

Design of a Highly Efficient and Water-Tolerant Sulfonic Acid Nanoreactor Based on Tunable Ordered Porous Silica for the von Pechmann Reaction

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ABSTRACT



Among a number of different sulfonic acid nanoreactors prepared, **5** having both acidic sites and phenyl groups located inside the mesochannels of SBA-15 was shown to be the most active and reusable catalyst in the von Pechmann reaction. The mesochannels, and covalently anchored organic groups, provide a synergistic means of an efficient approach of the reactants to acidic sites, enough space for the subsequent cyclization, and suitable hydrophobicity to drive out the water byproduct.

In recent years, organically functionalized ordered mesoporous silicas¹ with a tunable pore structure and tailored composition have received considerable interest for broad applications ranging from adsorbent,² gas separation,³ and catalysis⁴ to biological uses.^{1a,5} These classes of materials are mainly characterized by very large specific surface areas

(up to 2000 m²·g⁻¹), highly ordered pore systems, and well-defined and a tunable pore radius from approximately 2 to 50 nm. Moreover, the surface properties (inside the channels) and, therefore, the chemical functionalities of these materials can be uniformly modified by covalent anchoring of different organic moieties.^{4,1a} In other words, they combine in a single solid both the special chemical reactivity of the organofunctional groups and attractive properties including a mechanically stable structure, high surface area, and large ordered pores with narrow size distribution of an inorganic backbone. Therefore, it would be reasonable to consider these materials as numerous combined nanosize vessels with the same properties, where their size and functions can be pre-

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cisely adjusted through an inorganic organic cooperative mechanism on a molecular level. If such a hypothesis could be realized in practice, it would be possible to design and prepare a variety of sophisticated nanoreactors which possess multiple functional groups (nano reaction media), assembled in the interior of inorganic mesostructures (nano vessels).⁶

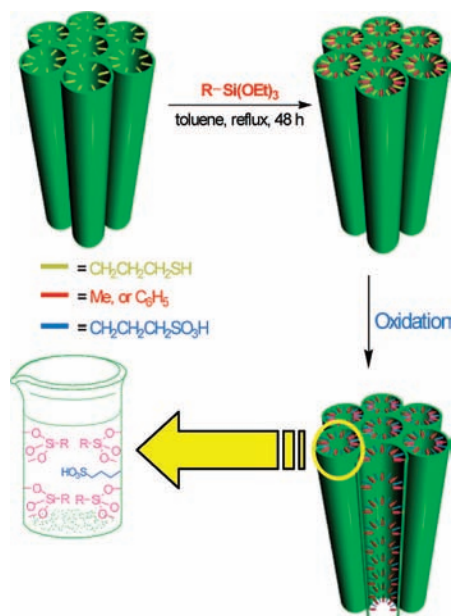


Figure 1. Schematic representation for the preparation of sulfonic acid based nanoreactors **1–5**. **1** = MCM-Pr-SO₃H,^{9d} R = none; **2** = MCM-Me-Pr-SO₃H, R = Me; **3** = MCM-Ph-Pr-SO₃H, R = Ph; **4** = SBA-15-Pr-SO₃H,^{9c} R = none; **5** = SBA-15-Ph-Pr-SO₃H, R = Ph.

Along the line of this hypothesis and in the course of our investigations into the development of new nanostructured catalysts,⁷ herein, we wish to disclose the preparation of five different sizes of modified sulfonic acid nanoreactors, in which the propyl sulfonic acid group and two kinds of organic groups are located inside the channels of both microporous and mesoporous silicas following published procedures with slight modifications.⁸ The preparation strategy for the nanoreactors **1–5** is shown in Figure 1.⁸

Nanoreactors **1–5** were characterized by thermogravimetric analysis (TGA), elemental analysis, surface analysis, transmission electron microscopy (TEM), and ion-exchange

pH analysis. Table 1 illustrates characteristics of the nanoreactors in some detail.⁸

