Research Article

Cellulose-Sulfuric Acid as an Efficient Biosupported Catalyst in One-Pot Synthesis of Novel Heteroaryl Substituted 1,4-Dihydropyridines

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An efficient method for the synthesis of new heteroaryl substituted dihydropyridine derivatives via a one-pot four-component coupling reaction of heteroaldehyde, 1,3-diketone, ethylacetoacetate, and ammonium acetate in the presence of cellulose-sulfuric acid as a biosupported solid acid catalyst was developed. The reaction gave the new derivatives of fused 1,4-dihydropyridines in lower reaction times and excellent yields (85–95%).

1. Introduction

1,4-Dihydropyridines exhibit interesting pharmacological and biological properties. For example, they have been used as calcium channel modulators for the treatment of cardiovascular disorders [1, 2]. They also present vasodilating [3], antifilarial [4], and antitubercular activities [5] and may serve as NADH mimics [6, 7]. Many methods have been reported for the synthesis of 1,4-dihydropyridine derivatives in view of the biological importance associated with these compounds. The best known procedure for preparation of symmetrical 1,4-dihydropyridines is the classical Hantzsch synthesis: a multicomponent condensation involving two molecules of β -ketoester, one molecule of aldehyde, and one molecule of ammonia [8, 9]. Other reported methods comprise the use of microwave [10–12], ionic liquids [13, 14], high temperature in refluxing solvent [15–24], TMSCl-NaI [25], and metal triflates [26, 27], which have their own drawbacks such as high temperature, expensive metal precursors, and prolonged reaction times. Thus, development of a simple, efficient, and versatile method for preparation of new derivatives of 1,4-dihydropyridine is a great challenge.

2. Experimental

2.1. General. Melting points were measured on an electrothermal 9100 apparatus and are uncorrected. ^1H NMR spectra were obtained on a Bruker DRX-500 Avance spectrometer, and ^{13}C NMR spectra were obtained on a Bruker DRX-125 Avance spectrometer. Chemical shifts of ^1H and ^{13}C NMR spectra were expressed in ppm downfield from tetramethylsilane. FT-IR spectra were recorded on a Shimadzu FT-IR-8400S spectrometer. Chemicals were purchased from Merck and Fluka and used without further purification.

2.2. Typical Procedure: Preparation of 3-Aryl-4-fromyl-1-phenylpyrazole. In a round bottomed flask, cyanuric chloride (1.83 g, 10 mmol) was added to dimethyl formamide (2 mL) which resulted in a white solid. To this product a solution of phenylhydrazone acetophenone (1 g, 5 mmol) in dimethyl formamide (15 mL) was added and stirred for 16 h at room temperature. To the resulted mixture, 15% Na_2CO_3 (20 mL) was added and the organic layer was extracted by diethylether ($2 \times 15\text{ mL}$). The ethereal solution was dried by MgSO_4 and filtered, and the filtrate evaporated under vacuum to

TABLE 1: Synthesis of heteroaryl substituted 1,4-dihydropyridines in the presence of cellulose-sulfuric acid catalyst.

Entry ^a	Ar	2	Time (min)	Product	Yield (%) ^b
a	Ph	Dimedone	42 (120) ^c	5a	90 (75) ^c
b	<i>p</i> -NO ₂ C ₆ H ₄	Dimedone	45	5b	95
c	<i>p</i> -ClC ₆ H ₄	Dimedone	40	5c	94
d	Ph	1,3-Cyclohexanedione	43 (125) ^c	5d	88 (72) ^c
e	<i>p</i> -NO ₂ C ₆ H ₄	1,3-Cyclohexanedione	45	5e	87
f	<i>p</i> -ClC ₆ H ₄	1,3-Cyclohexanedione	42	5f	86
g	Ph	1,3-Indanedione	39 (120) ^c	5g	90 (75) ^c
h	<i>p</i> -NO ₂ C ₆ H ₄	1,3-Indanedione	41	5h	86
i	<i>p</i> -ClC ₆ H ₄	1,3-Indanedione	37	5i	85

^a All products were characterized by ¹H NMR, ¹³C NMR, and IR data.

