Scientific contribution/Original research

Dehydrogenation of Hantzsch Dihydropyridines with Heterogeneous Cobalt Oxide Catalyst Supported in *N*-Doped Activated Carbon

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Abstract:
Hantzsch dihydropyridines represent an important source of hydrogen to be transfered to other unsaturated organic molecules, leading the formation of pyridine aromatic ring as driving force. The hydrogen transfer process was evaluated using 1,4-dyhydropyridines and heterogeneous cobalt catalyst supported over *N*-doped activated carbon. The 4-position of the dihydropyridine ring was substituted with *H* (**4a**), *Me* (**4b**) and *Ph* (**4c**) groups, showing that only **1** reacted to yield the corresponding pyridine compound indicating that the presence of steric hindrance took place on the reaction. Additionally; three solvents –tetrahydrofuran (THF), acetone, and acetonitrile– were tested, showing reactivity only with unsaturated ones, but not with THF. This observation indicates that dihydropyridine works as hydrogen donor and solvent as hydrogen aacceptor in the hydrogen transfer process.

Keywords: Hantzsch dihyropyridine; Heterogeneous cobalt oxide catalyst; Hydrogen transfer; Unsaturated solvents

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1. Introduction

NADPH bioorganic molecule (**1**) represents an important hydrogen donor agent in biological processes (Willner et al., 2021), moreover, when this molecule is used in synthetic transformations result as a too-expensive starting material (Lee et al., 2019). For this reason, dihydropyridine analogs are used instead this biomolecule (Kraatz et al., 2019). In this regard, Hantzsch 1,4-dihydropyridines play an important role as bioactive molecules because some of this family compounds are used as drugs such as nifedipine (**2**) and amlodipine (**3**) used to treat high blood pressure and to control angina (chest pain), working as calcium-channel blockers (Chatterjee et al., 2022) (**Figure 1**).

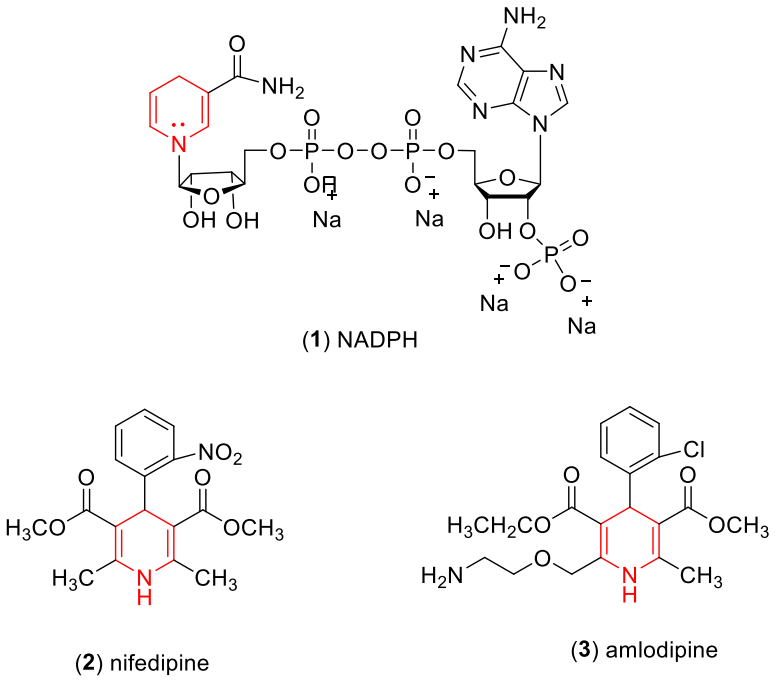


Figure 1. Structure of NADPH (**1**), and 1,4-dihydropyridine analogs nifedipine (**2**) and amlodipine (**3**). Dihydropyridine ring is showed in red.

