitory concentration of all compounds was determined to be 100 μg/mL. The zones of inhibition (mm) were measured after 24 h incubation at 37°C (Table 4).

Effectivity classified into four zones on the basis of the diameter of the zone of inhibition: 0–5 mm (poor activity); 6–10 mm (moderate activity); 11–15 mm (high activity); and above 16 mm (very high activity);

Each value is an average of three independent determinations.

EXPERIMENTAL

Melting points were determined on a digital melting point apparatus (EQ-730). ^1H and ^{13}C NMR spectra were measured on a BRUKER Avance II 500.1 spectrometer in $CDCl_3$ using TMS as the internal standard. IR spectra were recorded on a Bruker Alpha FT-IR spectrophotometer. MS were measured on an Accu TOF Mass spectrometer. Elemental analysis was carried out on an Elemental analyser EURO EA 3000.

Synthesis of diethyl 4-(phenyl-substituted)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylates (1a–1j). A mixture of an aromatic aldehyde (1 mmol), ethyl acetoacetate (2 mmol), ammonium acetate (1.3 mmol), and cobalt chloride hexahydrate (2 mol %) was vigorously stirred in water (2 mL) at 70°C for the stipulated period of time. Upon completion of the reaction (TLC), 1–2 mL of ethanol were added to facilitate granulation of a product and poured into crushed ice. A solid product was filtered off, washed several times with water and crystallized from aqueous ethanol. Sometimes the products were isolated as viscous oils. In such cases those were refluxed with 0.2 g of K-10 Montmorillonite clay as a solid state catalyst to facilitate formation of a solid product.

Diethyl 4-(furan-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1a). Yield 90%, mp 166°C. R_f 0.57. IR spectrum, ν, cm^{-1}: 3334 (NH), 2978 (C–H), 1686 (C=O), 1639(C=O), 1529 (=C–H and C=C),

Table 2. Optimization of catalysts with respect to yield, time, and temperature

Catalyst	Yield, %	Time, min	*T*, °C
KF/Alumina	71	120	78
Silica gel	75	500	–
Alumina sulphuric acid	80	200	70
$AlCl_3 \cdot 6H_2O$	70	180	60
$CoCl_2$	95	65	70

Table 3. Optimization of the catalyst concentration

Concentration of $CoCl_2$, mol %	Yield, %
6.0	95
4.0	95
2.0	95
1.0	75
0.5	70

Table 4. Zones of inhibition for compounds **1a–1j** against bacterial strains

Compound	Zone of inhibition, mm (100 μg/mL)		
	Pseudomonas aeruginosa	*Streptococcus epidermidis*	*Staphylococcus aureus*
1a	16	18	17
1b	0	14	18
1c	8	10	14
1d	10	12	12
1e	14	0	8
1f	12	7	0
1g	14	8	10
1h	0	10	9
1i	9	13	15
1j	14	8	0
Ciprofloxacin	18	20	20

1487 (C=C in furan), 1371 (CH_3 in O–CH_2–CH_3), 1325 (C–N in C_{Ar}–N), 1296 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 1.26 s (3H, CH_3), 2.33 q (2H, CH_2), 4.14 t (3H, CH_3), 5.20 s (1H, CH), 5.81 s (1H, NH), 5.94–7.27 m (3H, Ar-H). LC-MS (*m/z*): Found: *m/z* 343.27 $[M + Na]^+$. Calculated: $[M + Na]^+$ 343.35.

Diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1b). Yield 93%, mp 241°C. R_f 0.60. IR spectrum, ν, cm^{-1}: 3344 (N–H), 2986 (C–H), 1792 (C=O), 1716 (C=O), 1540 (=C–H and ring C=C), 1218 (C–O–C). LC-MS (*m/z*): Found: *m/z* 368.28 $[M + Na]^+$. Calculated: $[M + Na]^+$ 368.

Diethyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1c). Yield 85%, mp 170°C. R_f 0.54. IR spectrum, ν, cm^{-1}: 3342 (NH), 1703 (C=O), 1643 (C=O), 1523 (=C–H and ring C=C), 1485 (C=C), 1369 (sym. CH_3 in O–CH_2–CH_3), 1345 (C–N in C_{Ar}–N). ^{1}H NMR spectrum, δ, ppm: 1.23 t (3H, CH_3), 2.40 s (3H, CH_3), 4.09 q (2H, CH_2), 5.09 s (1H, CH), 5.80 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 14.88 (CH_3), 18.66 (CH_3), 59.35 (CH_2), 167.56 (C=O). ^{13}C NMR-DEPT spectrum, δ, ppm: 14.07 (CH_3), 18.66 (CH_3), 40.15 (CH), 61.90 (CH_2), 115.61 (CH, Ar), 128.74 (CH, Ar). LC-MS (*m/z*): Found: *m/z* 397.18 $[M + Na]^+$. Calculated: $[M + Na]^+$ 397.