^b Isolated yields.

^c Measured in the absence of the catalyst.

produce 1,3-diphenyl-4-formylpyrazole (1.12 g) in 90% yield. The product was identified by spectroscopic analysis and comparison of its melting point (mp = 146–148°C) with the reported one (mp = 145–147°C) [28].

Light yellow solid, IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 2850, 2750 (H–C=O), 1670 (C=O), 1590, 1520, 750, 690. ¹H NMR (500 MHz, CDCl₃): δ 10.11 (1H, s), 8.59 (1H, s), 7.89–7.84 (4H, m), 7.58–7.52 (5H, m), 7.44 (1H, t, *J* = 7.44 Hz) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 185.6, 155.2, 139.5, 131.8, 131.4, 130.1, 129.7, 129.4, 129.2, 128.4, 123.0, 120.2 ppm.

2.2.1. 3-(4-Nitrophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde. Yellow solid; FT-IR (neat) ($\nu_{\max}/\text{cm}^{-1}$): 1680 (HC=O), 1520, 1340 (NO₂). ¹H NMR (500 MHz, CDCl₃) δ 7.49 (1H, t, *J* = 7.40 Hz), 7.59 (2H, t, *J* = 7.90 Hz), 7.85 (2H, d, *J* = 7.74 Hz), 8.21 (2H, d, *J* = 8.70 Hz), 8.38 (2H, d, *J* = 8.70 Hz), 8.62 (1H, s), 10.13 (1H, s); ¹³C NMR (125 MHz, CDCl₃) δ 184.0 (HC=O), 151.7, 148.6, 139.1, 138.1, 134.0, 130.3, 130.1, 128.9, 124.2, 123.4, 120.2.

2.3. General Procedure for the Synthesis of 1,4-Dihydropyridines (5a–i). A mixture of 3-aryl-4-formylpyrazole (**1**) (1.0 mmol), 1,3-diketone (**2**) (1.0 mmol, dimedone or 1,3-cyclohexanedione or indanedione), ethylacetoacetate (**3**) (1.0 mmol), ammonium acetate (1.0 mmol), and cellulose-sulfuric acid (0.05 g) in ethanol (10 mL) was refluxed in an oil bath for the appropriate time (Table 1). The progress of the reaction was controlled by TLC, and after completion of the reaction the solvent was evaporated under reduced pressure to provide a residue which was purified by recrystallization from ethanol to furnish the desired 1,4-dihydropyridines (**5a–i**).

2.3.1. Ethyl 4-(1,3-Diphenyl-1H-pyrazol-4-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5a). Yellow powder, mp = 106–108°C; FT-IR (neat) ($\nu_{\max}/\text{cm}^{-1}$): 3300, 3200 (NH), 1695 (C=O), 1635 (C=C, olefinic); ¹H NMR (500 MHz, CDCl₃) δ 7.95 (2H, d, *J* = 7.32 Hz), 7.81 (1H, s), 7.69 (2H, d, *J* = 7.90 Hz), 7.41–7.47 (4H, m), 7.37 (1H, t, *J* = 7.38 Hz), 7.26 (1H, t, *J* = 7.38 Hz), 6.03 (1H, s), 5.32 (1H, s), 3.64, 3.97 (2H, m), 2.21, 2.25 (2H, d, *J* = 16.36 Hz), 2.19 (3H, s), 2.13,

2.23 (2H, d, *J* = 16.50 Hz), 1.08 (3H, s), 1.04 (3H, s), 0.92 (3H, t, *J* = 7.09 Hz); ¹³C NMR (125 MHz, CDCl₃/DMSO-*d*₆) δ 196.0 (C=O, ketone), 167.8 (C=O, ester), 152.2, 148.5, 142.8, 140.5, 135.2, 129.7, 129.6, 128.6, 128.3, 127.9, 127.5, 126.4, 119.3, 112.3, 107.1, 60.0, 51.1, 41.5, 33.1, 30.1, 28.3, 27.4, 19.6, 14.4. Anal. Calcd for C₃₀H₃₁N₃O₃: C, 74.82; H, 6.49; N, 8.73. Found: C, 74.73; H, 6.26; N, 8.56.