On the other hand, catalysis represents one of the most powerful tools to transform molecules (Rawat et al., 2022), and usually, transition metals are used to build this kind of molecules because of their redox, optical and/or magnetic properties (Tsuji, 2002). In terms of green chemistry, the use of first row bioavailable transition metals as base of catalysts is preferred mainly because of their abundance and reincorporation into the biological processes (McCleverty, 1999). Beller et al., (2013) reported the preparation of a cobalt oxide catalyst supported in an *N*-dopped activated carbon surface, starting with the synthesis of a homogeneous complex with pyridine-like ligands, followed by adsorption into activated carbon and finally, pyrolysis at 800°C to fix covalently the cobalt defined complex into the carboneous surface, and then, its application in the reduction of nitroarenes.

The current work describes the use of a heterogeneous cobalt oxide catalyst supported in *N*-doped activated carbon surface to dehydrogenate 1,4-dihydropyridines.

2. The Goal

The goal of the research was focused on the dehydrogenation of Hantzsch 1,4-dihydropyridines using a non-expensive heterogeneous cobalt oxide catalyst, testing several conditions such as temperature, load of catalyst, solvent and period of time, determining the optimal reaction conditions.

3. Methods

Catalyst was prepared according to the methodology described by Beller et al., (2013), and 1,4-dihydropyridines 4a-c were prepared according to a one-pot multicomponent modification of the methodology reported by Hantzsch (Bosica et al., 2020).

Cobalt oxide supported in *N*-doped activated carbon was prepared following the methodology described by Beller et al., (2013). A mixture of 1.0 equiv. of cobalt(II) acetate and 2.0 equiv. of 1,10-phenantroline to obtain the bisphenantrolinecobalt(II) acetate, following by the addition of 600 mg of vegetal activated carbon in ethanol and refluxing in etanol for 2 hours. At the end of the time, solvent was removed by vaccum and dried at 80°C for 0.5 hours. Pyrolysis took place at 800°C during 2 hours, obtaining a compound containing 57.8 % of carbon, 14.31% of nitrogen, 21.76% of oxygen and 6.6% of cobalt according to the Energy-dispersive *X-ray* Spectroscopy.

1,4-Dihydropyrines (4) were prepared mixing 2.0 equiv. of ethylacetoacetate, 1.0 equiv. of aldehide, an excess of NaOH and 2 drops of aqueous HCl (0.1 M) as catalyst in ethanol (**Figure 2**) in ethanol for 3 hours. At the end of the reaction, solvent was removed in vaccum and recristalization of product took place in a mixture of methylenechloride/hexane solvents. Melting points 4a: 182°C, 4b: 189°C, 4c: 270°C.

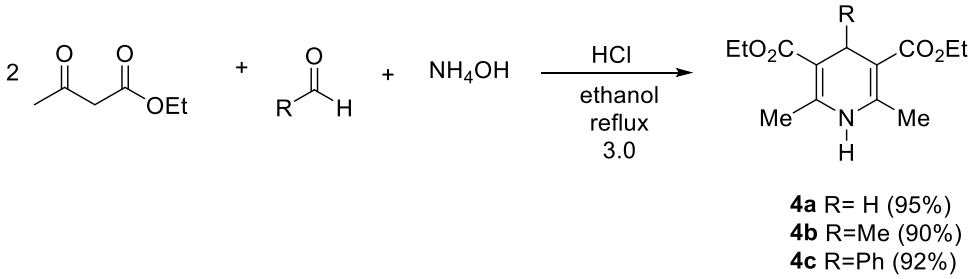


Figure 2. Synthesis of Hantzsch 1,4dihydropyridines by one-pot multicomponent reaction.

Dehydrogenation of **4** was tested employing 1 equiv. of the corresponding Hantzsch dihydropyridine and 5mol% of cobalt oxide catalyst in a reflux of 20 mL of solvent (tetrahydrofuran (THF), acetone and acetonitrile). Reaction was followed by thin-layer chromatography (TLC) and products were isolated by silica column using a mixture 8:2, hexane/ ethyl acetate **(Figure 3**).

