Covalently Bonded Ionic Liquid-Type Sulfamic Acid onto SBA-15: SBA-15/NHSO$_3$H as a Highly Active, Reusable, and Selective Green Catalyst for Solvent-Free Synthesis of Polyhydroquinolines and Dihydropyridines

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Received: 29.08.2014; Accepted after revision: 21.09.2014

Abstract: Amine-functionalized ordered mesoporous organic–inorganic hybrid materials are designed as solid supports to covalently immobilize the SO$_3$H group to achieve sulfamic acid (SBA-15/NHSO$_3$H) as a novel catalyst. SBA-15/NHSO$_3$H as ionic liquid-type heterogeneous catalyst could be separated easily from reaction products and recycled, showing superiority over homogeneous catalysts.

Keywords: SBA-15/NHSO$_3$H, supported sulfamic acid, multicomponent reaction, mesoporous solid

Use of recyclable catalysts can minimize the consumption of auxiliary substances, and time required to achieve separations, thus resulting in significant economic and environmental benefits.[1] Green chemistry aims to eliminate pollution by preventing it from happening in the first place and by using resources for chemical feedstocks that are renewable.[2] Porous nanoreactor-assisted organic synthesis using organic–inorganic hybrid channels has been utilized not only to accelerate a number of synthetically useful reactions, but also to increase reaction rate, yields, and recyclability as a powerful and green approach.[3] Using SBA-15 covalently bound organic groups can produce organic–inorganic mesochannels, providing synergistic means for an efficient approach of the reactants to acidic sites and suitable mesochannels to drive out the products and water for subsequent catalytic cycles.[3,4]

Polyhydroquinolines and dihydropyridines have attracted much attention due to their antitumor, bronchodilatory, antidiabetic, anti-inflammatory, antibacterial, and antimalarial properties.[5] Consequently, many different synthetic methods for producing polyhydroquinolines and dihydropyridines derivatives have been reported with systems using ionic liquids, molecular iodine, HClO$_4$–SiO$_2$, HY zeolites, CAN, hetrapolyacids, and polymers.[5,6] However, there exist significant drawbacks in many of these processes, such as the need for high temperatures or extended reaction times, large volumes of organic solvents, high catalyst loading, and low yields. In addition, the use of soluble metal catalysts requires catalyst separation. As a result, the challenge in this field is to develop waste-free and effective green approaches with high yields.

As part of our ongoing program to develop efficient and environmentally benign methods in synthetic organic chemistry,[7] our aim has been to investigate catalysts to accomplish multicomponent reactions with minimum byproducts and waste generation, as well as avoiding use of heavy metals. Herein we present the results of a program investigating the activity and efficiency of the sulfamic acid supported functionalized mesoporous SBA-15/NHSO$_3$H as a fast and waste-free approach to the synthesis of polyhydroquinolines and dihydropyridines under solvent-free conditions (Figure 1).

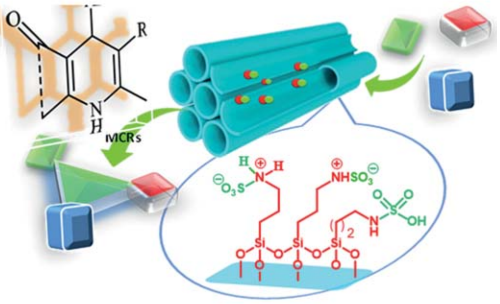
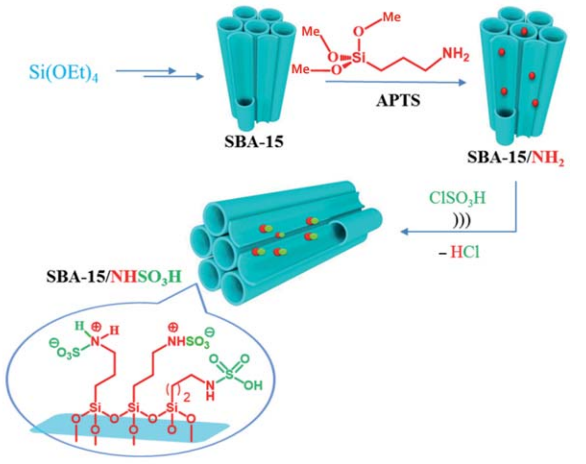


Figure 1 SBA-15/NHSO$_3$H promoted synthesis of polyhydroquinolines and dihydropyridines

The synthesis of SBA-15/NHSO$_3$H was achieved in three steps, with the first step having been described by Zhao et al. and our previous report.[7,8] The second step involved amine functionalization of the SBA-15 and third sulfonylation of the SBA-15/NH$_2$ (SBA-15/Pr-NH$_2$) to SBA-15/NHSO$_3$H (SBA-15/Pr-NHSO$_3$H) using chlorosulfonic acid based on a procedure from Zolfigol[9] (Scheme 1).

