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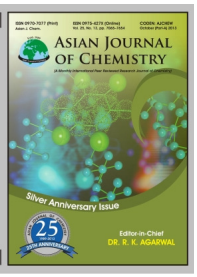

An Efficient One-Pot Multicomponent Synthesis of Dihydropyridines by using Succinic Acid as Mild Organocatalyst

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A simple, economic and mild protocol was achieved for the synthesis of 1,4-dihydropyridines catalyzed by succinic acid as a mild and effective organocatalyst at 80 ºC. This method furnishes better yield and associated with advantages like simple work up procedure without any toxic side products. The reusability of catalyst was also investigated. The method avoids use of toxic solvents and expensive catalysts and proceeds efficiently with the use of mild organocatalyst which makes the protocol environmentally benign.

Key Words: Succinic acid, Multicomponent reaction, Dihydropyridine.

INTRODUCTION

In modern synthetic organic chemistry, multicomponent reactions (MCRs) have emerged as efficient and powerful tools because the synthesis of complex organic molecules from simple and readily available substrates can be achieved in a fast and efficient manner without isolation of any intermediate[1-4]. In this type of reactions three or more components are reacted to form ideally one product, which contains the essential parts of all the initial reactants. Nowadays, multicomponent reactions have become important while developing environmentally friendly processes, as they are characterized by the reduction in number of synthetic steps, lower energy consumption as well as less waste production. Consequently, developing new multicomponent reactions and improving known multicomponent reactions are the areas of interest for researchers in synthetic organic chemistry.

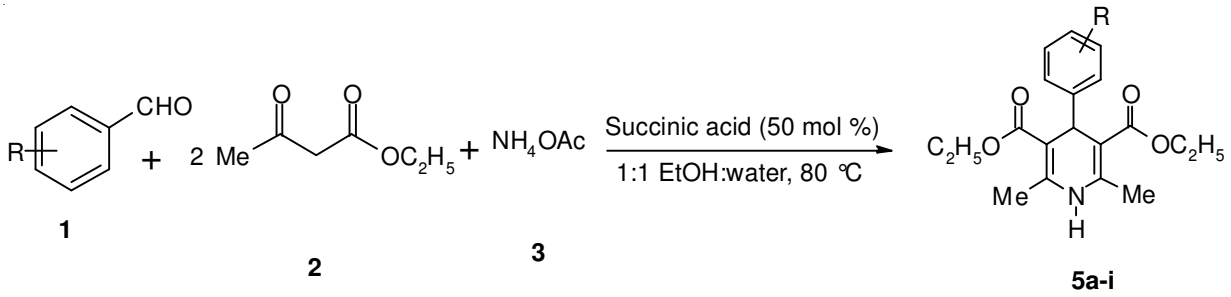
Generally, 1,4-dihydropyridine (DHP) derivatives are synthesized by Hantzsch reaction which involves the one pot four-component cyclocondensation of an aldehyde with an active methylene carbonyl compound and ammonia or ammonium acetate[5]. Dihydropyridine derivatives constitute an important class of calcium channel blockers and proved to be valuable as they are part of an important class of drugs used for the treatment of cardiovascular diseases, including hypertension[6]. Recent studies have also revealed that dihydropyridine derivatives exhibit several medicinal applications, including neuroprotectant[7], platelet antiaggregatory activity[8] and as chemo sensitizer in tumor therapy[9].

In view of the biological importance of dihydropyridines, several methods for their synthesis have been reported using microwaves[10], ionic liquids[11] and also in presence of catalysts such as TMSI[12], metal triflates[13], I_2[14], ceric ammonium nitrate[15], polymers[16] and organocatalyst[17]. However, the use of high temperatures, usage of excess organic solvents, expensive metal precursors, catalysts which are unsafe for the environment and longer reaction times limit the use of these methods. Also, some conventional Bronsted acids, such as sulfuric acid, nitric acid, hydrochloric acid and hydrofluoric acid are often used in organic syntheses and industrial processes. However, these acid catalysts are corrosive, toxic, harmful, difficult to handle, to dispose off and are difficult to remove from the reaction mixture[18]. For these reasons, there is a great effort to replace these conventional catalysts by new, non-toxic and efficient catalysts. Development of solid acid catalysts has received great attention in research activities and industrial processes[19,20].

