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1,4-Dihydropyridine/BF_3OEt_2 for the reduction of imines: Influences of the amount of added BF_3OEt_2 and the substitution at N-1 and C-4 of the dihydropyridine ring

Ingrid F. Zattoni [a], Lais D. Guanaes [a], Letícia B. Cerqueira [a], Roberto Pontarolo [a], Diogo R.B. Ducatti [b], M. Eugênia R. Duarte [b], Miguel D. Noseda [b], Angela C.L.B. Trindade [a], Alan G. Gonçalves [a,*]

[a] Departamento de Farmácia, Universidade Federal do Paraná, Av. Lothario Meissner, 3400, Jardim Botânico, Curitiba, Paraná, Brazil
[b] Departamento de Bioquímica e Biologia Molecular, Universidade Federal do Paraná, PO Box 19046, Curitiba, Paraná, Brazil

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ABSTRACT

We have evaluated four 1,4-dihydropyridines (DHPs **1a**, **1b**, **1c** and **1d**) as reducing agents, which presented free (hydrogenated) or phenyl-substituted N-1 and C-4 positions of the DHP ring. Reactions combining each of the DHP and different amounts of BF_3OEt_2 were evaluated for the reduction of imine **2a** (*N*-benzylideneaniline). DHP simultaneously substituted at N-1 and C-4 (**1a**), and DHP substituted at C-4 (**1b**) gave lower yields for reduction of **2a** in comparison with DHPs **1c** and **1d** (both unsubstituted at the C-4 position). By evaluating the amount of added BF_3OEt_2 to the reaction mixture, we have found that DHP **1c** (substituted at N-1) provided its best yield for amine **3a** (82%) when associated with stoichiometric amounts BF_3OEt_2, while DHP **1d** (N-1- and C-4-unsubstituted derivative) was more effective (90% yield) with catalytic quantities of the Lewis acid. The reaction system using DHP **1c** under stoichiometric BF_3OEt_2 could also be successfully applied with additional imine examples and under reductive amination conditions.

1,4-Dihydropyridines (DHPs) has long been used as reducing agents in organic reactions [1]. They were first recognized as the synthetic models of the naturally occurring Nicotinamide Adenine Dinucleotide system (NADH/NAD^+) [2–5]. In reduction reactions, DHPs act mainly as hydride (or electron) donors, by promoting the hydrogen transfer to an adequate substrate, with the concomitant formation of the oxidized version of the DHP, a pyridine or pyridinium salt [6–8]. DHPs have been utilized to reduce different organic functions, such as ketones [9], aromatic azides [10], alkenes [11], reductive amination/imine [12–14] enones [15], among others.

An important aspect factoring on the ability of DHPs to promote reduction reactions is related to the substitution pattern of the DHP ring, mainly in terms of the presence or absence of substituents located at the N-1 and C-4 positions [16]. These positions appear to be key in the reduction process, which is in accordance with the current accepted mechanisms for the hydrogen transfer involving DHPs. Studies involving the measuring of DHP activation energy for hydride donation indicate those lacking both N-1 and C-4 substituents as having superior capabilities in promoting reduction reactions [16–18]. It is worth mentioning that such comparative studies were performed based on electrochemical oxidation and theoretical evaluations of the DHPs studied, and they did not evaluate the comparison of the reaction output in terms of isolated yield of a reduced product. In fact, most of the published synthesis involving DHP-promoted reductions employs the Hantzsch ester (Fig. 1), which presents no substituents for either N-1 or C-4 position. The Hantzsch ester has been widely utilized in combination with Lewis acids [12–15], Bronsted acids [19,20] and phosphonic acid derivatives [21] to promote the reduction of diverse chemical functions. Even though the aforementioned statements lead to a general impression that the N-1 or C-4 substitution of the DHP ring reflects into inferior reducing agents, the fact that an *N*-substituted DHP (NADH/NAD^+ system) was evolutively elected in living organisms to promote metabolic reductions should be took into consideration.

Due to the scarceness of utilization of substituted N-1- and C-4-DHPs as reducing agents in the literature, as well as the lack of comparative synthesis using them, we herein investigated the reduction of imines promoted by examples of such DHPs, where a Hantzsch ester analogue was used for comparison purposes. The execution of the present work was also encouraged by a

* Corresponding author.
E-mail address: alan.goncalves@ufpr.br (A.G. Gonçalves).

