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SHORT COMMUNICATION

A suitable preparation of *N*-sulfonyl-1,2,3,4-tetrahydroisoquinolines and their ring homologs with a reusable Preyssler heteropolyacid as catalyst

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Abstract The preparation of *N*-sulfonyl-1,2,3,4-tetrahydroisoquinolines, *N*-sulfonyl-2,3,4,5-tetrahydro-1*H*-2-benzazepines and *N*-sulfonyl-1,2,3,4,5,6-hexahydrobenzazocine was catalyzed by a Preyssler heteropolyacid, $H_{14}[NaP_5W_{30}O_{110}]$, (PA), supported on silica ($PASiO_2$40) with excellent yields by means of the Pictet–Spengler reaction of *N*-aralkylsulfonamides with *s*-trioxane. The reactions proceed with 0.5 mol% of silica-supported catalyst in toluene at 70 °C. The catalyst can be recycled without appreciable loss of the catalytic activity.

Keywords Heterogeneous catalysis · Preyssler heteropolyacid · Pictet–Spengler reaction · *N*-sulfonyl-1,2,3,4-tetrahydroisoquinoliness · *N*-sulfonyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine · *N*-sulfonyl-1,2,3,4,5,6-hexahydrobenzazocine

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Introduction

Heterocycles are important compounds in organic chemistry. Most heterocycles have wide applications in medicine and in the fine-chemicals industry. Due to their wide range of biological activity, the suitable synthesis of these compounds has recently received a great deal of attention for the development of improved protocols toward clean, milder, and high-yielding approaches.

The Pictet–Spengler reaction is one the key reactions for the construction of the isoquinoline skeleton and indole alkaloids, which constitute an important class of naturally occurring bioactive substances. It was developed in 1911 by Pictet and Spengler, who used an acid-catalyzed cyclization of the intermediate imine formed by condensation of arylethylamine with a carbonyl compound [1]. Then, the reaction was modified to accept other β-phenethylamines such as *N*-alkyl, *N*-acyl, and *N*-sulfonyl derivatives, proceeding via iminium, *N*-alkyliminium, *N*-acyliminium, or *N*-sulfonyliminium ion formation, respectively, and subsequent intramolecular electrophilic substitution [2]. An acyl or sulfonyl substituent at the nitrogen atom increases the reactivity of the electrophilic partner.

1,2,3,4-tetrahydroisoquinolines and their derivatives are a common core structure of many alkaloids isolated from natural sources and show antitumoral, antimicrobial, anti-HIV, and other biological activities [3–7]. In particular, *N*-sulfonyl-1,2,3,4-tetrahydroisoquinolines and *N*-sulfonyl-2,3,4,5-tetrahydro-1-*H*-2-benzazepines are important synthetic intermediates in the preparation of 1,2,3,4-tetrahydroisoquinolines and 2,3,4,5-tetrahydro-1-*H*-2-benzazepines, respectively, as well as exist as substructures of various biologically active compounds [8]. The classical method to synthesize these compounds involves a sulfonylaminomethylation of

N-arylalkylsulfonamides [9–11] using various agents, for example, *s*-trioxane in acid medium [12].

On the other hand, the environmental problems, mainly associated with the handling and disposal of the inorganic acid, and their potential hazards have attracted the chemists' attention to the development of alternative processes using novel catalysts. There are numerous acid-catalyzed organic reactions, and the use of solid acid catalysts is very important in several industrial and environmental processes [13]. The use of solid (heterogeneous) catalysts in organic synthesis and in the industrial manufacture of chemicals is increasingly important since they provide green alternatives to homogeneous catalysts [14]. In recent times, the use of inorganic solids as catalysts in organic transformations is gaining much importance due to the proven advantage of heterogeneous catalysts, such as simplified product isolation, mild reaction conditions, high selectivity, easy recovery and catalyst reuse, and reduction in the generation of waste by-products [15–17].

Catalysis by heteropolyacids (HPAs) and related compounds is a field of increasing importance worldwide. Numerous developments are being carried out in basic research as well as in fine chemistry processes [17]. HPAs possess, on the one hand, a very strong acidity, and on the other hand, appropriate redox properties, which can be changed by varying the chemical composition of the heteropolyanion. Many researchers [18–22] have reviewed the reactions catalyzed by both heterogeneous and homogeneous systems. Although there are many structural types of HPAs, the majority of the catalytic applications use the most common Keggin-type HPAs [23], especially for acid catalysts, owing to their availability and chemical stability. Other catalysts such as Wells–Dawson and Preyssler heteropolyacids have begun to be used [24]. The Preyssler polyanion consists of a cyclic assembly of five PW_6O_{22} units, each derived from the Keggin anion, $[PW_{12}O_{40}]^{3-}$, by the removal of two sets of three corner-shared WO_6 octahedra [25]. The Heravi group has researched the efficiency of Preyssler heteropolyacids as a green and recyclable catalyst. The catalyst is more active and selective than the Wells–Dawson and Keggin heteropolyacids. Some advantages described by this author are high pH stability (0–12), high thermal stability, and a large number of acidic protons [26]. Preyssler catalyst molecule has a hole of 6.6 Å in diameter, in that 14 acidic protons are attached. Acid strength (butylamine valoration) of the Preyssler catalyst protons covers the range of 46.4–862.1 mV. Bulky substrate molecules or substructures could easily reach the acid sites. An important number of organic transformations using the Preyssler tungsten heteropolyacid catalyst $H_{14}[NaP_5W_{30}O_{110}]$ as well as coumarins [27], 2-amino-4-*H*-chromenes [28], and benzodiazepines [29] have been reported.