Due to our interest in the synthesis of heterocyclic compounds, by the application of new efficient catalysts in organic transformations, herein we report the synthesis of dihydropyridines by the condensation of ethyl acetoacetate with various aromatic aldehydes and ammonium acetate in ethanol:water (1:1) solvent system using succinic acid as an acid catalyst (**Scheme-I**). Succinic acid possesses high activity and results in good yield of synthesized derivatives.

EXPERIMENTAL

All the chemicals used were obtained from commercial source and used without purification. The reaction mixture



Scheme-I: Synthesis of dihydropyridine from aldehyde, ethyl acetoacetate and ammonium acetate

was heated on water bath with constant stirring which helped the mixing and uniform heating of the reaction mixture. Melting points were measured with DBK-programmable melting point apparatus. The purity of products and completion of reaction was checked by TLC on Merck silicagel 60 F_{254} plates. IR spectra were obtained using potassium bromide pellets on Bruker ALPHA FTIR Spectrometer. The ^{1}H NMR spectra were measured with Avance-300 spectrophotometer and chemical shifts are reported in ppm in $CDCl_3$ with TMS as an internal standard.

General procedure: To the reaction mixture containing benzaldehyde (1 mmol), ethyl acetoacetate (2 mmol) and ammonium acetate (1 mmol) in 1:1 ethanol:water (2 mL), 50 mol % succinic acid was added. Then the reaction mixture was heated at 80 ºC with constant stirring for 2 h. The progress of reaction was monitored by TLC. The reaction mixture was then filtered and washed with plenty of distilled water. The solid obtained was air-dried to afford the crude product which was recrystallized from ethyl alcohol to obtain pure product. Yield 90 %, m.p. 157-159 ºC.

Diethyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (5a): IR (KBr, ν_{max}, cm^{-1}): 3340, 3072, 1704; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.28 (6H, t, 2-OCH_2CH_3), 2.31 (6H, s, 2-CH_3), 4.19 (4H, q, 2-OCH_2CH_3), 5.21 (1H, s, -CH), 7.27 (1H, bs, -NH), 7.49-7.52 (5H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm) 14.7, 16.5, 42.9, 62.1, 102.1, 126.1, 128.6, 129.2, 142.9, 150.3, 167.7.

Diethyl-2,6-dimethyl-4-(2-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (5c): IR (KBr, ν_{max}, cm^{-1}): 3277, 3079, 2972, 1711; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.29 (6H, t, 2-OCH_2CH_3), 2.30 (6H, s, 2-CH_3), 4.18 (4H, q, 2-OCH_2CH_3), 5.20 (1H, s, -CH), 7.25 (1H, bs, -NH), 7.33-7.37 (4H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 14.2, 16.7, 39.9, 62.0, 102.4, 126.5, 127.9, 128.9, 130.4, 134.2, 143.4, 151.0, 167.9.

Diethyl-2,6-dimethyl-4-(4-chlorophenyl)-1,4-dihydropyridine- 3,5-dicarboxylate (5d): IR (KBr, ν_{max}, cm^{-1}): 3272, 3084, 2948, 1710; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.35 (6H, t, 2-OCH_2CH_3), 2.32 (6H, s, 2-CH_3), 4.20 (4H, q, 2-OCH_2CH_3), 5.23 (1H, s, -CH), 7.10 (1H, bs, -NH), 7.12-7.16 (2H, m, Ar-H) 7.21-7.26 (2H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 13.9, 16.5, 42.9, 62.3, 102.9, 128.2, 130.2, 131.3, 140.6, 150.1, 167.5.

Diethyl-2,6-dimethyl-4-(4-hydroxhphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (5e): IR (KBr, ν_{max}, cm^{-1}): 3312, 3054, 2952, 1705, 1455; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.28 (6H, t, 2 -OCH_2CH_3), 2.21 (6H, s, 2-CH_3), 4.24 (4H, q, 2-OCH_2CH_3), 5. 06 (1H, s, -OH), 5.30 (1H, s, -CH), 6.60 (1H, bs, -NH), 7.08-7.12 (2H, m, Ar-H) 7.14-7.19 (2H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 14.1, 16.1, 43.5, 61.9, 102.6, 115.1, 130.8, 136.5, 150.2, 155.1, 167.5.

