Sulfonic Acid Functionalized Silica: An Efficient Heterogeneous Catalyst for a Three-Component Synthesis of 1,4-Dihydropyridines under Solvent-Free Conditions[1)]

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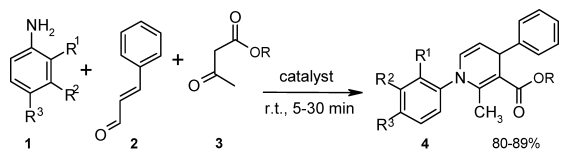
Sulfonic acid functionalized silica catalyzed the three-component reaction of aromatic amines, α,β-unsaturated aldehydes and β-keto esters forming the corresponding 1,4-dihydropyridines in short reaction times and in high yields.

Key words sulfonic acid functionalized silica; multicomponent reaction; 1,4-dihydropyridine; solvent-free condition

1,4-Dihydropyridines possess a wide range of pharmacological properties including neuroprotective, platel anti-aggregation and antidiabetic activities.[2—4)] They are well known as the most important calcium channel modulators.[5,6)] Some representative drugs such as nifedipine and niguldipine are frequently used for treatment of hypertension.[7)] 1,4-Dihydropyridines are also useful intermediates in the preparation of nitrogen heterocycles.[8,9)] The classical method for the synthesis of these compounds is the Hantzsch reaction involving a multicomponent condensation of an aldehyde with a 1,3-dicarbonyl compound and NH_3.[10)] This method is not suitable for the preparation of *N*-aryl-1,4-dihydropyridines and different other related valuable analogues.

In continuation of our work[11,12)] on the application of heterogeneous catalysts to useful synthetic methodologies we have discovered that sulfonic acid functionalizd silica is an active catalyst for the synthesis of 1,4-dihydropyridines by a one-pot three-component coupling of aromatic amines, α,β-unsaturated aldehydes and β-ketoester (Chart 1) which is complementary to the Hantzsch reaction.

A series of 1,4-dihydropyridines were successfully prepared following the above method (Table 1). The conversion proceeded at room temperature and within a short reaction time (5—30 min). The products were formed in high yields (80—89%). No additional solvent was required. Both ethyl and methyl acetoacetates were used to afford the products in almost similar yields. The conversion proceeded smoothly with aromatic amines to form the corresponding 1,4-dihydropyridines but with aliphatic amines, complex mixtures were obtained. The cinnamaldehyde derivatives containing nitro group in the aromatic ring also yielded the mixtures of products. However, imines derived from anilines and α,β-unsaturated aldehydes afforded the desired 1,4-dihydropyridines on treatment with β-ketoesters under the present reaction conditions. The structures of the products were established from their spectral (^{1}H-NMR and MS) data. While our this work was in progress a related method for the synthesis of 1,4-dihydropyridines using Cerric ammonium nitrate (CAN) as a catalyst has been reported.[13)] However, the time of conversion was 1 h for preparation of each product, the yields were lower than those obtained in the present method, the reaction conditions were homogeneous and the solvent (absolute ethanol) and inert atmosphere were required.



1 2 3 4

Catalyst: Sulfonic acid functionalized silica

Chart 1

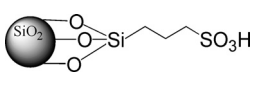


Fig. 1

The present catalyst, sulfonic acid functionalized silica works under heterogeneous conditions. In recent years heterogeneous catalysts have gained much importance due to eco-economical benefits. They offer simpler, less-costly, more reactive and more environmentally benign alternatives than their homogeneous counterparts. Sulfonic acid functionalized silica, an organic-inorganic hybrid (interphase) catalyst (Fig. 1) has efficiently been applied here for the synthesis of 1,4-dihydropyridines. The catalyst was prepared following known procedure[14,15)] by immobilization of propyl thiol group on silica using 3-mercaptopropyl trimethoxy silane and by subsequent selective oxidation of the thiol groups by aqueous H_2O_2 to sulfonic acid groups. It can easily be recovered by filtration and recycled. The recovered catalyst was utilized consecutively three times without loss of its activity.

In conclusion, we have developed an useful method for the synthesis of 1,4-dihydropyridines using sulfonic acid functionalized silica as an efficient catalyst. The mild, heterogeneous and solvent-free conditions, short reaction times, high yields, operational simplicity and reusability of the catalyst are the notable advantages of the protocol.

Experimental

To a mixture of an arylamine (1 mmol), cinnamaldehyde (1 mmol) and β-ketoester (1 mmol) sulfonic acid functionalized silica (15 mg) was added. The mixture was stirred at room temperature and the reaction was monitored by TLC. After completion, the mixture was diluted with EtOAc (10 ml) and filtered to recover the catalyst. The filtrate was dried over anhydrous Na_2SO_4 and evaporated. The residue was subjected to column chromatography (silica gel, hexane–EtOAc) to obtain pure 1,4-dihydropyridine derivatives.