Table 1. Characterization of Sulfonic Acid Based Nanoreactors

nanoreactor	S_{BET}^a	R	pore size ^b	V_p^c	proton capacity ^d
1	453	–	13.0	0.24	1.46
2	458	Me ^e	12.9	0.11	1.17
3	586	Ph ^e	12.9	0.07	1.20
4	430	–	31.5	0.67	1.77
5	356	Ph ^f	27.8	0.58	1.61

^a BET surface area (m²·g⁻¹). ^b BJH pore size (Å). ^c Total pore volume (cm³·g⁻¹). ^d mmol (–SO₃H)·g⁻¹; determined by pH analysis after ion-exchange. ^e Loadings of the methyl and phenyl group in **2** and **3** were 0.70 and 0.33 mmol·g⁻¹, respectively, based on TGA and elemental analysis. ^f Loading of the phenyl group in **5** was 0.37 mmol·g⁻¹, based on TGA and elemental analysis.

While several types of solid sulfonic acids, based on ordered mesoporous silicas, have been created in recent years,⁹ there have been only few reports about their applications as catalysts in chemical transformations. Moreover, to the best of our knowledge there is no report on the use of these materials as nanoreactors in the Pechmann condensation. The Pechmann reaction, a two-component (phenol and β -ketoester) coupling under acid catalysis, is a valuable and simple protocol for coumarin ring synthesis.¹⁰ In the conventional production of coumarins by the Pechmann reaction, concentrated sulfuric acid is used as the catalyst.¹¹ Several other acid catalysts, including Lewis acids, are known to affect this condensation.¹² However, moisture sensitivity of the majority of Lewis acids to the water produced in the Pechmann reaction renders them unsuitable for use in large-scale applications. Other methods may also utilize ionic liquids¹³ and microwave irradiation,¹⁴ but these methods also generated strongly acidic wastes and/or they utilize highly expensive and nonrecyclable reagents. To address the above-mentioned problems, a number of heterogeneous alternatives such as Nafion-H,¹⁵ zeolite H-BETA, Amberlyst 15,¹⁶

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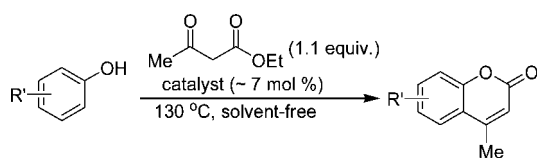
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Montmorillonite clay,¹⁷ and other solid acids¹⁸ have been employed for this purpose in the Pechmann condensation. Although, these methods are suitable for certain synthetic conditions, in many of these methods the yields of products were not always satisfactory and the catalytic activities were lower than homogeneous catalysts in most cases. Therefore, it seems that the major task of current research in chemistry is to replace both homogeneous and less efficient and traditional heterogeneous acid catalysis procedures by environmentally more acceptable protocols based on improved water-tolerant and recoverable catalysts.

The catalytic activity of Brønsted acid nanoreactors **1–5** was then tested in the coupling reaction of resorcinol (1,3-dihydroxyphenol) with ethyl acetoacetate under solvent-free condition (Table 2).¹⁹

Table 2. Pechmann Reaction of Different Substituted Phenols with Ethyl Acetoacetate Employing Nanoreactors **1–5** as Catalysts



entry	nanoreactor/catalyst	R'	time min/[h] ^c	yield ^{a,b} [%]
1	1	3-OH	60	30
2	2	3-OH	60	32
3	3	3-OH	60	30
4	4	3-OH	60	50
5	5	3-OH	60	90
6	<i>p</i> -TsOH	3-OH	60	65
7	H ₂ SO ₄	3-OH	60	60
9	SBA-15 ^c	3-OH	60	NR
10	silica gel ^c	3-OH	60	NR
11	5	2,3-(OH) ₂	25	95
12	5	3,5-(OH) ₂	10	94
13	5	2-Me-3-OH	25	92
14	5	3-Me-5-OH	25	90
15	5	3-Me	[7]	80
16	5	3-MeO	[5]	83
17	5	3,5-(Me) ₂	[10]	75
18	5	3-NH ₂	90	75
19	5	1-naphthol	[4]	65
20	5	4-OH	90	78

^a Isolated yields of pure products. ^b Conditions were as follows: phenol (10 mmol), ethyl acetoacetate (11 mmol), catalyst (~7 mol % equiv to acidic proton) at 130 °C. ^c 430 mg of SBA-15 or silica was used.