Diethyl-2,6-dimethyl-4-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (5f): IR (KBr, ν_{max}, cm^{-1}): 3342, 3032, 2964, 1702; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.08 (6H, t, 2-OCH_2CH_3), 2.02 (6H, s, 2-CH_3), 3.80 (3H, s, -OCH_3), 3.98 (4H, q, 2-OCH_2CH_3), 5.13 (1H, s, -CH), 7.10 (1H, bs, -NH), 7.04-7.09 (2H, m, Ar-H) 7.12-7.14 (2H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 14.1, 16.2, 45.0, 55.9, 62.4, 102.5, 115.1, 130.4, 134.6, 151.0, 157.1, 167.5.

Diethyl-2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine- 3,5-dicarboxylate (5h): IR (KBr, ν_{max}, cm^{-1}): 3314, 3076, 2921, 1725, 1534, 1386; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.12 (6H, t, 2-OCH_2CH_3), 2.09 (6H, s, 2 -CH_3), 4.01 (4H, q, 2-OCH_2CH_3), 5.12 (1H, s, -CH), 7.12 (1H, bs, -NH), 7.64 -7.69 (2H, m, Ar-H), 7.71-7.74 (2H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 14.6, 16.1, 44.1, 62.4, 103.1, 121.2, 130.4, 145.1, 148.4, 167.5.

Diethyl-2,6-dimethyl-4-(2-furyl)-1,4-dihydropyridine-3,5-dicarboxylate (5i): IR (KBr, ν_{max}, cm^{-1}): 3346, 3082, 1700, 1650, 1488; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.27 (6H, t, 2-OCH_2CH_3), 2.32 (6H, s, 2-CH_3), 4.16 (4H, q, 2-OCH_2CH_3), 5.18 (1H, s, -CH), 5.92 (2H, d, furyl ring Hs) 6.20 (1H, s, furyl ring H) 7.20 (1H, bs, -NH); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 14.9, 15.4, 31.5, 61.1, 102.0, 107.7, 111.2, 142.5, 150.9, 152.2, 167.1.

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(phenyl)-5(6*H*)-oxoquinoline-3-carboxylate (6a): IR (KBr, ν_{max}, cm^{-1}): 3050, 2940, 1715, 1630, 1605, 1460, 1375, 1215; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 0.93 (3H, s, -CH_3), 1.06 (3H, s, -CH_3), 1.12 (3H, t, -OCH_2CH_3), 2.22 (4H, m, 2 -CH_2), 2.36 (3H, s, -CH_3), 4.09 (2H, q, -OCH_2CH_3), 5.03 (1H, s, CH), 6.02 (1H, s, NH), 7.05-7.26 (5H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 14.62, 18.72, 21.26, 26.59, 36.05, 37.18, 59.49, 103.99, 111.54, 126.12, 127.87, 128.28, 145.40, 148.26, 151.87, 167.37, 195.11.

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(2-chlorophenyl)-5(6*H*)-oxoquinoline-3-carboxylate (6c): IR (KBr, ν_{max}, cm^{-1}): 3065, 2957, 1725, 1644, 1614, 1467, 1386, 1227; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 0.96 (s, 3H, -CH_3), 1.06 (s, 3H, -CH_3), 1.20 (t, 3H, -OCH_2CH_3), 2.03-2.22 (m, 4H, 2× CH_2), 2.40 (3H, s, CH_3), 4.06 (2H, q, -OCH_2CH_3), 5.10 (1H, s, -CH), 6.09 (1H, bs, -NH) 7.12-7.29 (4H, m, Ar-H)); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 196.01, 167.95, 149.60, 144.59,

144.35 133.57, 132.45, 130.05, 127.69, 126.70, 111.47, 105.57, 60.23, 51.16, 41.34, 36.34, 32.92, 29.78, 27.59, 19.60, 14.64.