2.3.2. Ethyl 2,7,7-Trimethyl-4-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5b). Yellow solid mp = 256–258°C; FT-IR (neat) ($\nu_{\max}/\text{cm}^{-1}$): 3250, 3200 (NH), 1695 (C=O), 1650 (C=C, olefinic), 1510, 1330 (NO₂); ¹H NMR (500 MHz, CDCl₃) δ 8.44 (2H, d, *J* = 8.88 Hz), 8.38 (2H, d, *J* = 8.88 Hz), 7.80 (1H, s), 7.70 (2H, d, *J* = 7.62 Hz), 7.47 (2H, t, *J* = 7.95 Hz), 7.32 (1H, t, *J* = 7.40 Hz), 5.86 (1H, s), 5.33 (1H, s), 3.95, 3.63 (2H, m), 2.41, 2.25 (2H, d, *J* = 16.46 Hz), 2.33 (3H, s), 2.25, 2.32 (2H, d, *J* = 16.30 Hz), 1.15 (3H, s), 1.07 (3H, s), 0.86 (3H, t, *J* = 7.12 Hz); ¹³C NMR (125 MHz, CDCl₃/DMSO-*d*₆) δ 196.1 (C=O), 167.4 (C=O, ester), 149.2, 148.0, 147.5, 142.7, 142.0, 140.3, 130.0, 129.8, 128.2, 127.0, 123.8, 119.5, 112.9, 107.7, 60.2, 51.0, 41.8, 33.3, 29.5, 28.0, 27.4, 20.0, 14.4. Anal. Calcd for C₃₀H₃₀N₄O₅: C, 68.42; H, 5.74; N, 10.64. Found: C, 68.25; H, 5.64; N, 10.75.

2.3.3. Ethyl 4-(3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5c). White solid, mp = 253–255°C; FT-IR (neat) ($\nu_{\max}/\text{cm}^{-1}$): 3300, 3200 (NH), 1690 (C=O), 1640 (C=C, olefinic), 1080 (C–Cl); ¹H NMR (500 MHz, CDCl₃) δ 7.98 (2H, d, *J* = 8.20 Hz), 7.97 (1H, s), 7.66 (1H, s), 7.54 (2H, d, *J* = 7.55 Hz), 7.32 (2H, d, *J* = 8.20 Hz), 7.30 (2H, m 2H), 7.14 (1H, t, *J* = 7.34 Hz), 5.13 (1H, s), 3.82, 3.44 (2H, m), 2.25, 2.22 (2H, d, *J* = 16.78 Hz), 2.16 (3H, s), 2.11, 2.07 (2H, d, *J* = 16.16 Hz), 0.95 (3H, s), 1.00 (3H, s), 0.75 (3H, t, *J* = 7.08 Hz); ¹³C NMR (125 MHz, CDCl₃/DMSO-*d*₆) δ 196.0 (C=O, ketone), 167.8 (C=O, ester), 150.3, 149.8, 143.9, 140.3, 133.8, 133.4, 130.8, 129.7, 129.6, 128.4, 127.7, 126.4, 119.1, 111.8, 106.6, 59.7, 51.1, 40.9, 33.0, 29.5, 27.9, 27.2, 19.1, 14.2. Anal. Calcd for C₃₀H₃₀ClN₃O₃: C, 69.82; H, 5.86; N, 8.14. Found: C, 69.67; H, 5.75; N, 8.05.

