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SHORT COMMUNICATION

ONE-POT SYNTHESIS OF POLYHYDROPYRIDINE DERIVATIVES VIA HANTZSCH FOUR COMPONENT CONDENSATION IN WATER MEDIUM: USE OF A RECYCLABLE LEWIS ACID [$Ce(SO_4)_2.4H_2O$] CATALYST

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ABSTRACT. An efficient and eco-friendly method for the synthesis of polyhydroquinoline derivatives using $Ce(SO_4)_2.4H_2O$ as mild and heterogeneous Lewis acid catalyst via the Hantzsch reaction in very short reaction time is reported. A mixture of an appropriate aldehyde, dimedone, ethyl acetoacetate and malononitrile in the presence of the $Ce(SO_4)_2.4H_2O$ at reflux conditions in water based media resulted in good to excellent yields of the corresponding products. The catalyst can be used as selective for some aromatic aldehydes in the reaction conditions.

KEY WORDS: $Ce(SO_4)_2.4H_2O$, Polyhydroquinoline, Hantzsch reaction, Muticomponent reaction, Dihydropyridine

INTRODUCTION

4-Substituted 1,4-dihydropyridines (1,4-DHPs) are an important class of drugs that exhibit several medicinal and biological applications, which include neuroprotectant and platelet anti-aggregatory activity, in addition to cerebral antiischemic activity in the treatment of Alzheimer's disease and as chemo sensitizer in tumor therapy [1]. Members of the 1,4-dihydropyridine family are being used as antimalarial, anti-inflammatory, antiasthamatic, antibacterial, tyrosine kinase inhibiting agents [2], and drugs for the treatment of congestive heart failure [3] and cardiovascular [4]. Therefore, their synthesis has been the focus of much interest for organic and medicinal chemists [5].

Numerous synthetic methods have been reported for the preparation of 1,4-dihydropyridines under classical or modified conditions [6-20]. However, the low yields, occurrence of several side products, use of stoichimetric amount of reagents, expensive metal precursors, catalysts that are harmful to environment, use of expensive and toxic transition metallic reagents, complicated work-up methods and longer reaction times limit the use of these methods. Therefore, for the increasing environmental and economical concerns in recent years, it is now essential for chemists to search environmentally reactions under natural conditions as many as possible.

Organic reactions under green solvents have attracted much interest from chemists particularly from the viewpoints of green chemistry. Green chemistry approaches are significant due to the reduction in by-products and waste produced, and lowering of energy costs. The possibility of performing multi-component reactions under green solvent conditions with a heterogeneous catalyst could enhance their efficiency from an economic as well as ecological point of view [21-24]. In this regard, a new, simple, mild and efficient method for the one-pot synthesis of 1,4-dihydropyrimidine derivatives is reported herein. As a part of our interest in heterogeneous catalyzed organic reactions [25-27], in this paper, we wish to report a

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$Ce(SO_4)_2.4H_2O$ catalyzed four-component Hantzsch reaction using a mixture of water-ethanol as a green solvent under reflux condition. In this study, $Ce(SO_4)_2.4H_2O$ has been employed as mild Lewis acid catalyst with high catalytic activity and reusability in H_2O-EtOH media for Hantzsch condensation. Moreover, the catalyst can be easily recovered after reactions and reused three times without any loss of its activity.

EXPERIMENTAL

General. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. NMR spectra were recorded at 500 (^{1}H) and 125.77 (^{13}C) MHz on Bruker DRX-500 Avance spectrometer at 500 and 125.77 MHz, respectively. All compounds were known in the literature, the NMR and IR spectra of the products were in agreement with earlier data.

