Short communication

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

Oriana D’Alessandro, Ángel G. Sathicq, Jorge E. Sambeth, Horacio J. Thomas, Gustavo P. Romanelli *

Centro de Investigación y Desarrollo en Ciencias Aplicadas “Dr. Jorge J. Ronco” (CINDECA-CCT-CONICET), Universidad Nacional de La Plata, Calle 47 N° 257, B1900AJK La Plata, Argentina

A R T I C L E   I N F O

Article history:
Received 11 September 2014
Received in revised form 24 October 2014
Accepted 20 November 2014
Available online 21 November 2014

Keywords:
Ce and manganese oxides
Hantzsch reaction
1,4-Dihydropyridine
2-Phenylpyridine
Green chemistry

A B S T R A C T

In this communication, four materials (CeO₂, CeO₂(Cu), MnOₓ, and MnOₓ(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 was the main product formed at 80 °C (76%), and 2-phenylpyridine was the main product at 40 °C (91%), in oxidant-free conditions, using CeO₂ 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.

© 2014 Published by Elsevier B.V.

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 activity [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, MnO₂, and Mn₃O₄, are intriguing composites used in organic synthesis as catalyst in several transformations, for example, oxidation of alcohols and hydroxy compounds, benzilic acid-type rearrangement, dehydrogenation, oxidative aromatization, and oxidation of amines [5].

Manganese oxides (MnOₓ) 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

MnOₓ and CeO₂ were synthesized by the co-precipitation technique according to D’Alessandro et al. [16]. MnOₓ(Cu) and CeO₂(Cu) were prepared via the wet impregnation method according to Tang [17].
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].

### 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 CeO₂ and CeO₂(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 MnOₓ and CeO₂ 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 (CeO₂, CeO₂(Cu), MnOₓ and MnOₓ(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 a 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 (m²/g) | Temperature of H₂ consumption peaks (°C) | Ox (%) | Base strength |
|-------------------|------------|---------------------|-----------------------------------------|--------|--------------|
| MnOₓ              | Mn₂O₈, MnO₂, Mn₃O₄, Mn₅O₈ | 22                  | 338                                     | 54.7   | 6–6.8        |
| CeO₂              | Ce₂O₃      | 137                 | 794                                     | 58.5   | 9.6–11.4     |
| CeO₂(Cu)          | CeO₂       | 138                 | 299° 344°<sup>+</sup>, 429 (shoulder)   | 50.5   | 5.4–6        |
| MnOₓ(Cu)          | Cu₃Mn₁O₄, Mn₂O₃, Mn₂O₅, Mn₁O₃, MnO₂ | 29                  | 279° (shoulder), 343° (shoulder), 365   | 59.5   | 5.4–6        |

<sup>*</sup> Peaks assigned to dispersed Cu species.
compare the conversion and selectivity of the synthesized catalysts. Table 3 shows the results obtained at 40 °C and Table 4 the ones corresponding to 60 °C.

Table 3 Selectivity in the Hantzsch reaction at 40 °C using the four synthesized catalysts.

| Entry | Catalyst | Time (h) | Selectivity 4 (%) | Selectivity 7 (%) |
|-------|----------|----------|-------------------|-------------------|
| 1     | None     | 30       | 23                | 77                |
| 2     | MnOx     | 2        | 16                | 84                |
| 3     | CeO2     | 2        | 4                 | 96                |
| 4     | MnOx(Cu) | 2        | 7                 | 93                |
| 5     | CeO2(Cu) | 2        | 5                 | 95                |

Reaction conditions: Benzaldehyde, 1 mmol; methyl acetocetate, 2 mmol; ammonium acetate, 1.2 mmol; catalyst, 50 mg; solvent-free, 40 °C; stirring. The conversion of benzaldehyde was 100% (2 h). Conversion and selectivity were estimated by GC analysis. Selectivities of 5 and 6 were 0%.

Production. In this case, an increase of the catalyst basicity could improve 1,4-dihydropyridine selectivity.