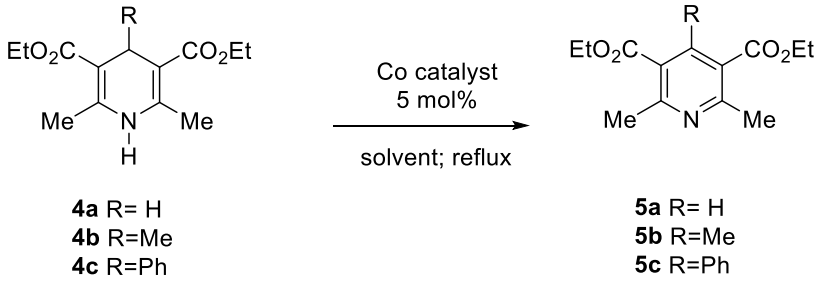


Figure 3. Dehydrogenation of 1,4-dihydropyridines using cobalt catalyst.

4. Results and Discussion

Three 1,4-dihydropyridines (4a, 4b and 4c) were tested, using three different solvents (THF, acetone and acetonitrile).

In the first attempt, 4a reacted with 5 mol% of cobalt oxide catalyst in the selected (**Table 1)**.

Table 1. Dehydrogenation of 4a with 5 mol% of cobalt oxide catalyst in a reflux of solvent during 2 hours. Product 5a was isolated by silica gel chromatography using an 8:2 mixture of hexane/ethyl acetate solvent.

Entry	Solvent	Yield
1	Tetrahydrofuran (THF)	Recovery of starting material
2	Acetone	63%
3	Acetonitrile	99%

According to **Table 1**, only unsaturated solvents allowed the formation of the product (**Table 1,** Rows 2 and 3), indicating the possible dependence of a hydrogen acceptor in the process. THF solvent does not contain double or triple bonds, and the possibility to transfer the hydrogen from 4a

did not take place. On the other hand, the higher boiling point of acetonitrile (82 °C) compared to acetone (56 °C) could be associated to the almost quantitative yield in the reaction showed in (**Table 1**, Row 3). In this instance, the reaction affords the pyridine 4a only in the presence of unsaturated solvents according to **Figure 4**.

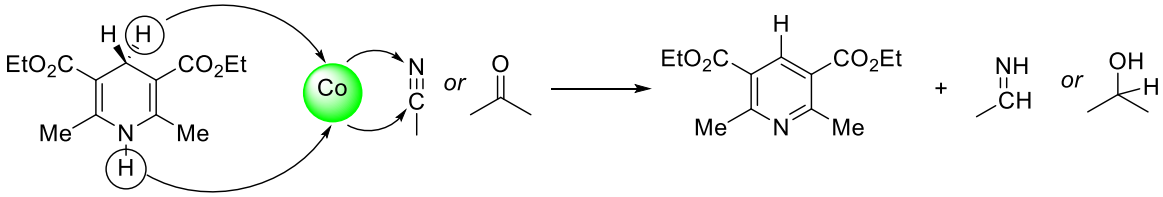
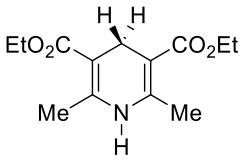
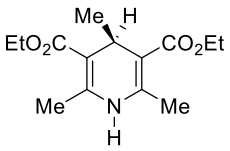
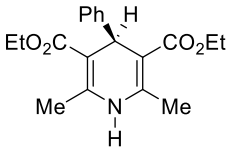


Figure 4. Hydrogen transfer from **4a** to unsaturated solvents.

In a second attempt, the substitution of the 4-position of the dihydropyridine **3** ring was evaluated. Results are shown in **Table 2**.