Calcined SBA-15 (1 g) reacted with a 0.01 M solution of (3-aminopropyl)triethoxysilane in dry toluene under reflux conditions for ten hours. The product was filtered, dried under vacuum, and then reacted with chlorosulfonic acid (3 mL). CHN analysis showed 0.62% nitrogen, which is equivalent to 0.45% SO$_3$H groups. Furthermore, pH analysis for SO$_3$H loading confirmed ca. 0.45% SO$_3$H (Figure 2).

SYNLETT 2014, 25, 2753–2756
Advanced online publication: 21.10.2014
DOI: 10.1055/s-0034-1379477; Art ID: st-2014-d0724-l



Scheme 1 Schematic representation of prepared SBA-15/$NHSO_3H$

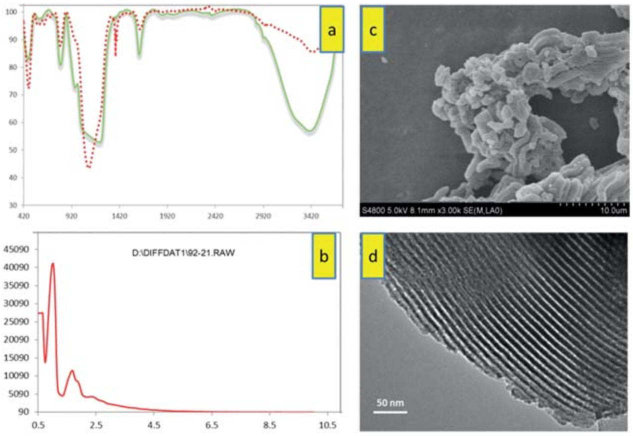


Figure 2 (a) FT-IR spectroscopic pattern; (b) XRD pattern [(–) freshly prepared; (…) used six times for **4a**], (c) SEM image of SBA-15/$NHSO_3H$; (d) TEM image of SBA-15/$NHSO_3H$.

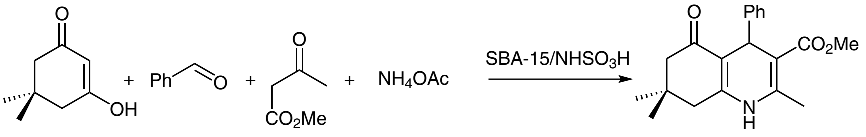
For our initial studies, dimedone, benzaldehyde, NH_4OAc, and methyl acetylacetonate were chosen as substrates for the model reaction to obtain the polyhydroquinolines (Table 1).[10] As shown in Table 1, the use of 5 mol% SBA-15/$NHSO_3H$ catalyst under solvent-free conditions led to the desired product after three hours in 93% yield (Table 1, entry 9).

To demonstrate the diversity of this methodology and to determine the scope of the process, the optimized conditions (Table 1, entry 9) were applied to prepare a series of polyhydroquinolines **4**, and the results are summarized in Table 2.

The catalytic activity of the heterogeneous sulfamic acid in the synthesis of dihydropyridines **5** by the condensation of aldehydes, β-dicarbonyl compounds, and ammonium acetate was next studied (Table 3).

The possibility of recycling the SBA-15/$NHSO_3H$ was also studied under optimum conditions. We therefore devised a set of experiments to recover and reutilize the sul-

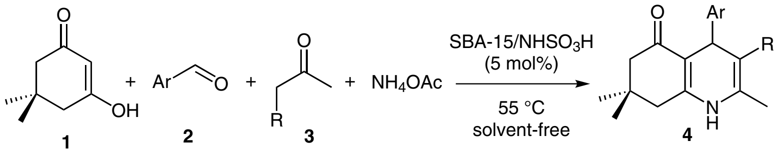
Table 1 Different Conditions in the Four-Component Synthesis of Polyhydroquinoline **4a**



Entry	Catalyst (mol%)	Solvent[a]	Time (h)	Temp (°C)	Yield (%)[b]
1	10	DMF	5	70	66
2	10	$CHCl_3$	5	70	58
3	10	EtOH	5	60	74
4	10	*n*-hexane	5	60	49
5	10	MeOH	5	60	72
6	2	solvent-free[c]	5	60	88
7	5	solvent-free[c]	5	60	95
8	8	solvent-free[c]	5	60	94
9	5	solvent-free[c]	3	55	93
10	5	solvent-free[c]	2	55	89
11	5	solvent-free[c]	2	70	91
12	–	EtOH	4	60	13

[a] Solvents (3 mL).
[b] Isolated yield.
[c] Solvent-free conditions.