As part of a project in the field of Green Chemistry that is being executed in Argentina, we have recently applied a Keggin and Wells Dawson heteropolyacid for synthesizing coumarins, by the Von Pechmann reaction [30], flavones and chromones [31].

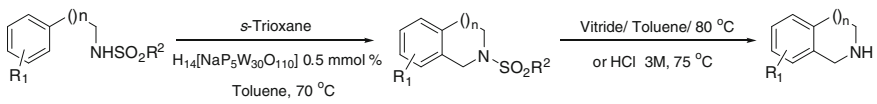
In this article, we describe a new and suitable procedure for preparing *N*-sulfonyl-1,2,3,4-tetrahydroisoquinolines, *N*-sulfonyl-2,3,4,5-tetrahydro-1*H*-2-benzazepines, and *N*-sulfonyl-1,2,3,4,5,6-hexahydrobenzazocine using $H_{14}[NaP_5W_{30}O_{110}]$ as heterogeneous catalyst. The intramolecular sulfonamidomethylation of the corresponding *N*-aralkylsulfonamides with formaldehyde formed from *s*-trioxane was carried out in toluene at 70 °C. The corresponding final desulfonylation of a number of selected compounds **II** was carried out using sodium *bis*(2-methoxyethoxy) aluminum hydride (Vitride®) in toluene at 80 °C, or HCl 3M hydrolysis at 75 °C, according to a reported procedure [12] to obtain 1,2,3,4-tetrahydroisoquinolines (Scheme 1).

The overall process defined as an intramolecular sulfonamidomethylation reaction was initially studied using substrate **Ia** (compounds: Table 1, Entry 1). Different reaction conditions were checked, such as reaction temperature, catalyst/reagent molar ratio, and reaction time. The best result was obtained using toluene as solvent at 70 °C, and a catalyst/reagent molar ratio of 0.005. Under these conditions, product **IIa** (product: Table 1, Entry 1) was obtained with high selectivity and free of by-products in 60 min (Table 1, Entry 1a). For $PASiO_2$40 **Ia** and a molar ratio 0.005, the yields of product **IIa** raised from 25% to 82% in 15–60 min at 70 °C (Table 1, Entries 1b and 1a). However, the yield was similar when the reaction time increased to 180 min (Table 1, Entries 1a and 1d). When the catalyst/**Ia** molar ratio was increased to 0.03, the observed yield of **IIa** was comparable to the results obtained with a molar ratio of 0.005 (Table 1, Entries 1c and 1a). When the reaction temperature was lowered to 50 °C, the yields decreased to 30% (Table 1, Entry 1e). No reaction was detected at room temperature. In the blank experiments conducted without Preyssler acid[1] and under the same conditions, no product was detected when substrate **Ia** dissolved in toluene was warmed at 70 °C for 2 h.

Using the optimized conditions—a molar ratio of substrate/catalyst of 0.005, 70 °C, toluene as solvent, and 60 min reaction time—several *N*-sulfonyl aryl alkylamines were tested. The catalytic activity of the $PASiO_2$40 acid was tested in the preparation of *N*-sulfonyl-1,2,3,4-tetrahydroisoquinolines, *N*-sulfonyl-2,3,4,5-tetrahydro-1*H*-2-benzazepines, and a *N*-sulfonyl-1,2,3,4,5,6-hexahydrobenzazocine. The use of just 0.5 mmol% of HPA is enough to push

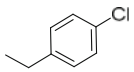
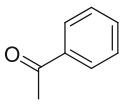
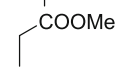
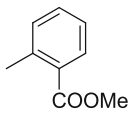
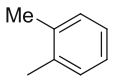
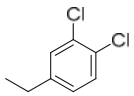
[1] The Preyssler acid $H_{14}[NaP_5W_{30}O_{110}]$, PA, was prepared by a literature method [32]. Silica-supported Preyssler acid was prepared by wet impregnation of Grace Davison silica (Grade 59, specific area = 250 m^2/g) with an acetone solution of the synthesized PA. A catalyst containing 40 wt% of PA was prepared. After impregnation, the samples were dried at room temperature in a vacuum desiccator for 8 h.