Table 2. Dehydrogenation of 4 using 5 mol% of cobalt oxide catalyst in reflux of acetonitrile during 2 hours. Product was isolated by crystallization in methylene chloride/hexane mixture of solvents.

Entry	Substrate	Yield
1	 **4a**	99%
2	 **4b**	Recovery of starting material
3	 **4c**	Recovering of starting material

According to the results observed in **Table 2**, 4-position plays an important role in the dehydrogenation process exhibiting a high sensitive steric hindrance. Only **4a** allowed the formation of product by means of the small substituent (H), instead the larger *-Me*, and *-Ph* substituents in 4b and 4c. This observation could show close interaction between the cobalt center and 4-position in the dihydropyridine ring (**Figure 5**).

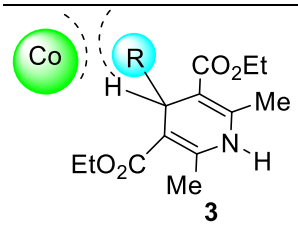


Figure 5. Steric hindrance in the approximation of cobalt catalyst to *4*-position in *3*.

In this way, the use of heterogeneous cobalt oxide catalyst was evaluated in the dehydrogenation process of Hantszch 1,4-dihydropyridines.

5. Conclusions

The use of Hantzsch dihydropyridines as hydrogen donors can occur, but the substituent in the *4*-position of the dihydropyridine ring plays an important role in the course of the reaction at using cobalt oxide catalyst. The structure of the solvent also resulted important because the requirement of an unsaturation as hydrogen acceptor for the reaction to proceed was essential. With these results, process to hydrogenate unsaturated organic molecules at using 4a as hydrogen donor and heterogeneous cobalt oxide supported in *N*-doped activated carbon as catalyst can be visualized.

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Conflicts of Interest: The authors declare no conflict of interest.

References

1. Bosica G, Demanuele K, Padrón JM, Puerta A. One-pot multicomponent green Hantzsch synthesis of 1,2-dihydropyridine derivatives with antiproliferative activity. Beilstein J Org Chem. 2020; 16: 2862-2869. DOI: 10.3762/bjoc.16.235
2. Falcone N, She Z, Syed J, Lough A, Kraatz H-B. Synthesis and biochemical evaluation of nicotinamide derivatives as NADH analogue coenzymes in ene reductase. ChemBioChem. 2019; 20: 838-845. DOI: 10.1002/cbic.201800661
3. Fukuzumi S, Lee Y-M, Nam W. Catalytic recycling of NAD(P)H. J Inorg Chem. 2019; 199: 1-9. DOI: 10.1016/j.jinorgbio.2019.110777
4. Karmakar S, Kumar Basak H, Paswan U, Kumar Pramanik A, Chatterjee A. Designing of next-generation dihydropyridine-based calcium channel blockers: An in silico study. J Appl Pharm Sci. 2022; 12: 127-135. DOI: 10.7324/JAPS.2022.120414
5. McCleverty J, Chemistry of the first-row transition metals. Oxford Chemistry Primers, Oxford University Press.1999.
6. Rawat V, Das A, Mohan Srivastava C, Heterogeneous catalysis in organic transformations. CRC Press, Boca Raton. 2022. DOI: 10.1201/9781003126270
7. Tsuji J, Transition metal reagents and catalysts: Innovations in organic synthesis. John Wiley & Sons Ltd, Baffins Lane, Chichester. 2002. DOI: 10.1002/0470854766
8. Wang C, O'Hagan MP, Willner B, Willner I. Bioinspired artificial photosynthetic systems. Chem Eur J. 2021; 28: e202103595. https://doi.org/10.1002/chem.202103595
9. Westerhaus FA, Jagadeesh RV, Wienhöfer G, et al. Heterogenized cobalt oxide catalysts for nitroarene reduction by pyrolysis of molecularly defined complexes. Nat Chem. 2013; 5: 537-543. DOI: 10.1038/nchem.1645