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Short communication

A study of the temperature effect on Hantzsch reaction selectivity using Mn and Ce oxides under solvent-free conditions

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ABSTRACT

In this communication, four materials (CeO_2, CeO_2(Cu), MnO_x, and MnO_x(Cu)) were prepared, characterized and tested as catalysts, in solvent-free conditions, for the multicomponent Hantzsch reactions to obtain alternatively the 1,4-dihydropyridine or 2-phenylpyridine depending on the reaction conditions. 1,4-Dihydropyridine **4** was the main product formed at 80 °C (76%), and 2-phenylpyridine **7** was the main product at 40 °C (91%), in oxidant-free conditions, using CeO_2 catalyst. It is the first report that shows that, not only the temperature but also the nature of the catalyst may change the product selectivity in Hantzsch reactions.

1. Introduction

A multicomponent reaction (MCR) is defined as three or more different starting materials that react to form a product, where most, if not all of the atoms, are incorporated in the final product. From an environmental perspective, the traditional methods of performing chemical synthesis are unsustainable, and MCRs provide an important solution since they are more cost-effective, effective and less wasteful. As one of the known MCRs, Hantzsch reaction has attracted much attention on the synthesis of 1,4-dihydropyridines due to their relevant biological activities and pharmacological uses [1–3].

In this regard, metal oxides represent one of the most important categories of solid catalysts, either as active phases or as supports. Metal oxides are utilized for their acid–base and redox properties and represent an important family of materials used in heterogeneous catalysis [4].

Manganese oxides, including MnO, MnO_2, and Mn_3O_4, are intriguing composites used in organic synthesis as catalyst in several transformations, for example, oxidation of alcohols and hydroxy compounds, benzylic acid-type rearrangement, dehydrogenation, oxidative aromatization, and oxidation of amines [5].

Meanwhile, cerium (IV) oxide has been extensively used as a catalyst in different transformations, for example, methane oxidation [6], N-formylation of amines [7], and 1H-benzo [g] pyrazolo [3,4-b] quinoline-5,10-dione [8]. Our research group has studied the use of manganese oxides (MnO_x) and cerium IV oxides in VOC (volatile organic compounds) abatement [9] and water–gas shift reaction, respectively [10].

Moreover, in recent years, much attention has been paid to the synthesis of 1,4-dihydropyridines (1,4-DHPs) due to their relevant biological activity [11–13]. The classical methods for the synthesis of 1,4-DHPs is the Hantzsch multicomponent synthesis between an aldehyde, a 1,3-dicarbonyl compound and a source of ammonia, for example, ammonium acetate or an amine in the presence of different acid–basic catalysts [14].

Recently the Cao groups reported the asymmetric synthesis of 2-arylpyridines. These compounds could be obtained as a major product in the Hantzsch reaction, by the one-pot multicomponent reaction of benzaldehyde, ethyl acetoacetate and ammonium acetate, at room temperature and long time periods, under solvent, heat, catalysis and oxidant-free conditions [15].

In this communication, we present a study of the multicomponent reaction between benzaldehyde, ethyl acetoacetate, and ammonium acetate in the selective synthesis of 1,4-dihydropyridine or 2-phenylpyridine (Scheme 1).

2. Experimental

2.1. Catalyst preparation

MnO_x and CeO_2 were synthesized by the co-precipitation technique according to D'Alessandro et al. [16]. MnO_x(Cu) and CeO_2(Cu) were prepared via the wet impregnation method according to Tang [17].

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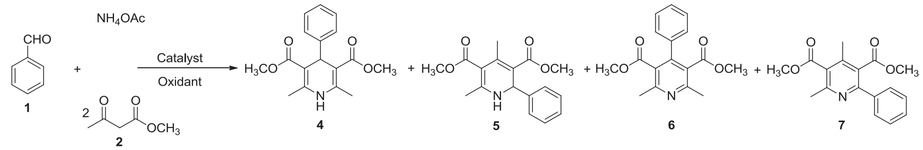

Scheme 1. Model reaction for the synthesis of 1,4-dihydropyridine or 2-phenylpyridine. Catalysts = CeO_2, CeO_2(Cu), MnO_x, MnO_x(Cu). Oxidant = air atmosphere.

2.2. Catalyst characterization

FTIR spectra were measured on Bruker Vertex 70 accumulating 32 scans at a resolution of 4 cm^{-1}. The XPS study was carried out in Multitechnique System equipment (SPECS) with a source of dual X-rays of Mg/Al and a hemispheric analyzer PHOIBOS 150 operating in FAT (fixed analyzer transmission) mode. A qualitative determination of the strongest base sites was determined by Hammett indicators; 25 mg of sample was shaken with 1 mL of a solution of Hammett indicator diluted in 10 mL methanol and left to equilibrate for 2 h, after which no further color changes were observed [18].