2.3.4. Ethyl 4-(1,3-Diphenyl-1H-pyrazol-4-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5d). Yellow powder, mp = 101–103°C; FT-IR (neat) ($\nu_{\max}/\text{cm}^{-1}$) 3300, 3200 (NH), 1690 (C=O); ^1H NMR (500 MHz, CDCl_3) δ 7.84 (1H, s), 7.82 (2H, d, J = 7.66 Hz), 7.69 (2H, d, J = 8.33 Hz), 7.42 (1H, t, J = 7.47 Hz), 7.35 (1H, t, J = 7.32 Hz), 7.25 (1H, t, J = 7.38 Hz), 6.32 (1H, s), 5.30 (1H, s), 3.74, 4.00 (2H, m), 2.30–2.35 (2H, m), 2.16 (3H, s), 1.93, 1.84 (2H, m), 1.84, 1.92 (2H, m), 1.01 (3H, t, J = 7.09 Hz); ^{13}C NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 196.3 (C=O, ketone), 167.7 (C=O, ester), 152.5, 150.6, 143.0, 140.4, 135.3, 129.8, 129.6, 128.4, 128.2, 127.9, 127.5, 126.4, 119.3, 112.9, 106.6, 60.1, 37.4, 27.6, 27.5, 21.4, 19.4, 14.5. Anal. Calcd for $\text{C}_{28}\text{H}_{27}\text{N}_3\text{O}_3$: C, 74.15; H, 6.00; N, 9.27. Found: C, 74.10; H, 6.26; N, 8.10.

2.3.5. Ethyl 2-Methyl-4-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5e). Yellow solid, mp = 202–203°C; FT-IR (neat) ($\nu_{\max}/\text{cm}^{-1}$) 3300, 3200 (NH), 1690 (C=O), 1640 (C=C, olefinic), 1510, 1330 (NO_2); ^1H NMR (500 MHz, CDCl_3) δ 8.31 (2H, d, J = 8.74 Hz), 8.25 (2H, d, J = 8.74 Hz), 8.04 (1H, s), 7.73 (1H, s), 7.62 (2H, d, J = 7.82 Hz), 7.37 (2H, t, J = 7.82 Hz), 7.20 (1H, t, J = 7.34 Hz), 5.22 (1H, s), 3.58, 3.86 (2H, m), 2.37 (2H, m), 2.28 (2H, m), 2.22 (3H, s), 1.84, 1.19 (2H, m), 0.80 (3H, t, J = 7.08 Hz); ^{13}C NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 196.5 (C=O, ketone), 167.7 (C=O, ester), 151.3, 149.1, 147.3, 144.1, 142.2, 140.2, 130.7, 130.0, 129.7, 128.3, 126.8, 123.6, 119.3, 113.2, 106.4, 59.9, 37.4, 27.4, 27.3, 21.5, 19.2, 14.4. Anal. Calcd for $\text{C}_{28}\text{H}_{26}\text{N}_4\text{O}_5$: C, 67.46; H, 5.26; N, 11.24. Found: C, 67.30; H, 5.16; N, 11.13.

2.3.6. Ethyl 4-(3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5f). White solid, mp = 257–258°C; FT-IR (neat) ($\nu_{\max}/\text{cm}^{-1}$) 3300, 3200 (NH), 1690 (C=O), 1645 (C=C, olefinic), 1070 (C–Cl); ^1H NMR (500 MHz, CDCl_3) δ 7.92 (2H, d, J = 8.41 Hz), 7.79 (1H, s), 7.72 (1H, s), 7.61 (2H, d, J = 7.79 Hz), 7.35 (2H, d, J = 8.41 Hz), 7.34 (2H, t, J = 7.53 Hz), 7.18 (1H, t, J = 7.38 Hz), 5.20 (1H, s), 3.91, 3.59 (2H, m), 2.34–2.31 (2H, m), 2.29–2.24 (2H, m), 2.17 (3H, s), 1.91, 1.89 (2H, m), 0.87 (3H, t, J = 7.10 Hz); ^{13}C NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 196.4 (C=O, ketone), 167.9 (C=O, ester), 151.3, 150.6, 143.7, 140.4, 142.0, 133.9, 133.6, 130.9, 129.6, 129.5, 128.4, 127.8, 126.4, 119.1, 113.0, 106.5, 59.8, 37.5, 27.4, 21.5, 19.1, 14.5. Anal. Calcd for $\text{C}_{28}\text{H}_{26}\text{ClN}_3\text{O}_3$: C, 68.92; H, 5.37; N, 8.61. Found: C, 68.74; H, 5.18; N, 8.52.