For the purpose of comparison, Table 2 also summarizes the catalytic activity of both *para*-toluenesulfonic acid (*p*-TsOH) and H₂SO₄ under the same reaction conditions (entries 6 and 7). As shown in Table 2, a low isolated yield of ≈ 30% for the corresponding coumarin was obtained when the microporous nanoreactors **1**, with an average pore size of 13 Å, were used, probably because of the fact that the catalytic activity must be related to the –SO₃H sites present within the less accessible micropores where the cyclization

reaction can be very difficult to accomplish and hindered (Table 2, entry 1). Similar results were also obtained with hydrophobic nanoreactors **2** and **3** (average pore size 12.9 Å), confirming that owing to the size restriction of nanoreactors the surface hydrophobization does not significantly improve the catalytic activity for the described reaction (Table 2, entries 2 and 3). On the other hand, we found that when nanoreactor **4**, with a mesoporous structure (pore diameter ≈ 31.5 Å), was employed instead, the yield of ~50% was obtained (Table 2, entry 4). This observation might be explained by the fact that the large mesochannels of SBA-15 in **4** can provide enough space to accommodate the starting materials with the aid of grafted sulfonic acid and still enough space to promote the cyclization (the Pechmann) reaction. Although this catalytic activity is better than the nanoreactors **1–3** having a smaller pore opening, it is still not satisfactory. We reasoned that under the neat condition the high affinity of the silica framework of SBA-15 in **4** for the water byproduct probably allowed a gradual desorption of the starting materials from the catalyst surface thus retarding the progress of the reaction. To circumvent this problem, we then prepared mesoporous nanoreactor **5** in which both sulfonic acid and the phenyl group are covalently assembled inside the mesochannels of SBA-15. A BET surface area of 356 m²·g⁻¹, a total pore volume of 0.58 cm³·g⁻¹, and a BJH pore diameter of 27.8 Å were measured for the material. These values are clearly smaller than those measured for **4** (Table 1), thus supporting the nanoreactor model proposed in Figure 1. To our delight, mesoporous nanoreactor **5** appeared to be much more reactive than both heterogeneous nanoreactors **1–4** and homogeneous catalysts (*p*-TsOH, H₂SO₄), affording 90% isolated yields of the desired coumarin (Table 2, entry 5 vs 1–4 and 6, 7). It was also detected that either mesoporous silica SBA-15 or amorphous silica showed almost no activity under the same reaction conditions (Table 2, entries 9 and 10).

The scope of this method was then further studied by conducting it from different substituted phenols using **5** as a nanoreactor. As summarized in Table 2, a catalytic amount of **5** (≈7 mol %) efficiently promotes the Pechmann reaction of a wide range of phenols under solvent-free conditions. Good to excellent yields of the corresponding coumarins were obtained regardless of structural variations in the phenols. It is also interesting to note that in the case of 3-aminophenol the reaction was completely chemoselective for the formation of a coumarin ring, a feature not observed with the previous heterogeneous and homogeneous systems (Table 2, entry 18).^{12a,b}

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The most important issue that should be considered for practical applications of heterogeneous systems is the lifetime of the catalyst and its degree of reusability. To resolve this issue, we designed a set of experiments by conducting successive condensation of resorcinol with ethyl acetoacetate (30 mmol scale) using nanoreactor **5** (7 mol % equiv to $-\text{SO}_3\text{H}$ capacity). After the completion of the first run to afford the corresponding coumarin in 90% yield (after purification), the catalyst was thoroughly washed with EtOH and ethyl ether and finally dried at 100 °C for 3 h. A new reaction was then accomplished with fresh reactants under the same reaction conditions. Gratifyingly, the recovered nanoreactor **5** was successfully used in six successive runs and exhibited consistent activity to afford an average yield of 87% (180 mmol total scale) with virtually no significant loss of performance. It is very important to note that for the reactions in which water participates as a reactant and product, only a few solid acids show acceptable performance and stability.²⁰ High stability of nanoreactor **5** was further assessed using transmission electron microscopy after the sixth reaction cycle and showed that the 2D-hexagonal structure of the catalyst remained intact during the catalysis and recycling process, while some pore enlargement has occurred (Figure 2).

