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ORIGINAL PAPER

Synthesis of tetrahydropyridines by one-pot multicomponent reaction using nano-sphere silica sulfuric acid

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Abstract A highly efficient protocol for the synthesis of 1,2,3,4-tetrahydropyridines in the presence of nano-sphere silica sulfuric acid (NS-SSA) was used for good yields by one-pot multicomponent reaction (MCRs). The reagent nano-sphere silica sulfuric acid (NS-SSA) has several advantages, such as easy workup, nontoxicity, convenience and high yields of products.

Keywords Tetrahydropyridines · Nano-sphere silica sulfuric acid · Multicomponent reaction

Introduction

One of the basic and essential heterocycles are tetrahydropyridines that have used to synthesize pharmaceutical compounds [1–7]. They have high biological activities associated with antiparasitic, antimicrobial, antiviral, antimalarial, anticancer, herbicidal and antihypertensive properties [8–25]. In addition, some of the derivatives of these compounds are used in a drug administered for the cause of permanent Parkinson's disease [26–28].

In recent decades, the use of solid-supported catalysts such as silica, alumina and titania has gained considerable attention both in industrial and academia research due to their unique properties, such as selectivity, efficiency and straightforward workup [29–36]. Considering the above points and along the line of our studies in design and application of new heterogeneous catalysts in chemical transformations [37–44], we report the synthesis, characterization and catalytic application of nano-sphere silica sulfuric acid (NS-SSA) that can be easily prepared from commercially available materials, for the synthesis of tetrahydropyridines by the one-pot multi-component reactions. This method shows high atom economy and high selectivity and is environmentally friendly as it reduces the number of synthesis steps [45, 46]. (Scheme 1).

Results and discussion

Initially, the nano-sphere silica was prepared according to the reported procedures.[43] Then, the catalyst was synthesized by the reaction of nano-sphere silica with chlorosulfonic acid in excellent yield (Scheme 2).

Nano-sphere silica sulfuric acid was characterized by transmission electron microscopy (TEM), FT-IR, XRD, EDS, N_2 adsorption–desorption techniques and thermal analysis [43].

To optimize the reaction conditions for the synthesis of tetrahydropyridine compounds, the reaction of

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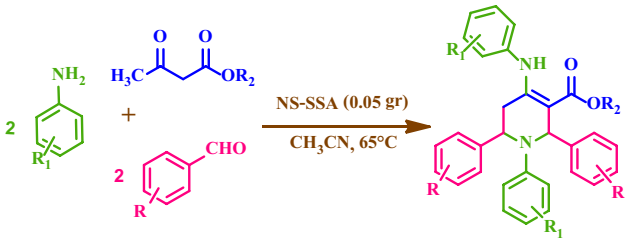
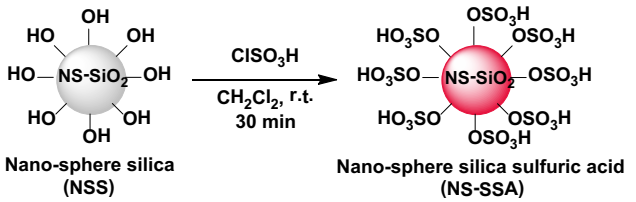


Scheme 1 Synthesis of tetrahydropyridines using nano-sphere silica sulfuric acid (NS-SSA)



Scheme 2 Synthesis of nano-sphere silica sulfuric acid

Table 1 Synthesis of compound **2c** using different catalysts

Entry	Catalyst	Yeild (%)
1	Citric acid	55
2	SSA	57
3	$FeCl_3$	65
4	[Msim]Cl	63
5	NS-SSA	86
6	I_2	50

Table 2 Optimization of reaction conditions

Entry	Amount of Catalyst (g)	Temp. (°C)	Time (h)	Yield (%)
1	–	65	6	–
2	0.005	65	3	46
3	0.01	65	4	62
4	0.03	65	4	68
5	0.05	65	3:20	86

4-bromoaniline, benzaldehyde and methyl acetoacetate was selected as a model reaction to provide compound **2c** (Table 4, entry 3).