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(4-chlorophenyl)-5(6*H*)-oxoquinoline-3-carboxylate (6d): IR (KBr, ν_{max}, cm^{-1}): 3274, 1705; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 0.93(3H, s, $-CH_3$), 1.08 (3H, s, $-CH_3$), 1.19 (3H, t, $-OCH_2CH_3$), 2.11-2.30 (4H, m, 2-CH_2), 2.37 (3H, S, $-CH_3$), 4.06 (2H, q, $-OCH_2CH_3$), 5.02 (1H, s, -CH), 5.98 (1H, bs, NH), 7.14-7.17 (2H, d, Ar-H), 7.22-7.26 (2H, d, Ar-H)); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 14.65, 18.76, 26.94, 32.60, 32.54, 50.77, 59.42, 104.55, 110.59, 114.70, 128.80, 138.87, 144.86, 149.53, 155.71, 167.48, 194.86.

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(4-hydroxyphenyl)-5(6*H*)-oxoquinoline-3-carboxylate (6e): IR (KBr, ν_{max}, cm^{-1}): 3285, 1690, 1617, 1229; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 0.95 (3H, s, $-CH_3$), 1.19 (3H, s, $-CH_3$), 1. 31 (3H, t, $-OCH_2CH_3$), 2.24-2.32 (4H, m, 2-CH_2), 2.45 (3H, s, $-CH_3$) 4.45 (2H, q, $-OCH_2CH_3$), 5.24 (1H, s, -OH), 5.52 (1H, s, -CH), 7.12-7.15 (2H, d, Ar-H), 5.72 (1H, bs, -NH). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 14.65, 18.76, 26.94, 32.60, 32.54, 50.77, 59.42, 104.55, 110. 59, 114.70, 128.80, 138.87, 144.86, 149.53, 155.71, 167.48, 194.86.

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(4-methoxyphenyl)-5(6*H*)-oxoquinoline-3-carboxylate (6f): IR (KBr, ν_{max}, cm^{-1}): 3275, 2957, 1705, 1647, 1605, 1497,1382, 1217, 1032, 766; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 0.93 (3H, s, $-CH_3$), 1.08 (3H, s, $-CH_3$), 1.22 (3H, t, $-OCH_2CH_3$), 2.02-2.11 (4H, m, 2-CH_2), 2.32 (3H, s, $-CH_3$), 3.75 (3H, s, $-OCH_3$), 4.01 (2H, q, $-OCH_2CH_3$), 4.82 (1H, s, -CH), 6.68 (2H, d, Ar-H), 7.12 (2H, d, Ar-H), 5.94 (1H, bs, -NH)); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 196.27, 168.03, 158.19, 149.24, 143.93, 140.16, 129.36, 113.66, 112.44, 106.61, 60.19, 55.52, 51.23, 41.22, 36.17, 33.06, 29.90, 27.55, 19.65, 14.68 (Fig. 1).