The catalysts synthesized in the present article have Lewis acid sites M1+ and Bronsted acid–weak Brønsted acid groups, and Lewis basic sites O− and O−. The principal difference between cerium and manganese catalysts is that the cerium catalyst presents basic sites of greater strength than the manganese catalyst. This characteristic was confirmed by a qualitative determination of the strongest basic sites by Hammett indicators and XPS techniques. The pH range obtained for the four catalysts were: CeO2, 9.6 < pH < 11.4; MnOx, 6 < pH < 6.8; CeO2(Cu), 6 < pH < 6.8; and MnOx(Cu), 5.4 < pH < 6, respectively. Thus, CeO2 is the most basic catalyst of the series, and it showed high selectivity to 1,4-dihydropyridine 4.

Finally, to improve 1,4-dihydropyridine 4 selectivity, we performed the next experiment at 100 °C. In all experiments, and using the four catalysts, the selectivity of 1,4-dihydropyridine 4 was less than 70%, and some unidentified side products were detected by TLC. Particularly, in the catalyst CeO2(Cu), where Cu was used as dopant agent, a secondary product 6 was detected, with a selectivity of 9%. Product 6 is the result of the subsequent oxidation of 1,4-dihydropyridine 4 in the corresponding pyridine 6. In this case Cu incorporation in the CeO2 catalyst improves its oxidant capacity. Several papers have reported that Cu-doped CeO2 improves the oxidant capacity. The increased catalytic activity of Cu-doped CeO2 is explained by the enhanced concentration of oxygen vacancies and the enhanced redox pair Cu2+/Cu+ cycles [21].

In all the experiments, the CeO2 catalyst showed to be the most selective for obtaining 2-phenylpyridine 7 and 1,4-dihydropyridine 4. For this reason, it was used in two additional experiments for performing the preparative synthesis of both compounds using the optimized reaction conditions. When an appropriate mixture of three substrates and the catalyst was stirred at 40 °C under solvent-free conditions, the corresponding 2-phenylpyridine 7 was formed with 91% yield, in a reaction time of 6 h. Under the same condition and at a temperature of 80 °C, the corresponding 1,4-dihydropyridine 4 was obtained with 74% yield in 1 h, indicating that the CeO2 catalyst is effective to

Table 4 Selectivity in the Hantzsch reaction at 60 °C using the four synthesized catalysts.

| Entry | Catalyst | Time (h) | Selectivity 4 (%) | Selectivity 7 (%) |
|-------|----------|----------|-------------------|-------------------|
| 1     | None     | 16       | 24                | 76                |
| 2     | MnOx     | 1        | 44                | 56                |
| 3     | CeO2     | 1        | 75                | 25                |
| 4     | MnOx(Cu) | 1        | 48                | 52                |
| 5     | CeO2(Cu) | 1        | 66                | 34                |

Reaction conditions: Benzaldehyde, 1 mmol; methyl acetocetate, 2 mmol; ammonium acetate, 1.2 mmol; catalyst, 50 mg; solvent-free, 80 °C; stirring. The conversion of benzaldehyde was 100% (1 h). Conversion and selectivity were estimated by GC analysis. Selectivities of 5 and 6 were 0%.
activate the formation of both products with the only change of reaction conditions.

The reusability of the CeO\textsubscript{2} catalyst was investigated in the sequential reaction. The results, showed that the catalyst was reused four consecutive runs and no appreciable loss of its catalytic activity was observed (74, 73, 73 and 71\% for 4, and 91, 91, 88 and 87\% for 7).

A plausible mechanism, similar to that reported in the literature using nano-sized MgO particles as catalyst, is presented in Fig. 1. The acid–base bifunctional sites of the catalyst facilitate the reaction, which can be visualized as proceeding through a Knoevenagel condensation product as a key intermediate (intermediate 1), a second key intermediate is an ester enamine (intermediate 2), which is produced by condensation of the second equivalent of the \(\beta\)-ketoester with ammonia, with further condensation between these two fragments giving the final product 4.

