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3-Carboxy-1-sulfopyridin-1-ium chloride ($[CPySO_3H]^+Cl^-$): an efficient catalyst for one-pot synthesis of hexahydroquinoline-3-carboxamides

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Abstract: 3-Carboxy-1-sulfopyridin-1-ium chloride ($[CPySO_3H]^+Cl^-$) was synthesized and evaluated as a recoverable catalyst for one-pot synthesis of hexahydroquinoline-3-carboxamide derivatives by a four-component reaction of an arylaldehyde, dimedone, acetoacetanilide and ammonium acetate. The $[CPySO_3H]^+Cl^-$ catalyst was characterized by infrared (IR), ^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR, elemental analysis and thermal gravimetric analysis (TGA).

Keywords: 3-carboxy-1-sulfopyridin-1-ium chloride; chlorosulfonic acid; hexahydroquinoline-3-carboxamide; nicotinic acid; one-pot reaction.

Introduction

Quinolines containing a 1,4-dihydropyridine (1,4-DHP) moiety show a variety of pharmacological properties [1–8]. Acetoacetanilide is an important building block in the synthesis of heterocyclic compounds with antimicrobial [9, 10] and analgesic activities [11]. The synthesis of hexahydroquinoline-3-carboxamides via a four-component reaction of acetoacetanilide, aromatic aldehyde, dimedone and ammonium acetate in the presence of *p*-toluenesulfonic acid [12] and without catalyst under harsh conditions has been reported [13]. Herein, we report that this reaction can be conducted under much milder conditions in the presence of another catalyst.

Results and discussion

In this study, 3-carboxy-1-sulfopyridin-1-ium chloride ($[CPySO_3H]^+Cl^-$) was successfully used as a catalyst in the reaction of arylaldehydes, dimedone, acetoacetanilide and ammonium acetate in ethanol at 70°C to furnish a series of hexahydroquinoline-3-carboxamides **5a–l** in excellent yields (Scheme 1). The catalyst was obtained by treatment of nicotinic acid with chlorosulfonic acid (Scheme 2). The structure of $[CPySO_3H]^+Cl^-$ was supported by infrared (IR), ^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR, thermal gravimetric analysis (TGA) and elemental analysis. In the IR spectrum, the stretching vibrations for O-H near 3151 cm^{-1}, for C=O at 1728 cm^{-1}, for C=N at 1633 cm^{-1}, for C=C at 1600 cm^{-1} and 1537 cm^{-1} and the SO_2 asymmetric and symmetric stretching at 1272 cm^{-1} and 1172 cm^{-1}, respectively, were observed. These results provide evidence that sulfonic acid moiety is part of the molecular structure of the catalyst.

The thermal behavior of $[CPySO_3H]^+Cl^-$ was studied by TGA. The thermal analysis indicated that the catalyst was stable up to 250°C. A slow decomposition could be observed starting around 300°C.

To optimize the reaction conditions, the four-component reaction of benzaldehyde, dimedone, acetoacetanilide and ammonium acetate was examined as a model reaction. The highest yield of **5a** was obtained for the reaction conducted in ethanol at 70°C in the presence of 20 mol% of $[CPySO_3H]^+Cl^-$. Under these optimized conditions, the reaction furnished products **5b–l** in the range of yields from 88% to 96%. The optimum reaction time was analyzed using thin-layer chromatography (TLC) and was found to vary from 25 min to 45 min. The structure of all products was fully supported by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis.

To study the recyclability of the catalyst, the synthesis of compound **5a** was conducted 5 times. Upon completion of the reaction, the catalyst was filtered, washed with dichloromethane (2×10 mL) and then reused in the subsequent preparation of **5a**. It was found that the initial yield of **5a** of 95% decreased only to 90% in the fifth preparation. Also, the catalyst retained its activity after several months of storage.

Conclusions

A simple and efficient one-pot procedure for the synthesis of hexahydroquinolines using $[CPySO_3H]^+Cl^-$ as an

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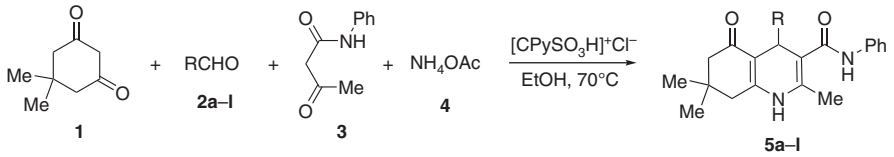
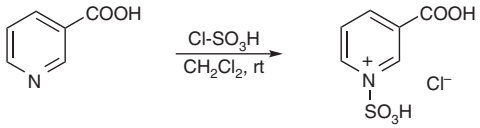


5a: R = Ph
5b: R = 4-Cl-C$_6$H$_4$
5c: R = 2-Cl-C$_6$H$_4$
5d: R = 3-Cl-C$_6$H$_4$
5e: R = 3-NO$_2$-C$_6$H$_4$
5f: R = 4-NO$_2$-C$_6$H$_4$
5g: R = 2-NO$_2$-C$_6$H$_4$
5h: R = 3-Br-C$_6$H$_4$
5i: R = 4-HO-C$_6$H$_4$
5j: R = 4-MeO-C$_6$H$_4$
5k: R = 4-N(Me)$_2$-C$_6$H$_4$
5l: R = CH(Me)$_2$

Scheme 1 Synthesis of hexahydroquinoline-3-carboxamides **5a–l**.



