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New heterogeneous catalysts for greener routes in the synthesis of fine chemicals

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Abstract

New strong Lewis acid SnTf-MCM-41 and SnTf-UVM-7 catalysts with unimodal and bimodal pore systems were prepared in a two-step synthesis in which the triflic acid (Tf) was incorporated to previously synthesized mesoporous tin-containing silicas. The Sn incorporation inside the pore walls was carried out through the Atrane method. The SnTf-UVM-7 catalysts were prepared by aggregating nanometric mesoporous particles defining a hierarchic textural-type additional pore system. Following these procedures, catalysts with different Si/Sn ratios—21.8 to 50.8 for SnTf-MCM-41 and 18.4 for SnTf-UVM-7—were prepared. These new materials were tested in the acylation of aromatic sulfonamides using acetic acid as the acylating agent and in the synthesis of (*dl*)-[α]-tocopherol through the condensation of 2,3,6-trimethylhydroquinone (TMHQ) with isophytol (IP). The activity data indicate that these heterogeneous catalysts are very active, corresponding to high yields in acylated compounds as 65.5% and very high selectivity to (*dl*)-[α]-tocopherol (94%, for a conversion of 98%).

Keywords: Heterogeneous catalysis; Mesoporous structures; Tin triflate; Acylated sulfonamides; (*dl*)-[α]-Tocopherol

1. Introduction

Today, there are significant demands by the pharmaceutical industry for new and efficient catalysts. Moreover, together with traditional criteria, such as good activity and selectivity, these new catalysts must include additional requisites, such as low cost and environmental friendliness. Whereas the cost of the process (including catalysts) is not a determinant constraint for specific high-added-value drugs, produced at low scale, it constitutes a first-order parameter when considering generic drugs for diseases affecting a broad population sector or a parapharmaceutical product, such as food complement and/or ingredient or a cosmetic, due to the high production costs involved.

Some newly developed drugs, including therapeutic agents for Alzheimer's disease [1], inhibitors of tRNA synthetases as antibacterial agents [2], and prostaglandin $F_{1\alpha}$ sulfonamides for the potential treatment of osteoporosis, incorporate the *N*-acyl sulfonamide moiety [3]. *N*-acyl sulfonamide synthesis usually starts with the coupling of the parent sulfonamides with acid chlorides or carboxylic anhydrides using trialkylamines, pyridine [2–5], or alkali hydroxides [6–8]. Unfortunately, with no exception, all of these methods lead to substantial waste products; for example, acid chlorides generate hydrochloric acid as byproduct, whereas the carboxylic anhydrides use only 50% of the molecule, achieving low atom economy. Less common reports mentioning this transformation under acidic conditions (Brönsted or Lewis acids) have not systematically examining the purpose and limitations of the reaction [9].

The use of carboxylic acids as acylating agents on alcohol or aromatics is rare [10–15] and usually associated with the presence of hypernucleophilic species (DCC, EDC, or 4-DMAP) (see Aldrich Chemical Company Technical Bulletin AL114). Otherwise, in the case of sulfonamide acylation, besides the above-described synthesis methodologies, routes using carbox-

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ylic acids as a source of carbocation in direct-coupling homogeneous and heterogeneous catalytic processes have been described [16–19]. These latter approximations, which have in common the presence of nucleophilic activators, overcome the undesirable wastes (because water is the main byproduct), and the entire carboxylate amount is reactive.

On the other hand, the synthesis of (*dl*)-[α]-tocopherol is of great importance for the pharmaceutical industry and also in the area of functional foods. In classical synthesis, this is done through the acid-catalyzed condensation of 2,3,6-trimethylhydroquinone (TMHQ) with isophytol (IP) using both Brønsted and Lewis acid catalysts. Corrosion caused by the acidic media, contamination of the wastewater with acids and zinc ions, and the difficult purification of (*dl*)-[α]-tocopherol by distillation under high vacuum at 200 °C are the main problems hindering industrial-scale synthesis [20]. Recently, data concerning the use of heterogeneous catalysts, the main merits of which are the simple separation of the solid catalyst from the reaction mass, the absence of washwater containing the dead catalyst, and a high purity of α-tocopherol, were published [21–23]. Unfortunately, high reaction temperatures and long reaction times are required, leading in many cases to diminished yields as a result of byproduct formation. Recently, some metal derivatives of triflic acid have been suggested as a cleaner alternative to using metal chlorides as Lewis acid and versatile catalysts in organic synthesis [24–26], avoiding such environmental problems as large amounts of waste mineral acids and zinc or aluminum residues, as well as the use of harmful organic solvents in industrial-scale processes.