Diethyl 4-(4-methoxphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1d). Yield 85%, mp 161°C. R_f 0.65. IR spectrum, ν, cm^{-1}: 3324 (N–H), 2974 (C–H), 1696 (C=O), 1649 (C=O), 1529 (=C–H and ring C=C), 1487 (C=C), 1371 (CH_3 in O–CH_2–CH_3), 1326 (C–N in C_{Ar}–N), 1295 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 0.88 s (3H, CH_3); 1.23 q (2H, CH_2), 2.33 t (3H, CH_3), 3.90 s (1H, CH), 4.07 s (1H, NH). LC-MS (*m/z*): Found: *m/z* 358.30 $[M + H]^+$. Calculated: $[M + H]^+$ 357.

Diethyl-2,6-dimethyl-4-(2-phenylethylene)-1,4-dihydropyridine-3,5-dicarboxylate(1e). Yield 85%, mp 224°C. R_f 0.70. IR spectrum, ν, cm^{-1}: 3334 (N–H), 2978 (C–H), 1686 (C=O), 1639 (C=O), 1487 (C=C), 1214 (C–O–C). LC-MS (*m/z*): Found: *m/z* 378.31. Calculated: $[M + Na]^+$ 378.

Diethyl 2',6'-dimethyl-1',4'-dihydro-2,4'-bipyridine-3',5'-dicarboxylate (1f). Yield 95%, mp 196°C. R_f 0.65. IR spectrum, ν, cm^{-1}: 3100 (N–H), 2927 (C–H), 1685 (C=O), 1632 (C=O), 1504 (=C–H and ring C=C), 1428 (C=C), 1377 (CH_3 in O–CH_2–CH_3), 1300 (C–N in C_{Ar}–N), 1266 (C–O–C). ^{1}H NMR, δ, ppm: 1.12 s (3H, CH_3), 2.32(q, 2H, CH_2), 2.48 t (3H, CH_3), 4.15 s (1H, CH), 4.72H s (1H, NH). LC-MS (*m/z*): Found: *m/z* 368.28 $[M + K]^+$. Calculated: $[M + K]^+ = 369$.

Diethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1g). Yield 75%, mp 173°C. R_f 0.65. IR spectrum, ν, cm^{-1}: 3343 (N–H), 2888 (C–H), 1702 (C=O), 1642 (C=O), 1523 (=C–H and ring C=C), 1485–1433 (C=C), 1369 (CH_3 in O–CH_2–CH_3), 1346 (C–N in C_{Ar}–N). ^{1}H NMR spectrum, δ, ppm: 1.19 t (3H, CH_3), 2.42 q (2H, CH_2), 2.466 s (3H, CH_3), 5.09 s (1H, CH), 6.46 s (1H, NH).

Diethyl 4-(furan-3-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1h). Yield 70%, mp 169°C. R_f 0.70. IR spectrum, ν, cm^{-1}: 3344 (N–H), 2960 (C–H), 1697 (C=O), 1644 (C=O), 1539 (=C–H and ring C=C), 1475 (C=C), 1369 (CH_3 in O–CH_2–CH_3), 1320 (C–N in C_{Ar}–N), 1296 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 1.23 t (3H, CH_3), 2.18 q (2H, CH_2), 2.32 s (3H, CH_3), 4.30 s (1H, NH), 5.19 s (1H, CH).

Diethyl 4-(3-bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1i). Yield 65%, mp 212°C. R_f 0.75. ^{1}H NMR spectrum, δ, ppm: 1.05 t (3H, CH_3), 2.12 s (3H, CH_3), 2.30 q (2H, CH_2), 5.00 s (1H, CH), 5.82 s (1H, NH).

Diethyl4-(4-bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1j). Yield 60%, mp 211°C. ^{1}H NMR spectrum, δ, ppm: 1.41 t (3H, CH_3), 2.32 s (3H, CH_3), 2.41 q (2H, CH_2), 4.41 s (1H, NH), 5.19 s (1H, CH).

CONCLUSIONS

A simple, efficient and green method of synthesis of substituted 1,4-dihydropyridines via a one-pot three component coupling of aromatic aldehydes, 1,3-dicarbonyl compounds and ammonium acetate catalysed by $CoCl_2$ and K-10 montmorillonite is developed. The advantages of this method include operational simplicity, short reaction time, use of relatively inexpensive, commercially available catalysts and high yields of products. Screening for antibacterial activity of products was carried out.

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