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Research Paper

Organocatalyzed oxidation of benzyl alcohols by a tetrazole-amino-saccharin: A combined experimental and theoretical (DFT) study

Luís M.T. Frija[a,*], Maxim L. Kuznetsov[a], Bruno G.M. Rocha[a], Lília Cabral[b], M. Lurdes S. Cristiano[b], Maximilian N. Kopylovich[a], Armando J.L. Pombeiro[a]

[a] Centro de Química Estrutural (CQE), Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais, 1049-001 Lisbon, Portugal
[b] CCMAR and Department of Chemistry and Pharmacy, F.C.T., University of Algarve, P-8005-039 Faro, Portugal

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ABSTRACT

A new catalytic system for the anaerobic oxidation of benzyl alcohols using a tetrazole-amino-saccharin organocatalyst has been established. In a solvent-free and microwave assisted process comprising aqueous *tert*-butyl hydroperoxide (TBHP) as oxidant, a variety of benzyl alcohols has been efficiently converted to aldehydes under mild conditions. Most reactions are complete within 30 min and the catalyst exhibits varied functional group compatibility. A catalytic cycle for the oxidation of the alcohols promoted by the tetrazole-amino-saccharin derivative is outlined involving radical species. DFT calculations performed for the oxidation of benzyl alcohol with and without organocatalyst show that the rate limiting step of the whole reaction is the cleavage of the O—O bond in TBHP with the subsequent hydrogen abstraction from the alcohol. The tetrazole-amino-saccharin organocatalyst assists the H-abstraction from benzyl alcohol by the bound $HO^{\bullet}$ radical. The simplicity, selectivity and softness of reaction conditions of the studied organocatalytic protocol suggest a great potential for extensive use in synthetic chemistry.

1. Introduction

The oxidation of alcohols to carbonyl compounds is a topic of interest in organic chemistry, both at laboratory and industrial level [1,2]. Consequently, a wide range of methods has been developed over the years to address this transformation [2]. Commonly, stoichiometric approaches are used because of their high selectivities and yields [1,2]. These include such recognized methods as Swern or Oppenauer oxidations or reactions with chromium(VI) or hypervalent iodine oxidants [2a,3]. However, these stoichiometric oxidants are not only relatively expensive but they also produce large quantities of toxic waste. Likewise, the swelling environmental apprehensions have led chemists to develop cleaner and greener reactions for chemical transformations [2].

Several approaches to catalytic alcohol oxidations based on transition metals or organocatalysts [4], as well as biocatalytic methods [5], have been described in recent times. However, despite this abundance of methods to select from, alcohol oxidation is still considered to be a challenging issue at the industrial scale. This occurs, in part, due to the large number of variables that have to be simultaneously optimized to make a feasible process, *e.g.*: (chemo)-selectivity, cost, safety, toxicity, environmental impact, *etc*. In particular, the majority of known methods for alcohol oxidation are unsustainable even at the laboratory level.

Recently, within our interest on alcohol oxidations we have developed a series of transition-metal containing catalytic systems where various homogeneous and heterogeneous metal frameworks were evaluated in cooperation with different oxidants and additives [6]. It should be mentioned that for some catalytic oxidations of secondary alcohols, the full conversion of substrates to the corresponding ketones under mild conditions was reached [6]. To further develop these studies, we turned our attention to the design of new and simple organic molecules as potential organocatalysts on the oxidation of alcohols, since transition metal-free processes are pre-requisites in many pharmaceutical and other synthetic procedures. As such, we turned our attention to thiazole derivatives in view of our interest and experience in this type of organic scaffolds [7]. Herein we present the catalytic studies of one of such molecules, a tetrazole-amino-saccharin, namely 3-((2-methyl-2*H*-tetrazol-5-yl)amino)benzisothiazole 1,1-dioxide (**5**) (Scheme 1), towards the oxidation of benzyl alcohols in a microwave assisted protocol.

* Corresponding author.
E-mail address: luisfrija@tecnico.ulisboa.pt (L.M.T. Frija).