Typical procedure for the preparation of 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-(4-hlorophenyl)-3-quinolinecarboxyl acid ethyl ester (Table 2, entry 2). In a typical general procedure, a mixture of benzaldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol) and ammonium acetate (1.5 mmol) in H_2O-EtOH (2:3, 5 mL) was refluxed thoroughly in the presence of catalytic amount of $Ce(SO_4)_2.4H_2O$ (20 mg, 5 mol%) to afford the 4-substituted-1,4-dihydropyridines. After completion of the reaction (15 min) confirmed by TLC, the mixture was filtered to separate from the soluble catalyst. The solid product was washed with H_2O and finally was recrystallised from ethanol and characterized. The structures of the products were confirmed from physical and spectroscopic data (IR and ^{1}H NMR) in comparison with the literature data. The selected spectral data of five representative 4-substitited 1,4-dihydropyridine derivatives are given below.

1,4,5,6,7,8-Hexahydro-2,7,7-trimethyl-5-oxo-4-(4-chlorophenyl)-3-quinolinecarboxyl acid ethyl ester (Table 2, entry 2). IR (KBr): 3391, 2970, 1706, 1636, 1495, 1378, 1238, 1074, 1027, 863 cm^{-1}; ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 0.92 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.19 (t, J = 7.2 Hz, 3H, CH_3), 2.13-2.33 (m, 4H, $2CH_2$), 2.37 (s, 3H, CH_3), 4.06 (q, J = 7.1 Hz, 2H, OCH_2), 5.03 (s, 1H, CH), 6.25 (s, 1H, NH), 7.15-7.25 (m, 4H, ArH), 7.21 (d, J = 8.0 Hz, 2H, ArH); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 14.23, 19.22, 27.17, 29.41, 32.47, 36.16, 40.87, 50.76, 59.89, 105.44, 111.52, 122.81, 129.16, 131.74, 140.25, 147.15, 149.28, 167.27, 195.52.

1,4,5,6,7,8-Hexahydro-2,7,7-trimethyl-5-oxo-4-(2,4-dichlorophenyl)-3-quinolinecarboxyl acid ethyl ester (Table 2, entry 3). IR (KBr): 3297, 2970, 1706, 1659, 1612, 1495,1238, 1121, 1074, 863, 770 cm^{-1}; ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 0.95 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.20 (t, J = 7.1 Hz, 3H, CH_3), 2.01-2.27 (m, 4H, $2CH_2$), 2.29 (s, 3H, CH_3), 4.07 (m, 2H, OCH_2), 5.36 (s, 1H, CH), 6.93 (s, 1H, NH), 7.11-7.36 (m, 3H, ArH); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 14.25, 19.18, 27.19, 29.31, 32.47, 35.87, 40.91, 50.78, 59.88, 104.78, 110.66, 126.59, 129.26, 129.26, 132.11, 132.93, 133.90, 142.90, 144.20, 149.40, 167.28, 195.49.

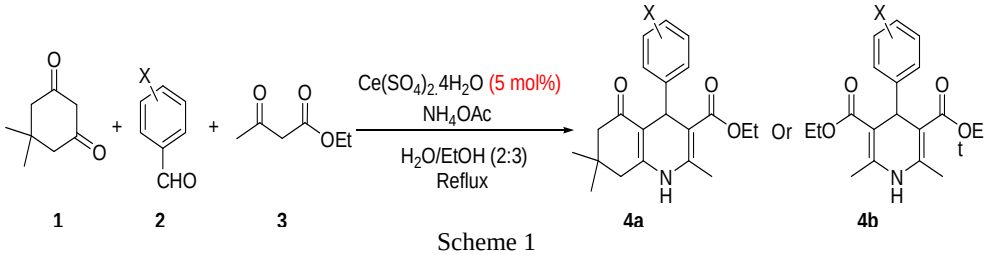
1,4,5,6,7,8-Hexahydro-2,7,7-trimethyl-5-oxo-4-(4-bromophenyl)-3-quinolinecarboxyl acid ethyl ester (Table 2, entry 4). IR (KBr): 3297, 2970, 1706, 1659, 1612, 1495,1285, 1238, 1074, 1027, 853 cm^{-1}; ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 0.94 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.21 (t, J = 7.2 Hz, 3H, CH_3), 2.14-2.32 (m, 4H, $2CH_2$), 2.37 (s, 3H, CH_3), 4.08 (q, J = 7.1 Hz, 2H, OCH_2), 5.03 (s, 1H, CH), 6.52 (s, 1H, NH), 7.01 (d, J = 7.9 Hz, 2H, ArH), 7.21 (d, J = 8.0 Hz, 2H, ArH); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 14.22, 19.32, 27.14, 29.41, 32.68, 36.38, 41.02, 50.76, 59.90, 105.67, 111.70, 119.81, 129.86, 130.95, 143.77, 146.15, 148.53, 167.22, 195.51.