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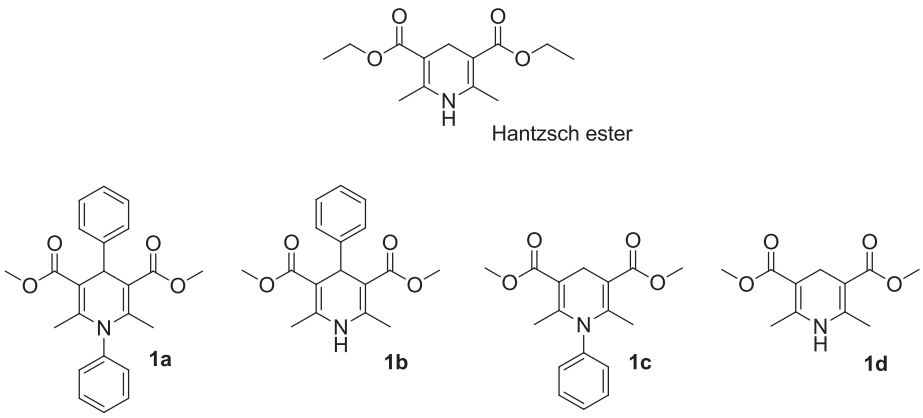


Fig. 1. Hantzsch ester and DHPs **1a**–**1d.**

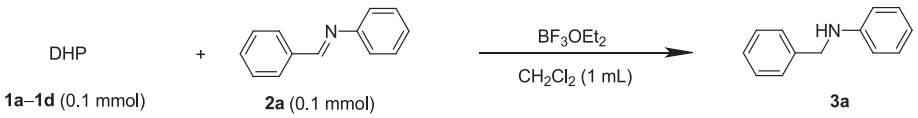
previous study [22], where some of the present authors have demonstrated the facile aromatization of DHPs with BF_3OEt_2, in the absence of added oxidizing agents. On that research, DHPs having unsubstituted or substituted N-1 and C-4 positions could all be successfully converted in their respective pyridines or pyridinium salts.

In this way, the first step of the present work was the preparation of DHPs **1a**–**1d**, which were meant to serve as the reducing agents to be evaluated. For all cases, the substituent located at N-1 or C-4 positions was the phenyl group, which translated into the readily available starting materials, aniline and benzaldehyde. DHP **1a** [22] and **1c** [23] were synthesized stepwise, from the appropriate enamine and enone. DHPs **1b** and **1d** were prepared through adaptations of the classic multicomponent Hantzsch synthesis [22,24–27]. As shown in Fig. 1, DHP **1a** was substituted at N-1 and C-4 positions, **1b** was substituted at C-4, while **1c** at N-1. Compound **1d**, the dimethoxyl analogue of the Hantzsch ester, was unsubstituted at both positions.

In order to compare DHPs **1a**–**1d** efficacies as reducing agents, we utilized imine **2a** (*N*-benzylideneaniline) [28] as substrate, which would be converted into amine **3a** [29] (see reaction shown in Table 1). This preference was based on the fact that (a) imines are known to be well reduced by DHPs, being sensitive probes for such reactions, even considering presumably weak reducing agents and (b) the pair **2a**/**3a** could be promptly isolated by chromatography and differentiated by TLC or NMR analysis.

The reaction setup herein initially tested (Table 1) was based on the previous conditions utilized for the aromatization of DHP **1a** [22]. The cited study employed a mixture of **1a** and three equivalents of BF_3OEt_2 in dichloromethane, at 0 °C for 5 h, under atmospheric air. In order to take full advantage from **1a** reducing potential, we first assumed that the use of inert atmosphere would help to direct the hydride transfer to the substrate to be reduced. This assumption was based on evidences [22] indicating that the oxygen present in the reaction media was crucial for the aromatization of **1a**. However, condition shown in entry 1 of Table 1, which used Argon atmosphere, gave no detectable reduced product from imine **2a**. By increasing the temperature from 0 °C to rt, and by extending the reaction time, it was possible to promote the reduction of **2a** to produce amine **3a** with 10% yield (entry 2). Even though the presence or absence of inert atmosphere greatly influences the aromatization of DHP **1a** [22], we noted that it did not

Table 1
Evaluation of DHPs **1a**–**1d** as reducing agents for imine **2a** in the presence of BF_3OEt_2.