The spectral (^{1}H-NMR and MS) and analytical data of the prepared 1,4-dihydropyridines are given below.

Product **4a**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.42—7.21 (10H, m), 6.21

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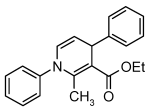
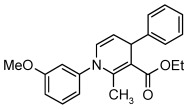
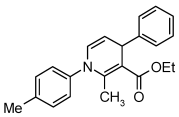
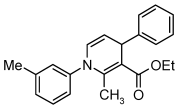
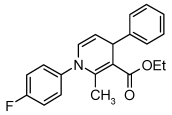
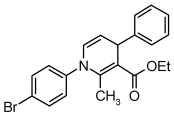
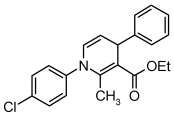
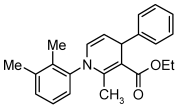
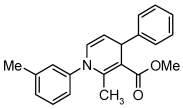
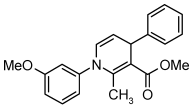
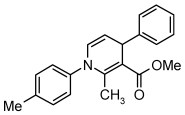
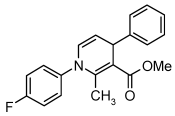
Table 1. Synthesis of 1,4-Dihydropyridines Using Sulfonic Acid Functionalized Silica[a)]

Entry	R	R^1	R^2	R^3	Product (**4**)	Time (min)	Isolated yield (%)
a	Et	H	H	H		5	89
b	Et	H	OMe	H		5	85
c	Et	H	H	Me		10	80
d	Et	H	Me	H		10	82
e	Et	H	H	F		30	86
f	Et	H	H	Br		30	84
g	Et	H	H	Cl		30	80
h	Et	Me	Me	H		15	80
i	Me	H	Me	H		10	85
j	Me	H	OMe	H		20	88
k	Me	H	H	Me		10	84
l	Me	H	H	F		20	86

a) The structures of the products were established from their spectral (^{1}H and MS) and analytical data.

(1H, d, J=7.5 Hz), 4.94 (1H, dd, J=7.5, 5.5 Hz), 4.72 (1H, d, J=5.5 Hz), 4.01 (2H, q, J=7.0 Hz), 2.10 (3H, s), 1.07 (3H, t, J=7.0 Hz); FAB-MS *m/z*: 319 (M^+); *Anal.* Calcd for $C_{21}H_{21}NO_2$: C, 79.00; H, 6.58; N, 4.39%. Found: C, 79.29; H, 6.69; N, 4.31%.

Product **4b**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.41—6.98 (6H, m), 6.85—6.79 (3H, m), 6.21 (1H, d, J=7.5 Hz), 4.98 (1H, dd, J=7.5, 5.5 Hz), 4.74 (1H, d, J=5.5 Hz), 4.03 (2H, q, J=7.0 Hz), 3.85 (3H, s), 2.16 (3H, s), 1.08 (3H, t, J=7.0 Hz); FAB-MS *m/z*: 349 (M^+); *Anal.* Calcd for $C_{22}H_{23}NO_3$: C, 75.64; H, 6.59; N, 4.01%. Found: C, 75.82; H, 6.42; N, 4.21%.

Product **4c**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.42—7.26 (7H, m), 7.15 (2H, d, J=8.0 Hz), 6.20 (1H, d, J=7.5 Hz), 4.95 (1H, dd, J=7.5, 5.5 Hz), 4.75 (1H, d, J=5.5 Hz), 4.02 (2H, q, J=7.0 Hz), 2.41 (3H, s), 2.17 (3H, s), 1.06 (3H, t, J=7.0 Hz) ; FAB-MS *m/z*: 333 (M^+); *Anal.* Calcd for $C_{22}H_{23}NO_2$: C, 79.28; H, 6.91; N, 4.20%. Found: C, 79.12; H, 6.80; N, 4.33%.

Product **4d**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.32—6.95 (9H, m), 6.08 (1H, d, J=7.5 Hz), 4.92 (1H, dd, J=7.5, 5.5 Hz), 4.63 (1H, d, J=5.5 Hz), 3.99 (2H, q, J=7.0 Hz), 2.40 (3H, s), 2.11 (3H, s), 1.08 (3H, t, J=7.0 Hz); FAB-MS *m/z*: 333 (M^+); *Anal.* Calcd for $C_{22}H_{23}NO_2$: C, 79.28; H, 6.91; N, 4.20%. Found: C, 79.14; H, 6.83; N, 4.31%.