1,4,5,6,7,8-Hexahydro-2,7,7-trimethyl-5-oxo-4-(4-methylphenyl)-3-quinolinecarboxyl acid ethyl ester (Table 2, entry 5). IR (KBr): 3297, 2970, 1706, 1648, 1612, 1495,1378, 1215, 1074, 1051, 863 cm^{-1}; ^1H NMR (500.13 MHz, $CDCl_3$): δ = 0.96 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.23 (t, J = 7.2 Hz, 3H, CH_3), 2.15-2.32 (m, 4H, $2CH_2$), 2.27 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 4.08 (q, J = 7.1 Hz, 2H, OCH_2), 5.04 (s, 1H, CH), 6.73 (s, 1H, NH), 7.01 (d, J = 7.9 Hz, 2H, ArH), 7.21 (d, J = 8.0 Hz, 2H, ArH); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 14.24, 19.24, 21.02, 27.21, 29.43, 32.67, 36.18, 40.98, 50.87, 59.76, 106.19, 112.11, 127.89, 128.61, 135.36, 143.49, 144.28, 148.67, 167.57, 195.64.

1,4,5,6,7,8-Hexahydro-2,7,7-trimethyl-5-oxo-4-(3-bromophenyl)-3-quinolinecarboxyl acid ethyl ester (Table 2, entry 9). IR (KBr): 3297, 2970, 1706, 1636, 1612, 1495,1402, 1214, 1074, 1074, 1051, 793 cm^{-1}; ^1H NMR (500.13 MHz, $CDCl_3$): δ = 0.96 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.23 (t, J = 7.2 Hz, 3H, CH_3), 2.15-2.32 (m, 4H, $2CH_2$), 2.34 (s, 3H, CH_3), 4.05-4.13 (m, 2H, OCH_2), 5.04 (s, 1H, CH), 7.01 (s, 1H, NH), 7.07-7.43 (m, 4H, ArH), 7.21 (d, J = 8.0 Hz, 2H, ArH); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 14.23, 19.23, 27.16, 29.41, 32.69, 36.75, 40.85, 50.80, 59.91, 105.44, 111.33, 122.08, 126.89, 129.14, 129.46, 131.12, 144.21, 149.30, 149.48, 167.25, 195.67.

RESULTS AND DISCUSSION

In the efforts to develop an efficient and environmentally benign methodology for the synthesis of DHPs we initiated our studies by subjecting catalytic amount of $Ce(SO_4)_2.4H_2O$ to the mixture of benzaldehyde, ethyl acetoacetate and ammonium acetate in H_2O as solvent at room temperature. Unfortunately, the resulted yield was poor (40% after 80 min). To effect the reaction, various solvent systems were screened at different temperatures. It was interesting to observe that different products could be obtained in different ratio of H_2O/EtOH as solvent. It was seen that the synthesis of DHP was efficiently catalyzed by $Ce(SO_4)_2.4H_2O$ in aqueous media at elevated temperature leading to high yield of product (Scheme 1).



Scheme 1

The reaction condition was then optimized by conducting the reaction in different temperatures and employing different catalyst loadings. The results are summarized in Table 1. It is evident that the best result was obtained by the application of 5 mol% of $Ce(SO_4)_2.4H_2O$ in H_2O/EtOH (2:3) as solvent at reflux condition (Table 1, entry 1). All compounds were known and their physical and spectroscopic data were compared with those of authentic samples and found to be identical [17-19].