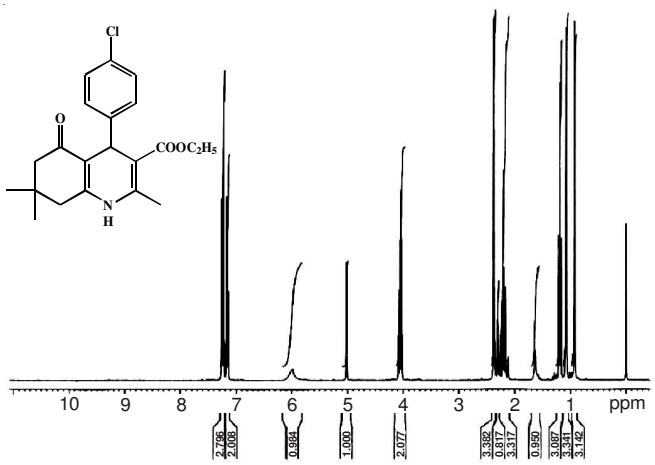


Fig. 1. NMR spectra of compound **6f**

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(4-nitrophenyl)-5(6*H*)-oxoquinoline-3-carboxylate (6g): IR (KBr, ν_{max}, cm^{-1}): 3285, 1690, 1617, 1536, 1355, 1229; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 0.92 (3H, s, $-CH_3$), 1.22 (3H, s, $-CH_3$), 1.29 (3H, t, $-OCH_2CH_3$), 2.35-2.39 (4H, m, 2-CH_2), 2.45 (3H, s, $-CH_3$) 4.24 (2H, q, $-OCH_2CH_3$), 5.26 (1H, s, -CH), 6.12 (1H, bs, -NH) 7.76-7.82 (2H, d, Ar-H), 7.90-7.97 (2H, d, Ar- H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 14.65, 18.76, 26.94, 32.60, 32.54, 50.77, 59.42, 104.55, 110.59, 114.70, 128.80, 138.87, 144.86, 149.53, 155.71, 167.48, 194.86.

RESULTS AND DISCUSSION

Initially, in the efforts to develop an efficient and mild methodology for synthesis of dihydropyridine derivatives, we initiated our studies by subjecting catalytic amount of succinic acid for model reaction between 4-methoxy benzaldehyde, ethyl acetoacetate and ammonium acetate in solvent free condition at room temperature. Unfortunately, the product was not observed on TLC plate even after 12 h of starting. To effect the reaction, various solvent systems were screened at different temperatures. When model reaction was carried out at room temperature in aqueous medium there slight improvement in the result was observed (Table-1, entry 2) even at prolonged reaction time. Furthermore, to improve the yield and to reduce the reaction time we have continued our efforts by employing different organic solvents such as ethanol, acetonitrile, tetrahydrofuran, dichloromethane, *n*-hexane and chloroform (Table-1). It is observed the reaction proceeds smoothly at 80 ºC in EtOH:water (1:1) solvent system (Table-1, entry 9) with 94 % yield of product in 2 h. In the case of solvents such as dichloromethane, *n*-hexane and chloroform (Table-1, entries 6-8) the conversions were quite similar to aqueous medium. Interestingly, the use of polar protic and aprotic organic solvents such as ethanol, acetonitrile and tetrahydrofuran (Table-1, entries 3-5) afforded good results for 1,4-dihydropyridine derivatives within 2.5-3.5 h.

TABLE-1
OPTIMIZATION OF REACTION CONDITIONS USING VARIOUS SOLVENTS[a]

Entry	Solvent	Time (h)[b]	Yield (%)[b]
1	Neat	12	00
2	Water	8.0	42
3	EtOH	2.5	87
4	CH_3CN	3.0	73
5	THF	3.5	71
6	CH_2Cl_2	8.0	42
7	*n*-Hexane	8.0	32
8	Chloroform	8.0	51
9	EtOH:water (1:1)	2.0	94
10	CH_3CN:water (1:1)	2.5	81
11	THF:water (1:1)	2.0	82
12	CH_2Cl_2:water (1:1)	4.0	75
13	*n*-Hexane:water (1:1)	4.0	76
14	Chloroform:water (1:1)	4.0	72

[a]Reactions were carried out on a 1 mmol scale (2 mL of solvent) in the molar ratio of 4-methoxy benzaldehyde:ethyl acetoacetate:ammonium acetate:catalyst = 1:2:1:1 at 80 ºC for appropriate time. [b]Isolated yield based on 4-methoxy benzaldehyde.

This can be explained in terms of a homogeneous solution of reaction mixture with the catalyst in polar organic solvent. In case of less polar organic solvents, the reactants were in a different phase with the catalyst, resulting poor yields of product. On other hand, for an aqueous medium, the reactants were in different phases with the water-soluble catalyst succinic acid and responsible for low reaction yield of product. Thus, the aqueous medium reaction took a similar reaction period to

less polar organic solvents. Carrying out the same reaction in a 1:1 mixture of various organic solvents and water (Table-1, entries 9-14) can indirectly prove this explanation. It was observed that the reaction completed within 4 h in a heterogeneous 1:1 mixture of less polar organic and water solvent systems (Table-1, entries 12 and 13). On other hand, a homogeneous 1:1 mixture of polar organic and water solvent systems showed comparable results with the polar organic solvent (Table-1, entries 9-11).