At first, the reaction was examined in the presence of 20 mol % of different catalysts during 2 h. Higher yield of product was obtained when nano-sphere silica sulfuric acid was utilized as catalyst (Table 1, entry 5). The results are summarized in Table 1.

In the next step, the model reaction was tested using different amounts of NS-SSA at the same temperature

Table 3 The effect of various solvents on the synthesis of tetrahydropyridines

Entry	Solvent	Time (h)	Yield (%)
1	CH_3CN	2	86
2	EtOH	4	46
3	MeOH	1	48
4	$(CH_3)_2CO$	24	0
5	Ethyl acetate	18	6
6	CH_2Cl_2	12	44
7	H_2O	–	0
8	THF	–	0

(Table 2). As it can be seen in Table 2, the best amount of the catalyst was 0.05 g. Moreover, the product yield was not changed by increasing the amount of the catalyst. The best results were obtained when the reaction was performed at 65 °C. Increasing the reaction temperature did not improve the results (Table 2).

In another study, we studied the synthesis of tetrahydropyridines in a variety of solvents. The results showed that acetonitrile is the best solvent in terms of time and product yield (Table 3).

In the next part, the generality and efficiency of nano-sphere silica sulfuric acid in the synthesis of tetrahydropyridines were explored under the optimized reaction conditions by the reaction of various anilines and arylaldehydes with a broad range of electron-releasing substituents, electron-withdrawing substituents and halogens on their aromatic rings, and different β-ketoester in the acetonitrile. As it can be seen in Table 4, all benzaldehyde derivatives, anilines and different β-ketoester afforded the desired tetrahydropyridines in high to excellent yields. All the target compounds were completely characterized by IR, ^{1}HNMR, ^{13}CNMR.

In summary, we have developed a method for the synthesis of nano-sphere silica sulfuric acid (NS-SSA) as an efficient and heterogeneous catalyst via the reaction of nano-sphere silica with chlorosulfonic acid. NS-SSA showed powerful activity in the one-pot multicomponent reaction leading to tetrahydropyridines in good to high yield.

Experimental section

General procedure for the synthesis of tetrahydropyridines

β-ketoester (1.0 mmol), aniline (2 mmol) and 0.05 g nano-sphere silica sulfuric acid (NS-SSA) in 10 ml CH_3CN was stirred at 65 °C for 20 min, aldehyde (2.0 mmol) was then added and stirring was continued until the formation of a solid. Then the reaction mixture was filtered and the solid

Table 4 The synthesis of tetrahydropyridines using nano-sphere silica sulfuric acid (NS-SSA)