Product **4e**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.29—7.02 (9H, m), 6.02 (1H, d, J=7.5 Hz), 4.88 (1H, dd, J=7.5, 5.5 Hz), 4.62 (1H, d, J=5.5 Hz), 3.99 (2H, q, J=7.0 Hz), 2.04 (3H, s), 1.03 (3H, t, J=7.0 Hz); FAB-MS m/z: 337 (M^+); *Anal.* Calcd for $C_{21}H_{20}FNO_2$: C, 74.78; H, 5.93; N, 4.15%. Found: C, 74.87; H, 5.84; N, 4.08%.

Product **4f**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.56 (2H, d, J=8.0 Hz), 7.40—7.26 (5H, m), 7.14 (2H, d, J=8.0 Hz), 6.18 (1H, d, J=7.5 Hz), 4.98 (1H, dd, J=7.5, 5.5 Hz), 4.75 (1H, d, J=5.5 Hz), 4.04 (2H, q, J=7.0 Hz), 2.18 (3H, s), 1.10 (3H, t, J=7.0 Hz); FAB-MS m/z: 399, 397 (M^+); *Anal.* Calcd for $C_{21}H_{20}BrNO_2$: C, 63.32; H, 5.03; N, 3.52%. Found: C, 63.51; H, 5.17; N, 3.44%.

Product **4g**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.40—7.21 (9H, m), 6.15 (1H, d, J=7.5 Hz), 5.01 (1H, dd, J=7.5, 5.5 Hz), 4.75 (1H, d, J=5.5 Hz), 4.01 (2H, q, J=7.0 Hz), 2.16 (3H, s), 1.08 (3H, t, J=7.0 Hz); FAB-MS m/z: 355, 353 (M^+); *Anal.* Calcd for $C_{21}H_{20}ClNO_2$: C, 71.29; H, 5.66; N, 3.96%. Found: C, 71.38; H, 5.73; N, 3.91%.

Product **4h**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.38—7.12 (8H, m), 6.17 (1H, d, J=7.5 Hz), 5.02 (1H, dd, J=7.5, 5.5 Hz), 4.73 (1H, d, J=5.5 Hz), 3.99 (2H, q, J=7.0 Hz), 2.29 (6H, s), 2.17 (3H, s), 1.10 (3H, t, J=7.0 Hz); FAB-MS m/z: 347 (M^+); *Anal.* Calcd for $C_{23}H_{25}NO_2$: C, 79.54; H, 7.21; N, 4.04%. Found: C, 79.68; H, 7.29; N, 4.18%.

Product **4i**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.33—6.95 (9H, m), 6.11 (1H, d, J=7.5 Hz), 4.93 (1H, dd, J=7.5, 5.5 Hz), 4.62 (1H, d, J=5.5 Hz), 3.53 (3H, s), 2.39 (3H, s), 2.11 (3H, s); FAB-MS m/z: 319 (M^+); *Anal.* Calcd for $C_{21}H_{21}NO_2$: C, 79.00; H, 6.58; N, 4.34%. Found: C, 79.18; H, 6.46; N, 4.45%.

Product **4j**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.57—7.05 (9H, m), 6.12 (1H, d, J=7.5 Hz), 4.96 (1H, dd, J=7.5, 5.5 Hz), 4.62 (1H, d, J=5.5 Hz), 3.81 (3H, s), 3.53 (3H, s), 2.03 (3H, s); FAB-MS m/z: 335 (M^+); *Anal.* Calcd for $C_{21}H_{21}NO_3$: C, 75.22; H, 6.27; N, 4.18%. Found: C, 75.11; H, 6.35; N, 4.27%.

Product **4k**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.51—7.32 (7H, m), 7.08 (2H, d, J=8.0 Hz), 6.14 (1H, d, J=7.5 Hz), 4.95 (1H, dd, J=7.5, 5.5 Hz), 4.64 (1H, d, J=5.5 Hz), 3.54 (3H, s), 2.37 (3H, s), 2.10 (3H, s); FAB-MS m/z: 319 (M^+); *Anal.* Calcd for $C_{21}H_{21}NO_2$: C, 79.00; H, 6.58; N, 4.39%. Found: C, 79.26; H, 6.69; N, 4.28%.

Product **4l**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.38—7.15 (9H, m), 6.08 (1H, d, J=7.5 Hz), 4.91 (1H, dd, J=7.5, 5.5 Hz), 4.65 (1H, d, J=5.5 Hz), 3.58 (3H, s), 2.06 (3H, s); FAB-MS m/z: 323 (M^+); *Anal.* Calcd for $C_{20}H_{18}FNO_2$: C, 74.30; H, 5.57; N, 4.33%. Found: C, 74.51; H, 5.48; N, 4.41%.

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References and Notes

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