In order to examine the scope and generality of this procedure, the methodology was extended to different aromatic aldehydes. The results are presented in Table 2. Both electron rich and electron deficient aromatic aldehydes reacted well to afford **4a** in good to high yields. It is an interesting that *para*-substituted benzaldehydes (entries 11-13, Table 2), whether the substituent is EDG or EWG, afforded the unexpected dihydropyrimidinones **4b**. It could be because of the steric effect of 4-aryl ring system. So $Ce(SO_4)_2.4H_2O$ can be acted as selective

catalyst to obtain 4-Substituted dihydropyridines **4a** or **4b** as products in Hantzsch reaction conditions.

Table 1. Optimizing the reaction conditions.

Entry	Solvent	Condition	Time (min)	Yield (%)	Products	Catalyst (g)
1	H_2O/EtOH (2:3)	Reflux	15	87	**4a**	0.02
2	H_2O/EtOH (1:2)	Reflux	25	86	**4a**	0.02
3	H_2O/EtOH (3:1)	R.T.	15	60	**4b**	0.04
4	H_2O/EtOH (2:1)	R.T.	35	45	**4b**	0.04
5	H_2O/EtOH (1:1)	Reflux	30	86	**4a**	0.02
6	EtOH	Reflux	48	94	**4a**	0.02
7	H_2O	Reflux	60	91	**4a**	0.02
8	H_2O	R.T.	80	40	**4a**	0.04

Table 2. $Ce(SO_4)_2.4H_2O$ catalyzed the synthesis of polyhydroquinoline derivatives through Hantzsch reaction.

Entry	Ar	Time (min)	Yields (%)[a]	TON[b]	M.p. (^oC)
1	C_6H_5	15	92	18.4	203-204
2	4-ClC_6H_4	15	87	17.4	243-245
3	2,4-$Cl_2C_6H_3$	15	90	18	241-243
4	4-BrC_6H_4	15	80	16	254-256
6	4-$CH_3OC_6H_4$	15	80	16	258-260
7	4-OHC_6H_4	20	82	16.4	237-238
8	1-naphthyl	15	81	16.2	198-200
9	3-BrC_6H_5	8	82	16.4	234-236
10	3-$CH_3OC_6H_5$	11	86	19.2	231-233
11	3-$NO_2C_6H_4$	20	95	19	162-164
12	4-$NO_2C_6H_4$	20	85	17	130-132
13	4-$(CH_3)_2NC_6H_4$	20	80	16	202-204

[a]Yields refer to isolated pure products. [b] Turn over number (TON) is the ratio of the number of moles of the product to the number of moles of the catalyst.

The recovery and reusability of $Ce(SO_4)_2.4H_2O$ was investigated due to the most important benefits for commercial applications. In these experiments, the reaction mixture was filtered and washed with H_2O. The soluble catalyst was easily reused after distillation of solvent, washing with $CHCl_3$ and drying at 60 ^oC.

The recycled catalyst was examined in next run in the reaction between 4-chlorobenzaldehyde, ethyl acetoacetate, dimedone and ammonium acetate. Pleasingly, $Ce(SO_4)_2.4H_2O$ was successfully recycled three times without any loss of its activity.

CONCLUSIONS

In conclusion, the present method is an operationally simple and environmentally friendly procedure for the synthesis of compound **4a** using catalytic amount of $Ce(SO_4)_2.4H_2O$. Also, $Ce(SO_4)_2.4H_2O$ can be used as selective for some aromatic aldehydes in the reaction conditions. In addition low cost, availability, recyclability, low toxicity, moderate Lewis acidity and moisture compatibility of the catalyst, good to excellent yields of products and short reaction time make this methodology a valid contribution to the existing processes in the field of 4-substituted-1,4-dihydropyridines derivatives synthesis.

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