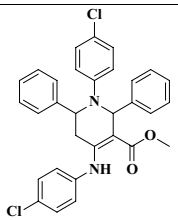
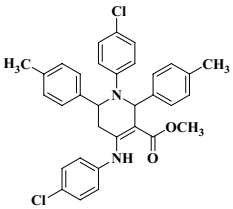
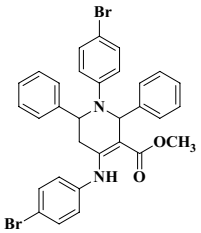
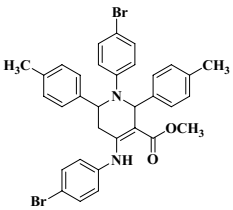
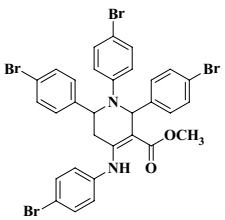
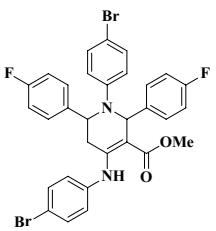
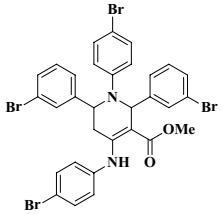
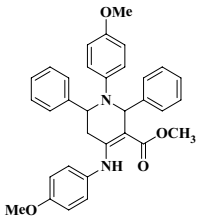
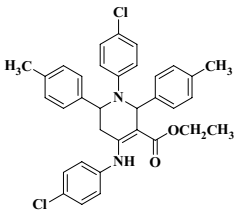
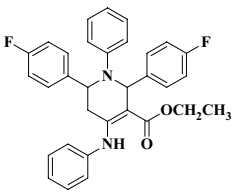
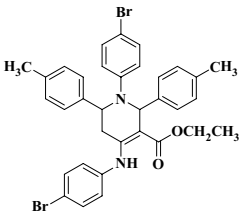
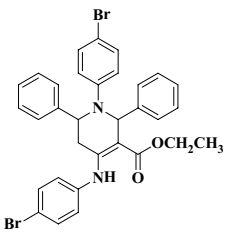
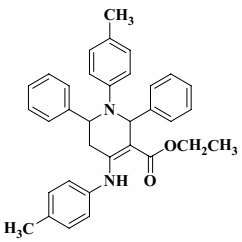
Entry	R	R_1	R_2	Product	Product number	Time (h)	Yield (%)	M.P. (°C) (Found)[ref.]
1	H	4-Cl	CH_3		2a	4	88	(217-220)[9]
2	4-CH_3	4-Cl	CH_3		2b	3:30	80	(211-213)[4]
3	H	4-Br	CH_3		2c	2	86	(245-248)[9]
4	4-CH_3	4-Br	CH_3		2d	3:30	80	(226-229)[9]
5	4-Br	4-Br	CH_3		2e	4:30	74	(226-229)[9]
6	4-F	4-Br	CH_3		2f	4	75	(239-241)[18]
7	3-Br	4-Br	CH_3		2g	6	75	(223-226)[9]

Table 4 continued

8	H	4-OCH_3	CH_3		2h	3	78	(292-294)[2]
9	4-CH_3	4-Cl	CH_2CH_3		2i	1	92	(228-231)[4]
10	4-F	H	CH_2CH_3		2j	3	78	(215-218)[28]
11	4-CH_3	4-Br	CH_2CH_3		2k	4:30	76	(239-241)[9]
12	H	4-Br	CH_2CH_3		2l	5:30	89	(227-230)[18]
13	H	4-CH_3	CH_2CH_3		2m	6	75	(223-226)[28]

so obtained was washed with acetonitrile. Since the solid does not solve in chloroform, it was separated from nano-sphere silica sulfuric acid (NS-SSA) by the addition of $CHCl_3$. Finally, a colorless powder resulted with filtering of solution and evaporation.

Methyl 1-(4-chlorophenyl)-4-((4-chlorophenyl)amino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (2a): White powder, mp 217–220 °C; IR(KBr): υ = 3325, 3086, 3063, 2949, 2868, 1651, 1600, 1504, 626 cm^{-1}. ^{1}HNMR (600 MHz; $CDCl_3$) = 2.709–2.665 (1H, m, J = 18 Hz), 2.87–2.82 (1H, m, J = 3 Hz), 3.937 (3H, s), 5.1–5.09 (1H, d, J = 6 MHz), 6.176–6.154 (2H, d, J = 12 Hz), 6.434-6.412 (2H, t, j = 12 Hz), 10.185 (S, 1H). ^{13}CNMR (150 MHz; $CDCl_3$) = 33.4, 51.2, 55.27, 58.3, 98.4, 114, 121.1, 126.2, 127, 128.7, 129, 131.4, 136, 142, 143.2, 145.4, 168.4.

Methyl 1-(4-chlorophenyl)-4-((4-chlorophenyl)amino)-2,6-di-p-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate (2b): White powder, mp 211–213 °C; IR(KBr): υ = 3248, 3087, 3023, 2950, 2857, 1651, 1605, 1585 cm^{-1}. ^{1}HNMR (600 MHz; $CDCl_3$) = 2.34–2.31(6H, d, *j* = 18 Hz), 2.69–2.6 (1H, m, *j* = 18 Hz), 3.92 (3H, s), 5.06–5.05 (1H, d, *J* = 6 Hz), 6.19–6.17 (2H, d, *j* = 12 Hz), 6.43–6.41 (2H, d, *j* = 12 Hz), 10.18 (1H, s). ^{13}CNMR (600 MHz; $CDCl_3$) = 20.99, 33.47, 51.1, 55, 58, 98.1, 113, 121, 126.2, 127, 128, 131, 136, 137, 139, 140.1, 168.4.