Table 2 SBA-15-Supported Sulfamic Acid for Synthesis of High-Functionalized Polyhydroquinolines **4**

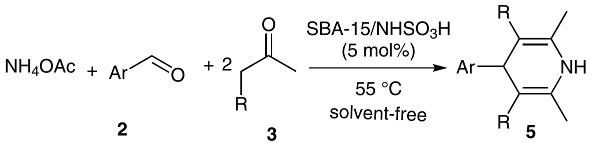


Entry	4	Ar	R	Time (h)	Yield of **4** (%)
1	**4a**	Ph	CO_2Me	3	93
2	**4b**	$2\text{-}ClC_6H_4$	CO_2Me	3	94
3	**4c**	$2\text{-}MeC_6H_4$	CO_2Me	4	90
4	**4d**	$4\text{-}ClC_6H_4$	CO_2Me	3	95
5	**4e**	$4\text{-}MeOC_6H_4$	CO_2Me	5	87
6	**4f**	$2\text{-}MeC_6H_4$	CO_2Et	5	89
7	**4g**	$2\text{-}ClC_6H_4$	CO_2Et	3	88
8	**4h**	$4\text{-}ClC_6H_4$	CO_2Et	3	94
9	**4i**	$4\text{-}O_2NC_6H_4$	CO_2Et	2.5	95
10	**4j**	$4\text{-}MeOC_6H_4$	CO_2Et	4	90

famic acid catalyst in the synthesis of methyl 2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydro-3-quinolinecarboxylate (**4a**) as a model polyhydroquinoline. It can be seen that the supported catalyst was highly recyclable under the optimized conditions, preserving almost unaltered its initial catalytic activity after six uses (Figure 3).

In summary, covalent functionalization of sulfamic acid onto mesoporous SBA-15 gives an inexpensive heterogeneous, green, and reusable catalyst for the synthesis of polyhydroquinolines and dihydropyridines by multicomponent reactions under solvent-free conditions.

Table 3 Solvent-Free Synthesis of DHPs Using SBA-15/$NHSO_3H$ Catalyst



Entry	5	Ar	R	Time (h)	Yield of **5** (%)
1	**5a**	Ph	CO_2Et	3	90
2	**5b**	$3\text{-}MeOC_6H_4$	CO_2Me	3	91
3	**5c**	$4\text{-}O_2NC_6H_4$	CO_2Me	4	92
4	**5d**	$4\text{-}ClC_6H_4$	CO_2Me	3	84
5	**5e**	$2\text{-}ClC_6H_4$	CO_2Et	5	90
6	**5f**	$3\text{-}ClC_6H_4$	CO_2Et	5	89
7	**5g**	$4\text{-}ClC_6H_4$	CO_2Et	3	88
8	**5h**	$4\text{-}O_2NC_6H_4$	CO_2Et	3	94
9	**5i**	Ph	CO_2Me	3	92

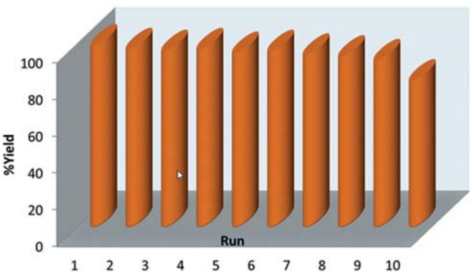


Figure 3 Recyclability study on the synthesis of **4a**

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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(10) **General Procedure for the Synthesis of Polyhydroquinolines and Dihydropyridines**
A mixture of aldehyde (1 mmol), β-dicarbonyl compound (1 or 2 mmol), NH_4OAc (2.5 mmol), dimedone (1 mmol, when used), and SBA-15/$NHSO_3H$ (5 mol%) was stirred at 55 °C. After complete disappearance of starting material as indicated by TLC, the resulting mixture was diluted with hot EtOAc (10 mL) and filtered. The catalyst was completely recovered from the residue.

Representative Spectroscopic Data

Methyl 2,7,7-Trimethyl-5-oxo 4-Phenyl-1,4,5,6,7,8-hexahydro-3-quinolinecarboxylate (4a)
^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.94 (s, 3 H), 1.09 (s, 3 H), 2.11–2.40 (m, 8 H), 3.62 (s, 3 H), 5.08 (s, 1 H), 7.08–7.31 (m, 5 H).

Diethyl 2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (5a)
IR (KBr): 3342, 1700, 1657, 1473, 1198, 1129 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.23 (t, $^3J_{HH}$ = 7.0 Hz, 6 H), 2.34 (s, 6 H), 4.12 (q, $^3J_{HH}$ = 7.0 Hz, 4 H), 4.91 (s, 1 H), 5.68 (s, 1 H), 7.07–7.43 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.91, 19.56, 39.43, 59.82, 103.14, 127.25, 127.32, 128.34, 129.61, 146.19, 148.25, 167.34.