2.3. Catalytic test

The Hantzsch reaction was carried out by stirring a mixture of 1 mmol of benzaldehyde, 2 mmol of methyl acetoacetate, 1.3 mmol of ammonium acetate, and 50 mg of the corresponding catalyst, without solvent, at 25, 40, 60, 80 and 100 °C, respectively. The sample was collected from the reaction mixture during the reaction at time intervals. The analysis was performed on a gas chromatography Shimadzu 2014 instrument fitted with a 30 mm × 0.32 mm SPB-1 capillary column.

3. Results and discussion

3.1. Catalyst characterization

In previous work D'Alessandro et al. [16] have described some characterization results. The results more relevant are summarized in Table 1. They have demonstrated: (i) the formation of Mn oxides and ceria and the presence of spinel of Cu by XRD; (ii) the BET surface area of CeO_2 and CeO_2(Cu) is higher than that of MnOx and MnOx(Cu); (iii) a positive effect in the reducibility of Mn species with Cu incorporation, and (iv) the formation of highly dispersed Cu species on MnO_x and CeO_2 by TPR [16]. Full characterization by FTIR and XPS is presented in the Supplementary materials.

3.2. Catalytic test

Initially, the condensation of methyl acetoacetate, benzaldehyde and ammonium acetate as Hantzsch model reaction was examined comparatively at different temperatures, 25, 40, 60, 80 and 100 °C respectively, and the reaction selectivity was evaluated using the prepared catalysts (CeO_2, CeO_2(Cu), MnO_x and MnO_x(Cu)) in solvent-free conditions.

In general, and as reported by Ananthakrishnan and Gazi [19], the Hantzsch reaction produces the corresponding 1,4-dihydropyridine **4** as the main product in the presence of the catalyst, solvent and heating. This is because the reaction proceeds via 1,4-addition (Michael-type), which is the thermodynamically favorable compound. Meanwhile, 2-phenylpyridine **7** can be obtained as the main product at 20 °C, in an open atmosphere, under solvent, oxidant and catalyst-free conditions, in a long reaction time of 72 h. In this case, the reaction proceeds through a 1,2-addition (kinetic control), and the reaction is a tandem reaction involving the construction of heterocyclic **5** and the aromatization to obtain 2-phenylpyridine **7** in the air presence as oxidant.

At first, we studied the reaction at 25 °C, and the optimum reaction conditions were examined employing benzaldehyde (1 mmol), methyl acetoacetate (2 mmol), ammonium acetate (1.2 mmol) and the catalyst (50 mg). The catalysts were tested and notable reductions of the reaction time were observed in all cases, with respect to the blank experiment (Table 2, entry 1). The result shows a **4**/**7** selectivity of 8/92% and the benzaldehyde conversion was 100% in 6 h. Similar results were obtained with the other three catalysts as shown in Table 2, entries 3–5. The experiments performed at 25 °C show that 2-phenylpyridine **7** can be obtained as the main product, in a short time period of 6 h, compared with the result obtained without a catalyst at 60 h under the same reaction conditions. In this case, the reaction proceeds through a 1,2-addition (kinetic control) and the selectivity is only dependent on the reaction temperature, with no effect of the catalyst type tested being observed. For this reason, 25 °C is an excellent temperature for performing the selective synthesis of 2-phenylpyridine **7**.

According to the literature, an increase in the reaction temperature increases the formation of 1,4-dihydropyridine **4**. For this reason, we performed the next experiments at 40 and 60 ° C, respectively, to

Table 1
Some relevant characteristics of synthesized catalysts.

Catalyst	XRD result	Surface area (m^2/g)	Temperature of H_2 consumption peaks (°C)	Oα (%)	Base strength
MnOx	Mn_2O_3 MnO_2 Mn_3O_4 Mn_5O_8	22	338 464	54.7	6–6.8
CeO_2	CeO_2	137	794	58.5	9,6–11,4
CeO_2 (Cu)	CeO_2	138	299[a] 344[a] 429 (shoulder) 763	50.5	5,4–6
MnOx (Cu)	$Cu_{1.5}Mn_{1.5}O_4$ Mn_2O_3 MnO_2 Mn_3O_4 Mn_5O_8	29	279 [a] (shoulder) 343[a] (shoulder) 365	59.5	5,4–6

[a] Peaks assigned to dispersed Cu species.