Methyl 1-(4-bromophenyl)-4-((4-bromophenyl)amino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (2c): White powder, mp 245-248 °C; IR(KBr): υ = 3256, 3084, 2948, 1651, 1599, 1578 cm^{-1}. ^{1}HNMR (600 MHz; $CDCl_3$) = 2.72–2.67 (1H, m, *j* = 3 Hz), 2.87–2.82 (1H, m, *j* = 3 Hz), 3.93 (3H, s), 5.1–5.09 (1H, d, *j* = 6 Hz), 6.11–6.09 (2H, d, *j* = 12 Hz), 6.39–6.37 (3H, d, *j* = 12 Hz), 10.17 (1H, s). ^{13}CNMR (600 MHz; $CDCl_3$) = 33.4, 51.2, 55.2, 58.2, 98.5, 108.4, 114.5, 119, 126.2, 127, 128.8, 131.5, 132, 136.8, 142.1, 143, 145.8, 168.4.

Methyl 1-(4-bromophenyl)-4-((4-bromophenyl) amino)-2,6-di-p-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate (2d): White powder, mp 226-229 °C; IR(KBr): υ = 3240, 3091, 2951, 2861, 1650, 1603, 1586 cm^{-1}. ^{1}HNMR (600 MHz; $CDCl_3$) = 2.33–2.31 (6H, d, *j* = 12 Hz), 2.71–2.67 (1H, m, *j* = 24 Hz), 3.92 (3H, s), 5.06–5.04 (1H, d, *j* = 6 Hz), 6.13–6.11 (2H, d, *j* = 12 Hz), 6.39–6.36 (2H, d, *j* = 18 Hz), 10.17 (1H, s). ^{13}CNMR (600 MHz; $CDCl_3$) = 21, 33.4, 51.1, 55, 57.9, 98.6, 108.2, 114.5, 119, 126.2, 127.2, 129, 131, 136.1, 137, 139, 140, 145.9, 155.4, 168.4.

Methyl 1,2,6-tris(4-bromophenyl)-4-((4-bromophenyl) amino)-1,2,5,6-tetrahydropyridine-3-carboxylate (2e): White powder, mp 226–229 °C; IR(KBr): υ = 3233, 3200, 2989, 1714, 1655, 1582 cm^{-1}. ^{1}HNMR (600 MHz; $CDCl_3$) = 2.1 (5H, s), 2.7–2.65 (1H, m, *j* = 3 Hz), 2.81–2.79 (1H, m, *j* = 18 Hz), 3.92 (3H, s), 5.03–5.02 (1H, d, *j* = 6 Hz), 6.30–6.26 (5H, m, *j* = 24 Hz), 7.13–7.11 (4H, m, *j* = 12 Hz), 10.18 (1H, s). ^{13}CNMR (600 MHz; $CDCl_3$) = 30.93, 33.4, 51.3, 54.9, 57.4, 98, 109, 114.5, 117.6, 119, 120.5, 121.3, 128, 131.8, 132, 136.5, 140.7, 142, 145, 155.1, 168.1.