The reaction condition was then optimized by conducting the model reaction employing different catalyts loading and at various temperatures (Table-2). It was gratifying to observe that similar high yield was resulted when the amount of catalyst was reduced from 1.0 to 0.5 equiv (94 % yields, Table-2, entry 8) within 2 h. It reveals that the reaction can also proceeds well in a catalytic manner of 0.5 equiv of succinic acid. However, conversion rate of reactant into product was poor when 0.2 equiv of catalyst was used for the model reaction. As shown in Table-2, the reaction temperature was also affecting the results of model reaction and increasing the reaction temperature led to a enhancement of the conversion rate in all cases. When 0.2 equiv of catalyst was employed, at ambient temperature, no result was observed on TLC plate, even at increasing reaction time up to 12 h (Table-2, entries 5 and 6). But, when reaction was carried at 80 ºC temperature with 0.2 equiv catalyst, the result was obtained with 40 % yield of product (Table-2, entries 10 and 11).

TABLE-2
OPTIMIZATION OF REACTION CONDITIONS WITH DIFFERENT CATALYST LOADINGS AND TEMPERATURES[a]

Entry	Conditions	Yield (%)[b]
1	Succinic acid (1.0 equivalent), 25 ºC, 12 h	18
2	Succinic acid (0.5 equivalent), 25 ºC, 2 h	16
3	Succinic acid (0.5 equivalent), 25 ºC, 8 h	18
4	Succinic acid (0.5 equivalent), 25 ºC, 12 h	20
5	Succinic acid (0.2 equivalent), 25 ºC, 2 h	00
6	Succinic acid (0.2 equivalent), 25 ºC, 12 h	00
7	Succinic acid (1.0 equivalent), 80 ºC, 2 h	94
8	Succinic acid (0.5 equivalent), 80 ºC, 2 h	94
9	Succinic acid (0.5 equivalent), 80 ºC, 8 h	94
10	Succinic acid (0.2 equivalent), 80 ºC, 2 h	34
11	Succinic acid (0.2 equivalent), 80 ºC, 12 h	40

[a]The reactions were carried out at 25-80 ºC for 2-12 h using 4-methoxy benzaldehyde (1 mmol), ethyl acetoacetate (2 mmol) and ammonium acetate (1 mmol) and succinic acid (0.2-1 mmol) in 2 mL ethanol: water (1:1). [b]Isolated yield based on 4-methoxy benzaldehyde.

To assess the reusability of succinic acid, recycling experiments were carried out with model substrates for four times. As succinic acid is soluble in water than in organic solvents, almost 100 % catalyst was easily recovered from reaction mixture after completion of reaction. After completion of reaction, the product was separated by filtration followed by washing with small amount of water. The catalyst was recovered quantitatively by concentrating the filtrate which could be effectively used in next few cycles.

With the optimized reaction conditions in hand, we next examined the feasibility of the succinic acid for synthesis of dihydropyridine derivatives by condensing variously substituted aromatic aldehydes, ethyl acetoacetate and ammonium acetate (**Scheme-I**) with 50 mol % succinic acid in ethanol: water (1:1) system at 80 ºC and results were incorporated in Table-3. The reactions proceeded efficiently to furnish the corresponding dihydropyridines (**5a**-**i**) in good to excellent yields. It is noteworthy that the methodology worked well even for heterocyclic aldehydes such as 2-furfuraldehyde (Table-3, entry 5i).

