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Efficient and suitable preparation of *N*-sulfonyl-1,2,3,4-tetrahydroisoquinolines and ring analogues using recyclable $H_6P_2W_{18}O_{62}\cdot 24H_2O/SiO_2$ catalyst

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ABSTRACT

Silica gel-supported $H_6P_2W_{18}O_{62}\cdot 24H_2O$ is an efficient and recyclable catalyst for the synthesis of biologically important molecules. Several substituted *N*-sulfonyl-1,2,3,4-tetrahydroisoquinolines and ring analogues can be prepared in very good yields and purity by direct reaction of *N*-aralkylsulfonamides and *sym*-trioxane by a Pictet-Spengler reaction in the presence of a catalytic amount of silica gel-supported $H_6P_2W_{18}O_{62}\cdot 24H_2O$. Reactions were performed in a low volume of toluene, at 70 °C and for a short time, typically 15 to 30 min. The title heterocyclic compounds were prepared in very good yields (60%–95%) using the described procedure results in a clean and useful alternative, which has the advantages of a greener methodology with operative simplicity, use of a reusable and non-corrosive solid catalyst, soft reaction conditions, low reaction times, and good yields.

1. Introduction

Sustainable Chemistry is becoming a wide field in Chemistry in general and in Organic Synthesis in particular. Among the 12 principles of Green Chemistry, one of the main subjects is the use of a green, recoverable and reusable heterogeneous catalyst [1].

Heteropolyacids (HPA) are well-defined molecular arrangements with remarkable and useful applications. Their main technological property is their reusability because of their solid state and the possibility of generating heterogeneous catalysis. Diverse electronic and molecular structures of HPA lead to their application in different areas such as medicine and materials science, among others; in the wide field of structural possibilities that the HPA have shown [2], the Wells-Dawson-type primary structure deserves to be mentioned. It has the formula $[X_2M_{18}O_{62}]^{-m}$ and can be considered as the result of the fusion of two XM_9O_{34} units, each one with a classic Keggin-type geometry [3]. Recently, we reported the use of the Wells-Dawson-structured HPA in the synthesis of diverse compounds such as flavones [4], coumarins [5], aryl and aralkyl cinnamates [6], quinoxaline derivatives [7] and azlactones [8], among others.

Moreover, 1,2,3,4-tetrahydroisoquinolines and derivatives are basic compounds inside many natural alkaloids, among them ecteinascidin, cherylline and latifine; many compounds of this type have shown diverse bioactivities such as anticonvulsant, antimicrobial, antitumor (against breast and prostatic cancer, and sarcoma), anti-HIV,

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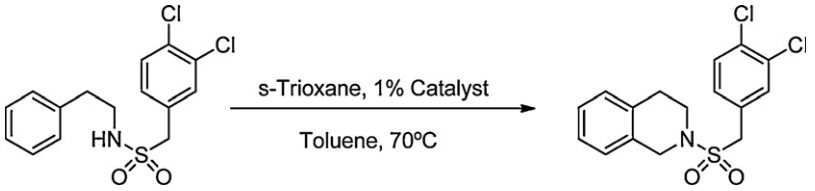

Scheme 1. Synthesis of *N*-(3,4-dichlorobenzylsulfonyl)-1,2,3,4-tetrahydroisoquinoline.

antihypertensive, antiarrhythmic, antiherpes, bronchodilator, and as Parkinson disease therapeutic drug, among others [9–13].

In particular, *N*-sulfonyl-1,2,3,4-tetrahydroisoquinolines and *N*-sulfonyl-2,3,4,5-tetrahydro-1*H*-2-benzazepines are very important precursors for 1,2,3,4-tetrahydroisoquinoline and 2,3,4,5-tetrahydro-1H-2-benzazepine synthesis, respectively, although they also exist as substructures of diverse biologically active compounds [14]. Also, the introduction of sulfur atoms in heterocyclic compounds is very important since they provide molecules useful for crop protection [15].

The classic way for synthesizing these compounds involves a sulfonylaminomethylation of *N*-arakylsulfonamides [16] using various agents such as *s*-trioxane in acid media [17]. Among many of the synthetic strategies for the formation of an isoquinoline skeleton are the Pummerer [18], Bischler-Napieralski [19], Friedel-Craft [20], Horner [21] and Pictet-Spengler reactions [22–25].