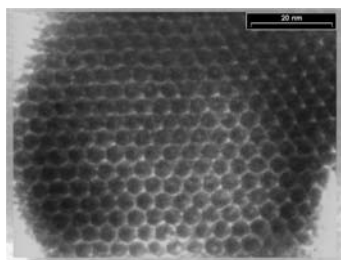


Figure 2. TEM image of nanoreactor **5** perpendicular to the mesochannels after the sixth reaction cycle. Scale bar: 20 nm.

To show whether the reaction is actually proceeding in a heterogeneous pathway inside the nanospace of the catalyst or whether it is conducting through a homogeneous manner, two parallel tests were performed, in which the reactions of resorcinol with ethyl acetoacetate in the presence of nanoreactor **5** were quenched (by dilution with CH_2Cl_2) after

(19) The experimental details for the preparation of nanoreactors **1–5** and their characterization are collected in the Supporting Information. General procedure for the Pechmann condensation using **5**: To the mixture of the phenolic compound (10 mmol) and ethyl acetoacetate (11 mmol) was added catalyst **1** (430 mg; ~ 7 mol %, $-\text{SO}_3\text{H}$ group) at 130 °C with constant stirring at the desired time as indicated in Table 2. The reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was diluted with ethanol and filtrated to obtain the crude product. The crude product was purified by column chromatography on silica gel (hexane:ethyl acetate; 10:1 to 4:1) and then recrystallized from hot ethanol to afford the pure coumarin derivatives in good to excellent yields (Table 2).

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15 min and filtered off ($\sim 51\%$ conversion). In the first experiment, CH_2Cl_2 was evaporated, and the residue was then subjected to further heating under solvent-free conditions at 130 °C. We found that no further catalytic activity was observed upon heating for 2 h, thus supporting the heterogeneous nature of the reaction. In the second experiment, the filtrate was evaporated and then treated with microporous nanoreactor **2** (≈ 7 mol %) for 2 h at 130 °C.

Interestingly, we found that although some conversion is still achieved in this case ($\approx 15\%$ additional conversion after 2 h), the reaction rate decreased significantly due to the poorer accessibility of the catalytic sites in **2**. It is also worth mentioning that this reaction was not completed even after prolonged (4 h) heating at 130 °C, thus further confirming that both **2** and **5** are active nonreactors through the proposed model in Figure 1.

In conclusion, we showed that among different kinds of sulfonic acid based nanoreactors with different pore size and organic groups nanoreactor **5**, in which both acidic sites and phenyl groups are located inside the mesochannels of SBA-15, is the most active catalyst in the Pechmann reaction. The catalyst is even more reactive than the homogeneous strong acids such as *p*-TsOH and H_2SO_4 under the same reaction conditions. We also demonstrated that uniformly distributed mesochannels and covalently anchored organic groups might indeed provide a synergistic means of the efficient approach of the starting materials to acidic sites, enough space for the subsequent cyclization, and suitable hydrophobicity to drive out the water which is formed during the reaction from mesochannels.²¹ This approach also opens a pathway to design and prepare a variety of sophisticated nanoreactors composed of different types of organic mediators (nanosolvents), active sites (nanocatalyst with different properties), and tunable inorganic nanostructures (nanovessels) for chemical transformations.

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Supporting Information Available: Experimental procedure and characterization data (TEM, TGA, BET, BJH, and N_2 adsorption–desorption isotherm) for nanoreactors **1–5**, general procedure for the Pechmann condensation using nanoreactor **5**, and copies of IR, ^1H , and ^{13}C spectra for all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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