Entry	DHP	BF_3Et_2O (mmol)	Atmosphere	Temperature	Reaction time (h)	Reduced product yield (%)
1	**1a**	0.3	Argon	0 °C	5	–
2	**1a**	0.3	Argon	rt	24	10[a]
3	**1a**	0.3	Air	rt	24	10[a]
4	**1a**	0.3	Air	rt	24	14[b]
5	**1b**	0.3	Air	rt	24	32[b]
6	**1c**	0.3	Air	rt	24	72[b]
7	**1d**	0.3	Air	rt	24	66[b]
8	**1a**	0.1	Air	rt	24	27[b]
9	**1b**	0.1	Air	rt	24	45[b]
10	**1c**	0.1	Air	rt	24	82[b]
11	**1d**	0.1	Air	rt	24	68[b]
12	**1a**	0.01	Air	rt	24	–
13	**1b**	0.01	Air	rt	24	7[b]
14	**1c**	0.01	Air	rt	24	21[b]
15	**1d**	0.01	Air	rt	24	90[b]

[a] product isolated from silica gel column;
[b] product isolated from preparative TLC plates.

make any difference, when considering the isolated yield of the **3a** from **2a** (compare entries 2 and 3). Therefrom, we assumed that our previous published reaction [22], which was simply developed for DHP aromatization, presumably do not match the best conditions to direct the hydride transfer to imine **2a**.

Condition outlined in entry 3 (Table 1) was repeated; however, instead of isolating amine **3a** from column chromatography, we utilized preparative TLC plates (entry 4, Table 1). From here, we decided to continue our evaluation by using purification with preparative TLC, because it was considered to be more practical and accurate for the determination of the isolated yields, at least for the scale of the reactions herein assayed. By employing entry 4 experimental setting, we then utilized DHPs **1b**–**1d** (see entries 5–7). As observed for **1a**, the other DHPs (**1b**–**1d**) were capable of reducing imine **2a** to produce **3a**. By comparing the isolated yields shown in entries 4–7, it was also observed that the C-4-unsubstituted DHPs (**1c** and **1d**) provided substantially higher yields than C-4-substituted **1a** and **1b**, with the simultaneously N-1- and C-4-substituted **1a** being the less effective DHP. These results indicated that the substitution of the C-4 position impaired hydrogen transfer to some extent [16], while the same effect could not be surely attributed to the N-1 substitution.

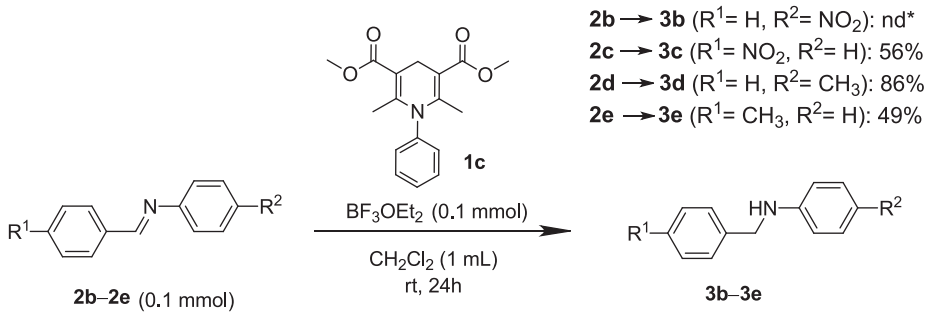
The conditions utilized for our preliminary tests (entries 1–7, Table 1) were conducted with excess of BF_3OEt_2 (3 equivalents), because it was critical for the aromatization of **1a**, as stated previously [22]. In order to verify if different amounts of the added Lewis acid would influence the yield of amine **3a** from imine **2a**, we repeated the conditions shown in entries 4–7 of Table 1, this time by employing catalytic and stoichiometric amounts of BF_3-OEt_2 (entries 8–15, Table 1). This evaluation generally indicated that the use of stoichiometric amounts of BF_3OEt_2 was more effective than operating reactions under excess or catalytic quantities of the Lewis acid, except for the Hantzsch ester analogue (**1d**), which gave the best yield of Table 1 (90%) with a catalytic proportion of BF_3OEt_2 (entry 15). On the other hand, DHP **1d** was less effective than *N*-substituted DHP **1c**, when using excess (compare entries 6 and 7) or stoichiometric amounts of BF_3OEt_2 (compare entries 10 and 11).