Methyl 1-(4-bromophenyl)-4-((4-bromophenyl)amino)-2,6-bis(4-fluorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (2f): white powder, mp 239-241 °C; IR(KBr): υ = 3233, 3200, 2989, 1714, 1655, 1582 cm^{-1}. ^{1}HNMR (600 MHz; $CDCl_3$) = 2.68 (2H, s), 2.82–2.64 (1H, m, *j* = 18 Hz), 3.82 (3H, s), 5.03–52.02 (3H, d, *J* = 6 Hz), 6.25 (1H, S), 6.32-6.30 (4H, m, *j* = 12 Hz), 10.18 (1H,s). ^{13}CNMR (600 MHz; $CDCl_3$) = 30.9, 33.5, 51.3, 54.9, 57.4, 97.9, 114, 120, 121.2, 126.9, 128, 129, 131.5, 136, 140.8, 142.9, 144.1, 155, 168.16.

methyl 2,6-bis(3-bromophenyl)-1-(4-bromophenyl)-4-((4-bromophenyl)amino)-1,2,5,6-tetrahydropyridine-3-carboxylate (2 g): white powder, mp 223–226 °C; IR(KBr): υ = 3233, 3200, 2989, 1714, 1655, 1582 cm^{-1}. ^{1}HNMR (600 MHz; $CDCl_3$) = 1.56 (4H, s), 2.71-2.66 (1H, m, *j* = 3 Hz), 2.83–2.78 (1H, m, *j* = 3 Hz), 3.93 (3H, s), 5.05–5.04 (1H, d, j = 6 Hz), 6.31–6.28 (2H, d, *j* = 18 Hz), 7.16–7.13 (5H, m, *j* = 18 Hz), 10.17 (1H, s). ^{13}CNMR (600 MHz; $CDCl_3$) = 33.3, 51.3, 55, 57.7, 97.6, 109.2, 114.6, 119.8, 122.7, 125, 127.7, 129.2, 130, 131, 132, 136.5, 144.2, 145.2, 155.2, 168.1.

Methyl 1-(4-methoxyphenyl)-4-((4-methoxyphenyl)amino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (2 h): white powder, mp 292-294 °C; IR(KBr): υ = 3233, 3200, 2989, 1714, 1655, 1582 cm^{-1}. ^{1}HNMR (400 MHz; CDCl3) = 1.99 (3H, s), 2.14 (3H, s), 2.68–2.65 (1H, m, *j* = 12 Hz), 2.68–2.65 (3H, d, *J* = 12 Hz), 3.78 (3H, S), 5.25–5.24 (1H, d, *J* = 4 Hz), 6.18–6.15 (2H, d, *j* = 12 Hz), 6.25–6.21(3H, t, *J* = 12 Hz), 6.74–6.72 (2H, d, *J* = 8 Hz), 6.89–6.87 (2H, d, *J* = 8 Hz), 7.09–7.07(3H, d, *J* = 8 Hz), 7.22–7.21(7H, d, *J* = 4 Hz), 10.01(1H,s). ^{13}CNMR (600 MHz; $CDCl_3$) = 19.6, 20.33, 33.2, 50.9, 54, 56, 97, 112, 124, 124.9, 126, 126.2, 126.26, 128, 128.3, 129, 129.4, 134, 143, 144, 144.2, 155, 167.

Ethyl 1-(4-chlorophenyl)-4-((4-chlorophenyl)amino)-2,6-di-p-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate (2i): white powder, mp 228-231 °C; IR(KBr): υ = 3230, 3173, 2979, 2864, 1646, 1604, 1504 cm^{-1}. ^{1}HNMR (600 MHz; $CDCl_3$) = 1.47–1.43 (3H, t, *j* = 24 Hz), 2.7–2.67 (1H, m, *j* = 18 Hz), 2.86–2.81 (1H, m, *J* = 3 Hz), 2.33–2.31 (6H, d, *j* = 12 Hz), 4.34–4.29 (1H, m, *j* = 3 Hz), 5.06–5.05 (1H, d, *j* = 6 Hz), 6.43–6.4 (5H, m, *j* = 18 Hz). ^{13}CNMR (600 MHz; $CDCl_3$) = 14.7, 20.9, 21.1, 33.4, 55.5, 59.8, 98.8, 114, 121, 126, 128.9, 129, 131, 136, 137, 139, 140.2, 145, 155.3, 168.1.