Scheme 1



I **II** **III**

Table 1 Preparation of *N*-sulfonyl-1,2,3,4-tetrahydroisoquinolines, *N*-sulfonyl-2,3,4,5-tetrahydro-1*H*-2-benzazepines and *N*-sulfonyl-1,2,3,4,5,6-hexahydrobenzazocine catalyzed by Preyssler catalyst[a]

Entry	Substrates I				Products II	Yields III (%)
	n	R^1	R^2		R^3	
1	1	**H**			**H**	**1a** 82 (79, 78)[b] **1b** 25[c] **1c** 83[d] **1d** 85[e] **1e** 30[f]
2	1	**H**			**H**	77
3	1	**3-Cl**			**H**	65
4	1	**H**			**H**	60
5	1	**H**			**H**	90
6	1	**H**			**H**	92
7	1	**4-CH_3O**			**H**	60
8	1	**3,4-(O CH_3)$_2$**			**H**	78
9	2	**H**			**H**	81
10	2	**H**			**CH_3**	91
11	3	**H**			**H**	76
12	4	**H**			**H**	-

[a] Reactions were performed at 70 °C in toluene, using 0.5 mmol% of Preyssler acid supported on silica, reaction time 60 min, substrate/*s*-trioxane molar ratio 1:3
[b] Yields in parentheses correspond to the first and second reutilization of the catalyst
[c] Reaction time 15 min
[d] Molar ratio 0.03
[e] Reaction time 180 min
[f] Reaction temperature 50 °C

the reaction forward; higher amounts of the catalyst did not improve the results. The experiments were run until the substrate was consumed or until no changes in the composition of the reaction mixture were observed by TLC. In all the cases, the desired products were obtained with high selectivity, and almost free of secondary products. Product **IIe** with $n = 4$, bearing a nine-membered ring was not formed (Table 1, Entry 12). In this case, the unchanged starting materials were recovered nearly quantitatively.[2]

[2] General procedure to prepare *N*-sulfonyl-1,2,3,4-tetrahydroisoquinolines, *N*-sulfonyl-2,3,4,5-tetrahydro-1*H*-2-benzazepines, and *N*-sulfonyl-1,2,3,4,5,6-hexahydrobenzazocine **II:** to a mixture of

The use of the supported catalysts allows an easy separation and recovery of the catalyst for its immediate reutilization. It is noteworthy to mention that the catalyst is recyclable and could be reused without significant loss of activity. It could be recovered by filtration by washing with toluene and drying. The recycled catalyst could be subjected to a second or even a third reaction. In the model reaction, the results of the first experiment and the subsequent ones were almost consistent in yield after three runs (82%, 79%, 78%; Table 1, Entry 1a).

The removal of the *N*-sulfonyl group from compounds **II** to give the fused heterocycles **III** was performed by reducing it with sodium *bis*(2-methoxyethoxy) aluminum hydride (Vitride°) reported previously by one of us [12].

The method described above provides a clean, simple, and useful alternative to prepare *N*-sulfonyl-1,2,3,4-tetrahydroisoquinolines and their ring analogs. The use of silica-supported Preyssler catalysts provides very good yields, also leading to an easy separation and recovery of the catalysts for further use. The catalytic activity, which is practically constant in consecutive reaction batches, and the high recovery of the catalysts allow for both low environmental impact and low cost. Other "green" advantages of the method are the low formation of wastes and the replacement of corrosive, soluble mineral acids.[3]

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Footnote 2 continued

N-aralkylsulfonamide (1 mmol) and *s*-trioxane (3 mmol) in toluene (2 mL), $H_{14}[NaP_5W_{30}O_{110}]$ (0.5 mmol%) (bulk or supported on silica) was added and stirred at 70 °C for 60 min. The solvent was evaporated, and then 10 mL of dichloromethane was added. The catalyst was filtered and washed with more dichloromethane (2 × 3 mL). The solution was dried over anhydrous Na_2SO_4. Filtration and concentration followed by recrystallization in acetone or ethyl acetate afforded the corresponding pure products. Spectra data of purified compounds are consistent with literature data [8].

[3] *N*−(4-chlorobenzylsulfonyl)-1,2,3,4-tetrahydroisoquinoline **IIa** ^{1}H-NMR ($CDCl_3$): δ = 2.8 (t, 2H, J = 5.9 Hz), 3.42 (t, 2H, J = 6.0 Hz), 4.21 (s, 2H), 4.35 (br, s, 2H), 6.97 (br d, 1H, J = 8.7 Hz), 7.10 (br d, 1H, J = 8.7 Hz), 7.17 (ov, m, 1H), 7.19 (ov, m, 1H), 7.28 (br, s, 4H); ^{13}C-NMR ($CDCl_3$): δ = 29.0, 43.7, 47.3, 56.7, 126.1, 126.5, 127.0, 127.4, 129.0, 131.9, 132.0, 133.3, 134.9; MS (EI, 70 eV): *m*/*z* (%) = 259 (14), 258 (18), 257 (15), 256 (49), 222 (14), 209 (18), 196 (36), 159 (12), 146 (13), 125 (100), 132 (72), 105 (26), 89 (13), 78 (12), 77 (12).

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