2.3.7. Ethyl 4-(1,3-Diphenyl-1H-pyrazol-4-yl)-2-methyl-5-oxo-4,5-dihydro-1H-indeno[1,2-b]pyridine-3-carboxylate (5g). Red solid, mp = 160–162°C; FT-IR (neat) ($\nu_{\max}/\text{cm}^{-1}$) 3280, 3180 (NH), 1680, 1670 (C=O), 1635 (C=C, olefinic); ^1H NMR (500 MHz, CDCl_3) δ 9.04 (1H, s), 7.90 (2H, d, J = 7.21 Hz), 7.76 (1H, s), 7.62 (2H, d, J = 7.92 Hz), 7.38–7.27 (m, 7H), 7.22–7.14 (3H, m), 5.12 (1H, s), 3.90, 3.67 (2H, m), 2.30 (3H, s), 0.79 (3H, t, J = 7.10 Hz); ^{13}C NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 192.8 (C=O, ketone), 167.8 (C=O, ester), 154.2, 152.1, 143.8, 140.4, 137.1, 134.6, 134.5, 131.5, 130.2, 129.6, 129.5, 128.5, 128.4, 128.0, 127.9, 126.3, 121.1, 119.1, 118.9, 110.1,

108.7, 60.0, 27.6, 19.3, 14.1. Anal. Calcd for $\text{C}_{31}\text{H}_{25}\text{N}_3\text{O}_3$: C, 76.37; H, 5.17; N, 8.62. Found: C, 76.43; H, 5.10; N, 8.46.

2.3.8. Ethyl 2-Methyl-4-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-5-oxo-4,5-dihydro-1H-indeno[1,2-b]pyridine-3-carboxylate (5h). Red solid, mp = 167–168°C; FT-IR (neat) ($\nu_{\max}/\text{cm}^{-1}$) 3300, 3180 (NH), 1690, 1680 (C=O), 1640 (C=C, olefinic), 1510, 1330 (NO_2); ^1H NMR (500 MHz, CDCl_3) δ 9.31 (1H, s), 8.21 (2H, d, J = 8.84 Hz), 8.15 (2H, d, J = 8.84 Hz), 7.77 (1H, s), 7.60 (2H, d, J = 8.58), 7.30–7.37 (3H, m), 7.24–7.15 (4H, m), 5.08 (1H, s), 3.86, 3.75 (2H, m), 2.33 (3H, s), 0.80 (3H, t, J = 7.10 Hz); ^{13}C NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 192.7 (C=O, ketone), 167.6 (C=O, ester), 154.2, 149.5, 147.3, 144.4, 141.5, 140.1, 136.9, 134.4, 131.6, 130.3, 130.1, 129.7, 129.4, 128.5, 126.9, 123.6, 121.2, 119.2, 119.1, 109.7, 108.2, 60.1, 27.8, 19.4, 14.2. Anal. Calcd for $\text{C}_{31}\text{H}_{24}\text{N}_4\text{O}_5$: C, 69.91; H, 4.54; N, 10.52. Found: C, 69.70; H, 4.38; N, 10.34.