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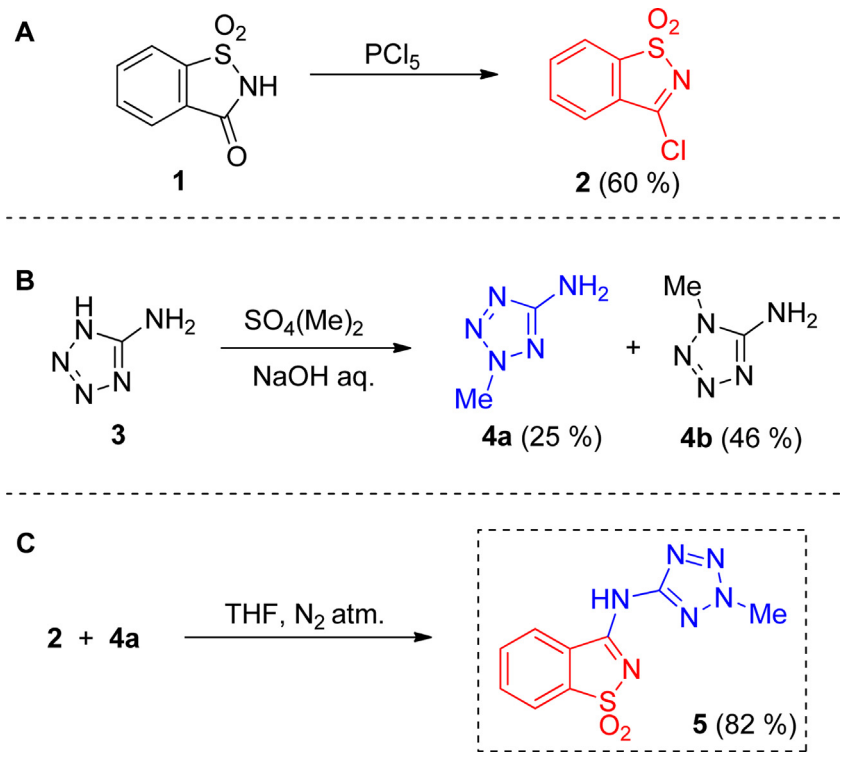

Scheme 1. Synthetic approach used to prepare the tetrazole-amino-saccharin 5.

2. Experimental section

2.1. General methods

Unless otherwise noted, solvents and starting materials were obtained from Aldrich. All chemicals used were of reagent grade without further purification before use. Column chromatography was performed using silica gel 60 MN and aluminium-backed silica gel Merck 60 F254 plates were used for analytical thin layer chromatography (TLC). Melting points were recorded and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Bruker Avance II 300 (UltraShield^{TM} Magnet) spectrometer operating at 300 MHz (^{1}H) and 75 MHz (^{13}C). The chemical shifts are reported in ppm using TMS as internal standard. Carbon, hydrogen and nitrogen elemental analyses were carried out by the Microanalytical Service of the Instituto Superior Técnico – University of Lisbon. FT-IR spectra (4000–400 cm^{-1}) were recorded on a VERTEX 70 (Bruker) spectrometer using KBr pellets. Mass spectra were obtained on a VG 7070E mass spectrometer by electron ionization (EI) at 70 eV. Chromatographic analyses were performed in a Fisons Instruments GC 8000 series gas chromatograph with a DB-624 (J&W) capillary column (DB-WAX, column length: 30 m; internal diameter: 0.32 mm), FID detector and the Jasco-Borwin v.1.50 software; GC conditions: $T_{injection}$ = 240 °C, $T_{initial}$ = 140 °C (1 min) raised 10 °C min^{-1} to 220 °C (1 min), carrier gas: He.

2.2. Synthesis of organocatalyst (*5*) and precursor compounds *2* and *4a*

3-Chloro-1,2-benzisothiazole-1,1-dioxide (saccharyl chloride, **2**), 2-methyl-(2*H*)-tetrazole-5-amine (**4a**) and 3-((2-methyl-2*H*-tetrazol-5-yl)amino)benzisothiazole 1,1-dioxide (**5**) were synthesised using protocols reported previously [6a,8].

2.3. Catalytic assays via MW irradiation

Experiments with 2.5–5.0 mmol of substrates and 6.25–12.50 mmol of oxidant were conducted using a focused Anton Paar Monowave 300 microwave reactor in 10 mL glass vessels with 10 mm internal diameter, sealed with rubber membranes in a stirred mode with simultaneous cooling (IR temperature detector). The targeted temperature together with a maximum microwave power (50 or 100 W) was set. The targeted temperature was reached within a few minutes. During the course of the reaction, the microwave power (20–30 W) as well as the pressure (1–10 bar) varied. At the end of the reaction, the reaction mixture was cooled down to room temperature and the vessel cap was carefully opened to slowly release the pressure.

2.4. Gas-chromatography analysis

Succeeding the MW-assisted reaction, 7 mL of acetonitrile together with acetophenone (1.25–2.50 mmol; internal standard) were added to the reaction mixture. A final solution aliquot (1 mL) was removed and centrifuged, and the supernatant was analyzed by GC for quantification of oxidation products.

2.5. Isolation and purification of oxidation products

Succeeding the MW-assisted reaction of benzyl alcohol (0.27 g, 2.5 mmol), 20 mL of acetonitrile were added to the obtained reaction mixture followed by evaporation of the solvent under reduced pressure (50 °C) to obtain a crude oil. In turn, 10 mL of distilled water was added to this crude and the mixture was extracted with CH_2Cl_2 (2 × 30 mL) and washed by brine. The organic layers were combined and dried with $MgSO_4$. After separation of $MgSO_4$ by filtration and evaporation of the volatile materials under reduced pressure (50 °C), the mixture was purified by flash silica gel column chromatography (*n*-hexane:diethyl ether = 6:1) to give 0.184 g (68% yield) of benzaldehyde (**7a**). ^{1}H NMR ($CDCl_3$): δ 10.06 (1H, s),