Scheme 2 Preparation of [CPySO$_3$H]$^+$Cl$^-$.

ionic organocatalyst in ethanol at 70°C was decribed. Simplicity of the preparation, easy work-up, high yields and recyclability of the catalyst are the advantages of this method.

Experimental

Melting points were measured on an Electro-thermal 9100 apparatus and are uncorrected. Unless stated otherwise, ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in CDCl$_3$ on a Bruker Avance DRX-400 spectrometer. Fourier-transform infrared (FT-IR) spectra were obtained for potassium bromide pellets on a Shimadzu SP-1100 instrument. The TGA was conducted using a Mettler TGA instrument. The thermograms were recorded at a heating rate of 10°C/min in the range of temperature from 25°C to 600°C in an inert atmosphere. Elemental analyses were done on a Carlo-Erba EA1110 analyzer.

Catalyst preparation

The catalyst was synthesized according to the reported method for the preparation of a similar catalyst [14, 15]. A solution of chlorosulfonic acid (10 mmol) in CH$_2$Cl$_2$ (15 mL) was added dropwise to a solution of nicotinic acid (10 mmol) in CH$_2$Cl$_2$ (25 mL), and the mixture was stirred for 2 h at room temperature. The resulting precipitate was filtered, washed with CH$_2$Cl$_2$ (2×10 mL) and dried in a desiccator under reduced pressure to give [CPySO$_3$H]$^+$Cl$^-$ as a white stable powder: Yield 94%; IR: 3157 (O-H stretch), 1731 (C=O stretch), 1631 (C=N stretch), 1621, 1533 (aromatic C=C stretch), 1176, 1107 cm^{-1} (SO$_2$ asymmetric and symmetric stretch); ^{1}H NMR (DMSO-d_6): δ 11.74 (br s, 2H), 9.27 (d, J = 1.6 Hz, 1H), 9.05 (dd, J = 6.0, 1.6 Hz, 1H), 8.82 (m, 1H), 8.06 (m, 1H); ^{13}C NMR (DMSO-d_6): δ 164.0, 147.5, 145.2, 144.4, 129.7 127.2. Anal. Calcd C$_6$H$_6$NSO$_5$Cl: C, 30.07; H, 2.52, N, 5.85. Found: C, 30.13; H, 2.64, N, 5.89.

General procedure for synthesis of hexahydroquinoline-3-carboxamides 5a–l

A mixture of aromatic aldehyde (1 mmol), dimedone (1 mmol, 0.14 g), acetoacetanilide (1 mmol, 0.18 g) and ammonium acetate (1.2 mmol, 0.09 g) in the presence of [CPySO$_3$H]$^+$Cl$^-$ (0.05 g, 0.2 mmol) was stirred in ethanol (5 mL) at 70°C for 15–45 min. Completion of the reaction was indicated by TLC monitoring. Then, the mixture was cooled to ambient temperature, and the resultant precipitate of **5a–l** was crystallized from ethanol. All products were characterized by IR, ^{1}H NMR and ^{13}C NMR, and the data for known compounds were compared with those of the authentic samples reported in the literature. Yields for known compounds: **5a**: 95%, reported: 78% [15], 89% [12]; **5b**: 96%, reported: 92% [12]; **5d**: 93%, reported 74% [15]; **5e**: 95%, reported: 83% [12]; **5f**: 94%, reported: 83% [12]; **5g**: 92%, reported: 84% [15]; **5i**: 87%, reported: 76% [15]; **5j**: 88%, reported: 94% [12].

4-(2-Chlorophenyl)-2,7,7-trimethyl-5-oxo-*N*-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxamide (5c) Reaction time 20 min; yield 90%; white solid; mp 225–227°C; IR: 3265 (N-H stretch), 2956 (aliphatic C-H stretch), 1677 (C=O), 1645 (C=O), 1498 (C=C stretch), 752 cm^{-1} (aromatic C-H out of plane bending); ^{1}H NMR: δ 0.96 (s, 3H, CH$_3$), 1.06 (s, 3H, CH$_3$), 1.95 (s, 3H, CH$_3$), 1.98 (d, J = 13 Hz, 1H), 2.13 (d, J = 16 Hz, 1H), 2.32 (d, J = 16 Hz, 1H), 2.41 (d, J = 16 Hz, 1H), 5.35 (s, 1H, CH), 6.97–7.29 (m, 7H, Ar), 7.53 (d, J = 7.6 Hz, 2H, Ar), 8.74 (s, 1H, NH), 9.72 (s, 1H, NHCO); ^{13}C NMR: δ 19.5, 27.1, 29.3, 32.6, 35.3, 41.2, 50.5, 108.6, 110.9, 120.3, 124.0, 127.7, 128.3, 128.9, 129.7, 131.0, 131.6, 138.1, 140.4, 143.5, 148.6, 165.8, 194.9 (C=O). Anal. Calcd for C$_{25}$H$_{25}$ClN$_2$O$_2$: C, 71.33, H, 5.99, N, 6.66. Found: C, 71.13, H, 6.04, N, 6.59.