Ethyl 2,6-bis(4-fluorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (2j): white powder, mp 215-218 °C; IR(KBr): υ = 3242, 3090, 3061, 3027, 2909, 1647, 1603, 1585, 1451 cm^{-1}. ^{1}HNMR (600 MHz; $CDCl_3$) = 1.485–1.45 (3H, t, *j* = 18 Hz), 2.71–2.67 (1H, m, *j* = 18 Hz), 2.87–2.82 (1H, m, *J* = 3 Hz), 4.49–4.44 (1H, m, *J* = 3 Hz), 5.1–5.09 (1H, d, *j* = 6 Hz), 6.43–6.38 (1H, t, *j* = 3 Hz), 10.23 (1H, s). ^{13}CNMR (600 MHz; $CDCl_3$) = 14.7, 33.48, 51.14, 55.07, 58.01, 98.58, 113, 121, 126, 127, 128, 129, 131, 136.1, 137, 139, 140, 145, 155, 168.4.

Ethyl 1-(4-bromophenyl)-4-((4-bromophenyl)amino)-2,6-di-p-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate (2 k): white powder, mp 239–241 °C; IR(KBr): υ = 3234, 2922, 1647, 1603 cm^{-1}. ^{1}HNMR (600 MHz; $CDCl_3$) = 1.47–1.43 (3H, d, *j* = 3 Hz), 2.33–2.31 (6H, d, *j* = 12 Hz), 2.71–2.67 (1H, t, *j* = 24 Hz), 2.85–2.83 (1H, m, *j* = 3 Hz), 4.34–4.29

(1H, m, $j = 3$ Hz), 5.06–5.05 (1H, d, $j = 6$ Hz), 6.14–6.12 (2H, d, $j = 12$ Hz), 6.39–6.37 (3H, m, $j = 12$ Hz), 10.22 (1H, s). ^{13}CNMR (600 MHz; $CDCl_3$) = 14.7, 20.9, 21.1, 33.4, 55, 58, 59.9, 98.9, 108.2, 114.5, 118.9, 126, 127.2, 129, 131.5, 136.1, 137, 139, 140, 145, 155, 168.1.

Ethyl 1-(4-bromophenyl)-4-((4-bromophenyl)amino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (2 l): white powder, mp 227-230 °C; IR(KBr): υ = 3256, 3084, 2948, 1651, 1599, 1578 cm^{-1}. ^{1}HNMR (600 MHz; $CDCl_3$) = 2.686–2.681 (1H, d, $j = 0.3$ Hz), 2.84–2.82 (1H, d, $j = 12$ Hz), 4.33–4.31(1H, m, $j = 12$ Hz), 5.1–5.09 (1H, d, $j = 12$ Hz), 7.29–7.27 (7H, m, $j = 12$ Hz), 10.2 (1H, s). ^{13}CNMR (600 MHz; $CDCl_3$) = 14.7, 33.4, 55.2, 58.2, 59.9, 98.8, 108.4, 114.5, 119.1, 126.4, 127.2, 128.3, 131.6, 136.9, 142.1, 143.1, 145.5, 155.2, 168.1.

Ethyl 2,6-diphenyl-1-(p-tolyl)-4-(p-tolylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (2 m): white powder, mp 223-226 °C; IR(KBr): υ = 3239, 3024, 2919, 2854, 1617, 1649, 15942 cm^{-1}. ^{1}HNMR (600 MHz; $CDCl_3$) = 1.44 (3H, s), 2.25 (3H, S), 2.14 (3H, S), 2.74–2.7 (1H, m, $J = 24$ Hz), 4.32–4.31 (1H, m, $j = 6$ Hz), 4.44–4.43 (1H, m, $J = 6$ Hz), 6.16–6.14 (2H, d, $j = 12$ Hz), 6.88–6.85 (4H, m, $j = 18$ Hz), 10.19 (1H, s). ^{13}CNMR (600 MHz; $CDCl_3$) = 14.8, 20.1, 33.5, 55.1, 58.2, 59.5, 97.7, 112, 125, 126.1, 127, 128, 129.3, 135, 143, 144, 156.4, 168.2.

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