TABLE-3
SYNTHESIS OF DIHYDROPYRIDINES BY USING SUCCINIC ACID[a]

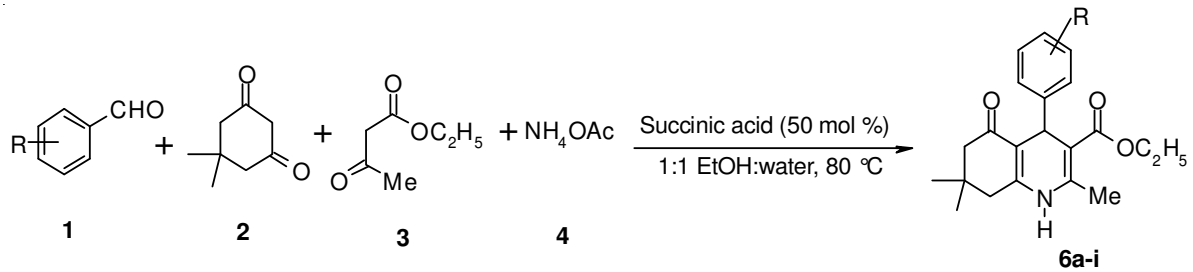
Entry	R	Time (h)	Yield[b] (%)	Melting point (ºC)	
				Observed	Reported
5a	C_6H_5	2.5	90	155-157	157-159[21]
5b	4-MeC_6H_4	2.0	90	118-120	121-122[23]
5c	2-Cl C_6H_4	2.5	89	129-130	130-131[23]
5d	4-Cl C_6H_4	2.5	92	150-151	149[21]
5e	4-OHC_6H_4	3.0	92	224-226	227-228[21]
5f	4-OMe C_6H_4	2.0	94	156-157	158-160[21]
5g	C_6H_5 CH=CH	3	88	140-141	141-143[21]
5h	4-NO_2 C_6H_4	3	88	201-202	202-203[24]
5i	2-Furyl	2.5	89	158-160	160-161[22]

[a]Reactions were carried out at 80 ºC for appropriate time using aldehydes (1 mmol), ethyl acetoacetate (2 mmol) and ammonium acetate (1 mmol) and succinic acid (0.5 mmol) in 2 mL ethanol:water (1:1). [b]Isolated yield based on aldehydes.

With these results in hand, we extend this protocol further for unsymmetrical Hantzsch multi-component condensation for the synthesis of dihydropyridine derivatives by condensation of 1:1:1:1 mole ratio of substituted aromatic aldehydes, ethyl acetoacetate, dimedone and ammonium acetate **(Scheme-II)** with 50 mol % succinic acid in ethanol:water (1:1) system at 80 ºC and results were reported in Table-4. In most of the cases, the desired dihydropyridine derivatives were obtained in high yields. Both electron rich and electron deficient aromatic aldehydes afforded equally good yields.

Conclusion

We have described a simple and efficient one-pot procedure for Hantsch multi-component reaction for synthesis of



Scheme-II: Synthesis of dihydropyridine from aldehyde, dimedone, ethyl acetoacetate and ammonium acetate

TABLE-4
SYNTHESIS OF DIHYDROPYRIDINES BY USING SUCCINIC ACID[a]

Entry	R	Time (h)	Yield[b] (%)	Melting point (ºC)	
				Observed	Reported[25]
6a	C_6H_5	2.0	92	201-202	203 - 204
6b	4-MeC_6H_4	2.0	90	259-260	261-262
6c	2-Cl C_6H_4	2.5	90	204-205	207-208
6d	4-Cl C_6H_4	2.0	94	243-244	245-246
6e	4-OHC_6H_4	3.0	92	232-233	233-234
6f	4-OMe C_6H_4	2.0	94	253-254	256-257
6g	4-NO_2 C_6H_4	2.5	92	238-240	240-242
6h	C_6H_5 CH=CH	3.0	89	202-203	204-206
6i	2-Furyl	3.0	90	245-246	246-248

[a]The reactions were carried out at 80 ºC for appropriate time using aldehydes (1 mmol), ethyl acetoacetate (1 mmol), dimedone (1 mmol) and ammonium acetate (1 mmol) and succinic acid (0.5 mmol) in 2 mL ethanol:water (1:1). [b]Isolated yield based on aldehydes.

symmetrical and unsymmetrical 1,4-dihydropyridine derivatives using catalytic amount of succinic acid as a non-toxic, non-corrosive and inexpensive organocatalyst. The mildness of the conversion, experimental simplicity, excellent yields make this procedure attractive to synthesize dihydropyridine derivatives. By recycling experiments, it is shown that succinic acid can be quantitatively recovered and reused effectively for many times.

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