4-(3-Bromophenyl)-2,7,7-trimethyl-5-oxo-*N*-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbox amide (5h) Reaction time 15 min; yield 96%; yellow solid; mp 211–213°C; IR: 3276 (N-H stretch), 3062 (aromatic C-H), 2956 (C-H stretch), 1674 (C=O stretch), 1643 (C=O stretch), 752 cm^{-1} (aromatic C-H out of plane bending); ^{1}H NMR: δ 0.96 (s, 3H, CH$_3$), 1.10 (s, 3H, CH$_3$), 2.13 (s, 1H), 2.18–2.20 (m, 1H), 2.22–2.28 (m, 2H), 2.36 (s, 3H, CH$_3$), 5.40 (s, 1H, CH), 6.09 (s,1H, NH), 7.08 (m, 1H, Ar), 7.11–7.15 (m, 1H, Ar), 7.21–7.25 (m, 1H, Ar), 7.28–7.27 (m, 2H, Ar), 7.31–7.35 (m, 2H, Ar), 7.45–7.48 (m, 2H, Ar), 7.61 (s, 1H, NH); ^{13}C NMR: δ 19.0, 27.3, 29.5, 32.5, 36.6, 50.8, 108.2, 111.6, 119.9, 120.0, 123.2, 127.5, 127.7, 128.8, 129.1, 131.2, 131.8, 133.9, 139.8, 139.9, 145.3, 151.4, 151.5, 167.3, 193.7 (C=O). Anal. Calcd for C$_{25}$H$_{25}$BrN$_2$O$_2$: C, 64.25, H, 5.41, N, 6.02. Found: C, 63.83, H, 5.64, N, 6.09.

4-(4-(Dimethylamino)phenyl)-2,7,7-trimethyl-5-oxo-*N*-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxamide (5k) Reaction time 30 min; yield 92%; orange solid; mp 248–250°C: IR: 3269 (N-H

stretch), 3066 (aromatic C-H), 2952 (C-H stretch), 1674 (C=O stretch), 1637 (C=O stretch), 754 cm^{-1} (aromatic C-H out of plane bending); ^1H NMR: δ 0.87 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.11–2.26 (m, 4H), 2.37 (s, 3H, CH_3), 2.39 (s, 6H, $2CH_3$), 4.82 (s, 1H, CH), 6.72 (d, J = 8 Hz, 2H), 6.94 (s, 1H, Ar), 7.04 (m, 1H, Ar), 7.23–7.34 (m, 4H, Ar), 7.36 (d, J = 4 Hz, 2H, Ar), 7.52 (s, 1H, NH), 9.72 (s, 1H, NHCO): ^{13}C NMR: δ 18.0, 27.2, 29.2, 32.5, 37.0, 40.1, 40.5, 50.7, 76.8, 77.1, 77.4, 108.3, 111.0, 111.05, 112.9, 119.8, 123.8, 128.7, 128.8, 133.6, 138.3, 141.3, 149.1, 167.0, 195.0 (C=O). Anal. Calcd for $C_{27}H_{31}N_3O_2$: C, 75.50, H, 7.27, N, 9.78. Found: C, 75.33, H, 7.35, N, 9.69.

4-Isopropyl-2,7,7-trimethyl-5-oxo-*N*-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxamide (5l) Reaction time 45 min; yield 90%; yellow solid; mp 234–236°C, IR: 3296 (N-H stretch), 2956 (aliphatic C-H stretch), 1664 (C=O), 1637 (C=O), 1490 (C=C stretch), 752 cm^{-1} (aromatic C-H out of plane bending); ^1H NMR: δ 0.74 (d, J = 4.4 Hz, 3H), 0.758 (d, J = 4.4 Hz, 3H, CH_3), 1.05 (s, 6H, $2CH_3$), 1.64 (m, 1H), 2.01 (s, 3H, CH_3), 2.07 (d, J = 16 Hz, 1H), 2.16 (d, J = 16 Hz, 1H), 2.22 (d, J = 2 Hz, 1H), 2.33 (d, J = 4.4 Hz, 1H), 3.81 (d, J = 2 Hz, CH), 7.00 (m, 1H, Ar), 7.26 (br s, 2H, Ar), 7.62 (m, 2H, Ar), 8.48 (s, 1H, NH), 9.62 (s, 1H, NHCO); ^{13}C NMR: δ 17.3, 18.2, 19.7, 27.01, 30.1, 32.3, 35.3, 38.2, 51.2, 107.1, 109.0, 120.1, 123.3, 128.9, 136.2, 140.1, 152.1, 169.7, 194.6 (C=O). Anal. Calcd for $C_{22}H_{27}N_2O_2$: C, 75.18, H, 7.74, N, 7.97. Found: C, 74.96, H, 7.85, N, 8.05.

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