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Bifunctional solid catalysts for chemoselective hydrogenation–cyclisation–amination cascade reactions of relevance for the synthesis of pharmaceuticals

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ABSTRACT

The benzodiazepines olanzapine and clozapine are nowadays manufactured by a three-step process with a final yield below 50%. An approach to environmentally-friendly intensive processes consists in the development of multifunctional solid catalyst able to catalyze multistep reactions. Here, a bifunctional metal-acid solid catalyst has been prepared and is able to carry out hydrogenation–cyclisation–amination reactions in a cascade process. The catalytic system is illustrated for the synthesis of these important antipsychotics, being an alternative for the current industrial process that requires three steps batch reactions, using mineral acids and bases, and stoichiometric amounts of $SnCl_2$.

1. Introduction

The use of recoverable solid catalysts is not common for the synthesis of complex molecules.[1] To our knowledge, there are only a limited number of examples of complex molecules that present more than two solid-catalysed consecutive steps during their synthesis,[2,3] in particular bifunctional catalysts. Most often, the synthesis of potential drugs is performed with homogeneous catalysts, which are known to catalyse chemo-, regio- and stereoselective reactions.[4]

In the last years, the design and development of structured solid materials with well-defined catalytic sites has experienced important advances[5] and highly active and, more importantly, highly selective solid catalysts have been prepared.[6,7] However, in most cases, application of these catalysts is limited to relatively simple reactions with standard substrates, and preparation of more complex molecules, including drugs, remains scarce.

Schizophrenia is an important mental disorder in developed countries, imparting severe personal and social dysfunction to people. It is calculated that 1% of the population can suffer the illness. Two of the most used drugs for its treatment are the benzodiazepines olanzapine **1** and clozapine **2** (Fig. 1), which are known as atypical antipsychotics.[8] Compound **1** is a top-ten best-seller drug marketed by Eli Lilly & Co.[9] for the treatment of schizophrenia and bipolar disorder and **2** is indicated for treatment-resistant schizophrenia when other drugs have failed.[10]

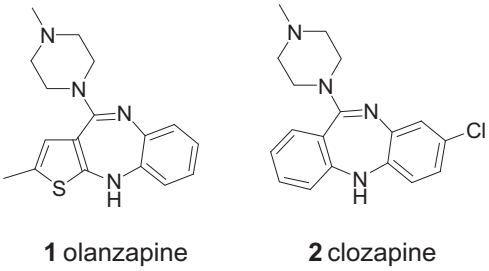

Figure 1. Structure of the benzodiazepines whose syntheses are studied in this work.

Syntheses of **1** and **2** are based on three batch processes that involve the use of mineral acids and bases, as well as other polluting chemicals such as $SnCl_2$ in stoichiometric amounts. Therefore, it would be of interest to substitute all these reagents by a solid catalyst that could perform the three reactions, i. e., chemoselective hydrogenation, cyclisation and amination, in one-pot through a cascade process. Such a process should require a bifunctional catalyst with metal and acid sites. Therefore, we have prepared a high surface area structured aluminosilicate, supporting metal

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nanoparticles, that is, able to couple the three steps in just one, while: (1) avoiding the use of pollutant stoichiometric reagents, (2) decreasing by-products and avoiding solvents and (3) saving energy. The different solids tested as catalysts in this work are listed in Table 1.

Table 1
List of acid solids employed in this work as catalysts with some of their physicochemical properties

Solid	Si/Al	BET surface ($m^2 \times g^{-1}$)
SiO_2–Al_2O_3	6	<100
Al–MCM-41	15	680
	60	1100
ITQ-2	15	620
	25	710
	50	850
TiO_2	—	<100
ZrO_2–SO_4	—	100