Keeping this background in mind, and with the aim of designing a greener approach to the above set of reactions, we have prepared new surfactant-assisted mesoporous heterogeneous Sn triflate–silica catalysts. These new family of catalysts combine the high hydrophilic surface and accessible pore system typical of mesoporous silicas with the presence of well-dispersed and anchored tin triflate species able to act as strong acid Lewis catalytic sites. The system architecture has been built up, taking into account the described activity of metal triflate complexes and the compatibility of Sn(IV) and Si(IV) centers in silica networks. Thus we anticipate that our materials will combine the strong Lewis acidity of anchored tin triflate with the water-sink capability of the hydrophilic silica network, becoming efficient coupling-dehydrating agents or active Friedel–Crafts solid catalysts.

Here we report that these new materials are effectively able to facilitate the green acylation of aromatic sulfonamides using acetic acid as an acylating agent. These catalysts are also highly active in the synthesis of (*dl*)-[α]-tocopherol through the condensation of 2,3,6-trimethylhydroquinone (TMHQ) with isophytol (IP).

2. Experimental

2.1. Catalyst preparation

All of the synthesis reagents (tetraethyl orthosilicate [TEOS], triethanolamine [$N(CH_2–CH_2–OH)_3$, hereinafter TEAH3], hexadecyltrimethylammonium bromide [CTABr], $SnCl_2$, triflic acid, NaOH, HCl, and ethanol) were analytically pure and were used as received from Aldrich. The unimodal (SnTf-MCM-41) and bimodal (SnTf-UVM-7) porous catalysts were prepared in a two-step synthesis in which the triflic acid was incorporated into previously synthesized mesoporous tin-containing silicas. The Sn incorporation inside the pore walls was carried out using the Atrane method [27], which enables preparation of a unimodal or bimodal porous mixed oxide working under strong (pH 11 to 12) or moderate (pH 8 to 9) basic conditions, respectively. The resulting tin-doped silicas are designated Sn-MCM-41 and Sn-UVM-7, respectively.

2.1.1. Synthesis of Sn-MCM-41

In a typical synthesis, the molar ratio of the reagents in the mother liquor was adjusted to $2 - x$ Si:x Sn:7 TEAH3:0.5 NaOH:0.52 CTABr:180 H_2O. For example, the Si/Sn = 37 mesoporous material ($x = 0.05$) (working pH = 11) was obtained as follows: 0.5 g (0.0125 mol) of NaOH was dissolved at 60 °C in 23 mL (0.172 mol) of TEAH3, and after a few minutes, 10.7 mL (0.0478 mol) of TEOS and 0.36 g (0.0016 mol) of $SnCl_2$ were added while stirring, and the mixture was heated at 130 °C for 5 min. The resulting solution was cooled to 110 °C, and 4.68 g (0.0128 mol) of CTABr was added under stirring. Then 80 mL (4.44 mol) of water was added under vigorous stirring at a mixing temperature of 60 °C; shortly, a white suspension appeared. This mixture was aged at room temperature for 24 h. The resulting mesostructured powder was filtered off, washed with water and ethanol, and air-dried. Finally, to open the mesopore system, the surfactant was extracted from the as-synthesized solid using an acetic acid/ethanol solution ($CTMA^+/H^+$ exchange). Here ca. 1 g of mesostructured powder was suspended in a solution containing 8 mL of CH_3COOH (80%) and 120 mL of ethanol (99%), and this mixture was heated at reflux (60 °C) for 2 h under stirring. Later, after renewing the CH_3COOH/ethanol solution, and to complete the extraction process, the suspension was reheated at 60 °C for 16 h under stirring. The resulting (mesoporous) powder was collected by filtration, washed with ethanol, and air-dried.

2.1.2. Synthesis of Sn-UVM-7

This mesophase was prepared almost exactly as for Sn-MCM-41, starting from silatrane and stannatrane complexes and working in a TEAH3-rich medium (i.e., using the Atrane route) and in the absence of NaOH (with an apparent working pH of ca. 9.3). Thus the molar ratio of the reagents in the mother liquor was adjusted to $2 - x$ Si:x Sn:7 TEAH3:0.52 CTABr:180 H_2O ($x = 0.1$). In a typical synthesis to obtain the Si/Sn = 26 bimodal porous material, a mixture of TEOS (10.5 mL; 0.047 mol), $SnCl_2$ (0.56 g, 0.0024 mol), and TEAH3 (23 mL, 0.172 mol) was heated at 150 °C for 10 min to prepare Atrane complexes. The resulting solution was cooled to 110 °C, and 4.68 g of CTABr (0.0128 mol) was added. Then 80 mL of water was slowly added under vigorous stirring at 80 °C. After a few minutes, the resulting suspension was aged at room temperature for 4 h. The resulting mesostructured solid was then separated by centrifugation, washed with water and ethanol,