The Pictet-Spengler strategy consists in the formation of an imino-intermediate from the condensation of an arylethylamine and a carbonyl compound and then an intramolecular aromatic electrophilic substitution for generating the isoquinoline structure. The reaction conditions can be modified in the way that an acyl or sulfonyl substituent in the nitrogen atom increases the reactivity of the electrophilic pair, favoring the advance of the reaction. In this way, many attempts were made modifying the Pictet-Spengler reaction conditions, including solvent-free conditions [26], Grignard reagents [27,28], and the use of diverse types of catalysts as superacids [29], BINOL-phosphoric acid [30], Preyssler heteropolyacids [31], and iridium salts [32].

In the present work we describe the preparation and characterization of the Wells-Dawson-type HPA with formula $H_6P_2W_{18}O_{62}.24H_2O$ (WD), and the 40% silica gel-supported analog (WD40); also we present their use as a recyclable acid catalyst in the synthesis of *N*-sulfonyl-1,2,3,4-tetrahydroisoquinolines and ring analogues. For example, Scheme 1 shows the synthesis of *N*-(3,4-dichlorobenzylsulfonyl)-1,2,3,4-tetrahydroisoquinoline using this procedure.

2. Experimental

Chemicals were purchased from Aldrich, Fluka and Merck chemical companies and were freshly used after purification by standard procedures (distillation and recrystallization). All the reactions were monitored by TLC on precoated silica gel plates (254 mm). Flash column chromatography was performed with 230 to 400 mesh silicagel. All the yields were calculated from crystallized products. All the products were identified by comparison of physical data (mp, TLC and NMR) with those reported or with those of authentic samples prepared by the respective conventional methods using sulfuric acid as catalyst. Melting points of the compounds were determined in sealed capillary tubes and are uncorrected. The ^{1}H-NMR and ^{13}C-NMR spectra were obtained on a Bruker instrument 400 MHz model as $CDCl_3$ solutions, and the chemical shifts were expressed in δ units with Me_4Si (TMS) as the internal standard.

2.1. Preparation of catalyst

$H_6P_2W_{18}O_{62}.24H_2O$ (WD) was synthesized as described elsewhere [33] from an aqueous solution of α/β $K_6P_2W_{18}O_{62}{\cdot}10H_2O$ salt. The WD silica-supported catalyst was obtained by wet impregnation of Grace Davison silica (Grade 59, specific area = 250 m^2/g) with an aqueous solution of the synthesized WD. A catalyst containing 0.4 g/g of WD acid was prepared ($0.4WDSiO_2$). Then, samples were dried at room temperature in a vacuum desiccator for 8 h.

2.2. Catalyst characterization

Bulk and supported catalysts were characterized by ^{31}P MASNMR measurements. The ^{31}P MAS-NMR spectra were recorded in Bruker MSL-300 equipment operating at frequencies of 121.496 MHz. A sample holder of 5 mm diameter and 17 mm in height was used. The spin rate was 2.1 kHz, and several hundreds of pulse responses were collected. Chemical shifts were expressed in parts per million with respect to 85% H_3PO_4 as an external standard for ^{31}P-NMR.

FTIR spectra were obtained in Nicolet IR.200 equipment. Pellets in BrK and a measuring range of 400 to 4000 cm^{-1} were used to obtain the FT-IR spectra of the solid samples at room temperature.

Specific surface areas (S_{BET}) of the catalysts were determined by nitrogen adsorption/desorption technique using Micromeritics ASAP 2020 equipment.

The acidic properties of samples were determined by potentiometric titration using a solution of *n*-butylamine in acetonitrile in a Metrohm 794 Basic Titrino apparatus. A 0.05 ml portion of *n*-butylamine (0.1 N), in acetonitrile, was added to a known mass of solid (between 0.1 and 0.05 g) using acetonitrile as solvent, and stirred for 3 h. Later, the suspension was titrated with the same base at 0.05 ml/min. The electrode potential variation was measured in a Metrohm 794 Basic Titrino apparatus with a double junction electrode.