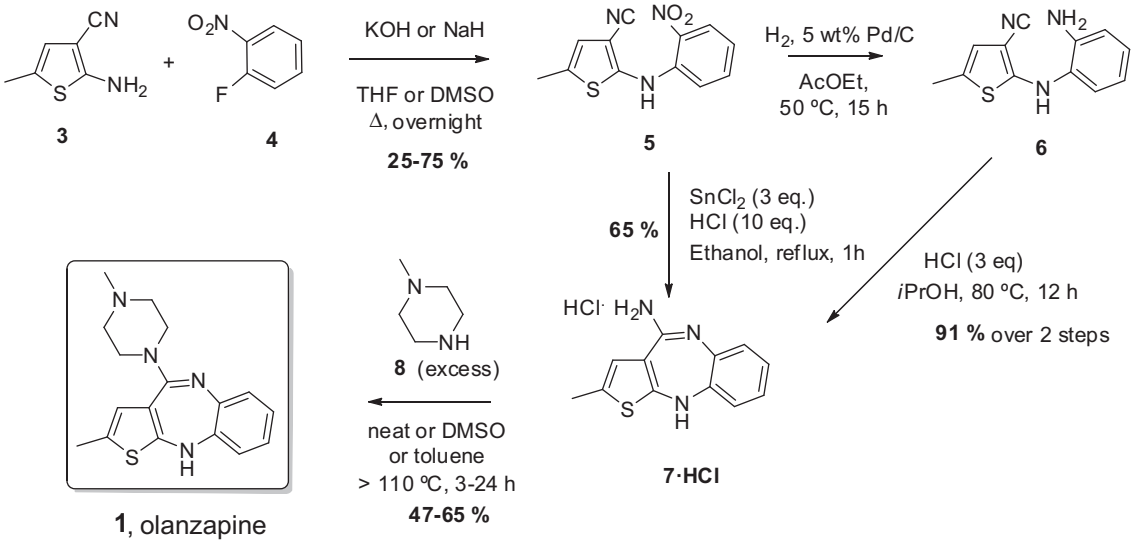
2. Results and discussion

2.1. Olanzapine

The general synthetic routes for olanzapine **1**, including the industrial one, are given in Scheme 1.[9,11]

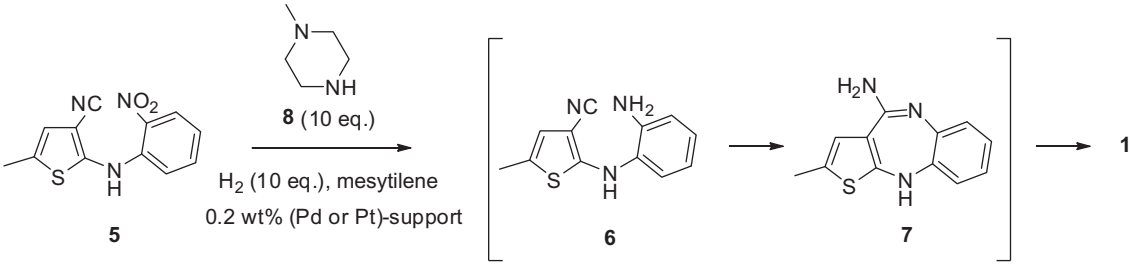
cyclisation with HCl in excess.[13] However, a catalytic hydrogenation of the nitro group with Pd/C followed by cyclisation in alcoholic HCl solution to produce **7**·**HCl** was claimed in a later patent. Finally, olanzapine **1** is obtained from **7**·**HCl** at high temperatures and long reaction times. The overall yield of olanzapine **1** from the common intermediate **5** in the industrial synthesis was below 48%, while 2 Kg of by-products per Kg of olanzapine **1** were produced. We have envisaged the use of a bifunctional solid catalyst with enough acidity for the Brönsted-catalysed steps and metal nanoparticles (Pt or Pd) for the hydrogenation step (Scheme 2). This solid could provide all the catalytic active sites needed to get **1** directly from **5**. Starting with this idea, a series of solid acids with sites of different strength were prepared and their characteristics are given in Table 1. Pt and Pd were then incorporated to the acid supports (see Experimental)[7,14] and the first set of results are given in Table 2.

It can be seen there that olanzapine **1** could be obtained from **5** in one-pot though still with lower yields than those reported in the patent literature for the three-step process. Importantly, we have observed that amine **8** can be present in the reaction mixture from the beginning, rendering the set-up easier. The cascade reaction with the bifunctional solid catalyst starts with the chemoselective hydrogenation of the nitro group in **5** to form the amine **6**, which cyclises to the imine **7** under acid conditions. Finally, a second acid-



Scheme 1. Reported syntheses of olanzapine **1**.

The key compound for the formation of the thienobenzodiazepine ring is the diarylamine **5**, which is obtained by nucleophilic substitution of amine **3** on fluoride **4**.[12] In the original patent, **5** is directly transformed to aminobenzodiazepine **7**·**HCl** by reduction of the nitro group with stoichiometric amounts of $SnCl_2$ and later catalyzed process, namely transamination of **8** with the amine group in **7**, gives **1**. The Pt-supported on sulfated acid zirconia and amorphous or structured Al–MCM-41 silica–alumina,[15] which present different acidities[15c,16] (entries 1–3) were able to form the thienobenzodiazepine ring **7** at 140 °C under H_2. Unfortunately,



Scheme 2. Proposed one-pot synthesis of olanzapine **1**.