4. Conclusions

The prepared materials were used as reusable catalysts, in a solvent-free condition, for the multicomponent Hantzsch reaction between benzaldehyde, methyl acetoacetate, and ammonium acetate. A detailed study of the reaction temperature was performed in order to increase the selectivity of the two products, 1,4-dihydropyridine 4 and 2-phenylpyridine 7. In both cases, the more selective catalyst was CeO\textsubscript{2}. 1,4-Dihydropyridine 4 was the main product formed at 80 °C and 2-phenylpyridine 7 was the main product at 25 °C. In both processes, the catalyst was reused four consecutive runs and no appreciable loss of its catalytic activity was observed. The use of a solid acid catalyst instead of the usual soluble acid catalyst contributes to a reduction in waste generation by allowing an easy separation and recovery without any loss of its catalytic activity.

Acknowledgments

The authors are grateful to CONICET, UNLP and ANPCYT of Argentina for financial support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.catcom.2014.11.022.

References

[1] D.M. D’Souza, T.J.J. Müller, Chem. Soc. Rev. 36 (2007) 1095–1120.
[2] V. Estévez, M. Villacampa, J.C. Menéndez, Chem. Soc. Rev. 39 (2010) 4402–4421.
[3] H.M. Hügel, Molecules 14 (2009) 4936–4972.
[4] M.B. Gawande, R.K. Pandey, R.V. Jayaram, Catal. Sci. Technol. 2 (2012) 1113–1125.
[5] A.J. Fatiadi, Synthesis (1976) 65–104.
[6] Lj. Kundakovic, M. Flytzani-Stephanopoulos, J. Catal. 179 (1998) 203–221.
[7] S.M. Sajadi, M. Maham, R. Akbar, Lett. Organ. Chem. 11 (2014) 49–54.
[8] A. Gharih, B.R.H. Khorasani, M. Jahangir, M. Roshani, R. Safae, Org. Chem. Int. 2013 (2013) 1–5.
[9] L. Lamaita, M.A. Peluso, J.E. SamBeth, H.J. Thomas, Appl. Catal. B Environ. 61 (2005) 114–119.
[10] E. Poggio Fraccari, O. D’Alessandro, J. SamBeth, G. BaroneTTi, F. Marinho, Fuel Process. Technol. 119 (2014) 67–73.
[11] B. Maleki, R. Tavebee, M. Kermanian, S.S. Ashrafi, J. Mex. Chem. Soc. 57 (2013) 290–297 (and the references cited herein).
[12] C. Avendano, J.C. Menendez, Med. Chem. Rev. 1 (2004) 419–444.
[13] R. Mannhold, B. Jablonka, W. Voigt, K. Schönaeger, E. Schraven, J. Med. Chem. 27 (1992) 229–235.
[14] A. Sathicq, G. Romanelli, A. Ponzinibbio, G. BaroneTTi, H. Thomas, Lett. Org. Chem. 7 (2010) 511–518.

Fig. 1. Plausible mechanism for the formation of 1,4-dihydropyridines in the presence of CeO\textsubscript{2}.
[15] L. Shen, S. Cao, J. Wu, J. Zhang, H. Li, N. Liu, X. Qian, Green Chem. 11 (2009) 1414–1420.
[16] O. D’Alessandro, H.J. Thomas, J.E. Sambeth, React. Kinet. Mech. Catal. 107 (2012) 295–309.
[17] X. Tang, J. Chen, Y. Li, Y. Li, Y. Xu, W. Shen, Chem. Eng. J. 118 (2006) 119–125.
[18] D.G. Cantrell, L.J. Gillie, A.F. Lee, K. Wilson, Appl. Catal. A Gen. 287 (2005) 183–190.
[19] R. Asanthakrishnan, S. Gazi, Catal. Sci. Technol. 2 (2012) 1463–1471.
[20] D. Zhang, Y. Qian, L. Shi, H. Mai, R. Gao, J. Zhang, W. Yu, W. Cao, Catal. Commun. 26 (2012) 164–168.
[21] R. Prasad, G. Rattan, Bull. Chem. React. Eng. Catal. 5 (2010) 7–30.