2.3.9. Ethyl 4-(3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-2-methyl-5-oxo-4,5-dihydro-1H-indeno[1,2-b]pyridine-3-carboxylate (5i). Red solid, mp = 189–191°C; FT-IR (neat) ($\nu_{\max}/\text{cm}^{-1}$) 3300, 3190 (NH), 1680 (C=O), 1640 (C=C), 1090 (C–Cl); ^1H NMR (500 MHz, CDCl_3) δ 9.16 (1H, s), 7.86 (2H, d, J = 8.86 Hz), 7.74 (1H, s), 7.59 (2H, d, J = 7.68 Hz), 7.32 (2H, d, J = 8.42 Hz), 7.30–7.35 (3H, m), 7.13–7.26 (4H, m), 5.06 (1H, s), 3.89, 3.73 (2H, m), 2.30 (3H, s), 0.83 (3H, t, J = 7.11 Hz); ^{13}C NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 192.8 (C=O, ketone), 167.7 (C=O, ester), 154.2, 150.8, 144.0, 140.2, 137.0, 134.5, 133.7, 133.2, 131.6, 130.8, 130.2, 129.6, 128.6, 128.5, 128.1, 126.5, 121.1, 119.1, 119.0, 109.9, 108.5, 60.1, 27.7, 19.3, 14.2. Anal. Calcd for $\text{C}_{31}\text{H}_{24}\text{ClN}_3\text{O}_3$: C, 71.33; H, 4.63; N, 8.05. Found: C, 71.17; H, 4.45; N, 8.16.

3. Results and Discussion

In continuation of our ongoing interests on the synthesis of 1,4-dihydropyridine derivatives [29, 30], we have developed an efficient method for the synthesis of the target products via a one-pot four-component coupling reaction of heteroarylaldehyde (**1**) (prepared by the reaction of related arylhydrazone and DMF in the presence of 2,4,6-trichloro-1,3,5-triazine (TCT)) [28], 1,3-diketone (**2**), ethylacetate (**3**), and ammonium acetate in the presence of cellulose-sulfuric acid as a biosupported solid acid catalyst (Scheme 1). The reaction gave new derivatives of 1,4-dihydropyridines in lower reaction times (38–45 min) and excellent yields (85–95%) (Table 1).

The reactions (entries **a**, **d** and **g**) were also carried out in the absence of cellulose-sulfuric acid in the same conditions which furnished the desired products in much longer reaction times (120–125 min) and lower yields (Table 1).

In order to optimize the effect of the amount of catalyst on the efficiency of the reaction, the preparation of **5a** was selected as model reaction under reflux condition. This study gave the optimized amount of the catalyst as 0.05 g/mmol of substrate. The effect of different solvents (EtOH, MeOH, CH_3CN , 1,4-dioxane, and DMF) on the preparation of **5a** showed that EtOH was the solvent of choice. Therefore,

SCHEME 1: Efficient synthesis of fused 1,4-dihydropyridines.

all the reactions described in this report were carried out under optimized conditions (Table 1). The catalyst which was prepared according to the literature reports [31–33] is recoverable and was run for three consecutive cycles, furnishing the product (5a) without loss of catalytic activity. The structures of all products were deduced from ¹H NMR, ¹³C NMR and IR spectral analyses. ¹H NMR showed H-4 proton at 5.06–5.33 ppm as singlet which clearly confirmed the formation of 1,4-dihydropyridine moiety.

4. Conclusions

In summary, we have developed a convenient and facile protocol for the synthesis of new heteroaryl substituted 1,4-dihydropyridines in the presence of cellulose-sulfuric acid as an efficient biosupported solid acid catalyst in lower reaction times (37–45 min) and excellent yields (85–95%). The simple procedures combined with easy recovery and reuse of the catalyst make this method economic, environmentally benign, and user-friendly process for the synthesis of these biolabile fused 1,4-dihydropyridine derivatives. The method is amenable for iterative combinatorial library generation.

Conflict of Interests

The authors declare no conflict of interests.

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