The fact that the best reduction conditions herein found consisted of utilizing (a) DHP **1d** added of catalytic amounts of BF_3-OEt_2, or (b) DHP **1c** added of stoichiometric BF_3OEt_2, could lead to a number of tentative explanations. We understand that in the case of DHP **1c**, in order to perform the hydrogen transfer, the DHP could require its own activation with boron trifluoride, plus the transitory BF_3-imine association, thus requiring larger amounts of BF_3OEt_2 in the reaction mixture. This is accordance with findings of De Kok and coworkers [30], which propose the activation of *N*-substituted DHPs through the association of a Lewis acid with the oxygen of the carbonyl groups attached to the DHP ring. Differently, for DHP **1d** reaction, the catalytic amount of added BF_3OEt_2 would be sufficient to activate imine **2a**, while any further amount of the Lewis acid would not match the best condition for hydrogen transfer, probably due to the higher reactivity of **1d** in comparison to **1c**. This hypothesis can be related with the lower $\Delta G_{\text{H-D (X-H)}}$ involved in hydride dissociation for the Hantzsch ester (42.57 kcal.mol^{-1}) in comparison to its *N*-substituted derivative (45.14 kcal.mol^{-1}) [16].

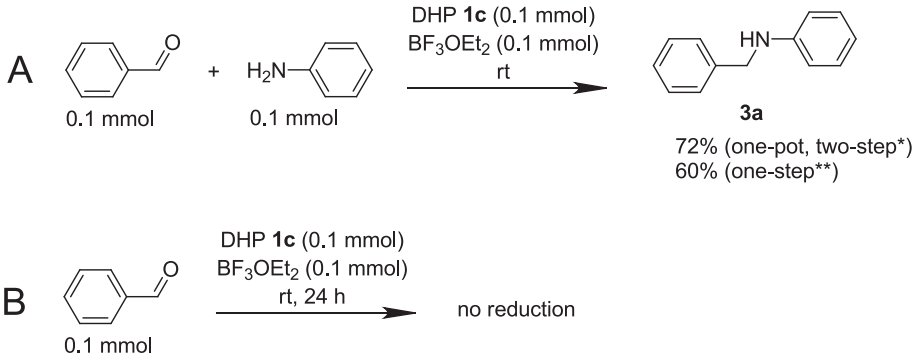
As discussed above, as well as previously stated [16], N-1, C-4-unsubstituted DHPs constitute more powerful reducing agents, in comparison to their substituted counterparts. Based on the results here exposed, it was possible to found conditions in which the less reactive N-1-substituted derivative (**1c**) could approximately match the maximum effectiveness of the Hantzsch ester analogue (**1d**). Although the following matter is complex and involve diverse factors, the present findings could provide an insight of why the NADH/NAD$^+$ system throve through the evolutionary barriers as an *N*-substituted DHP, which is responsible to promote the metabolic reductions in living cells. Perhaps, one of the reasons lies on the fact that the reactivity of an *N*-substituted DHP could be more efficiently modulated, especially considering the high complex intracellular environment. Considering more practical matters, reduction reactions requiring highly controlled hydride transfer could be benefit from the use of less reactive DHPs, such as those presenting substituents at N-1 of the DHP ring.

Based on the literature, the superiority of DHP **1c** over **1d** (entries 10 and 11, Table 1), even despite of using selected conditions, was somewhat unexpected. In this way, we decided to further exploring the use of **1c** under stoichiometric amounts of BF_3OEt_2. First, by using the same conditions [31] of entry 10 (Table 1), DHP **1c** was evaluated with imines **2b**–**2e** [28,32–34] (Scheme 1), which presented *p*-nitro or *p*-methyl substituents located at the benzaldehyde- or aniline-derivative moieties, considering imine **2a** scaffold. From these experiments, we noted that the best yield (**3d** [35], 86%) was attained with imine **2d**, which was modified at the aniline moiety with electron-donor methyl group. By contrast, when the imine scaffold was substituted at the same position, but with the highly electron-withdrawing nitro group, the expected product could not be detected. Imines **2c** and **2e**, both modified at the benzaldehyde moiety, gave intermediate close yields for the corresponding amines **3c** [35] and **3e** [35] (56% and 49%, respectively).

Results shown in Scheme 1 could be related to the mechanism of the reactions herein described, where the substitution of the aniline moiety in **2b** and **2d** structures interfered with the availability of the electron pair of the imine nitrogen. In the case of **2b**, the interaction of the imine nitrogen with the Lewis acid could be compromised, thus hindering the imine carbon to be the hydride acceptor in the reaction course. Exactly the opposite effect could be expected for imine **2d**. In this way, the first step of the reaction mechanism could be the Lewis acid-base interaction between boron trifluoride and the imine nitrogen. This proposition approximates with the accepted mechanism [1,8], when a DHP



Scheme 1. Reduction of imines **2b**–**2e** using DHP **1c**, under stoichiometric amounts of BF_3OEt_2, and the respective isolated yields of amines **3c**–**3e**. *nd: product not detected.



Scheme 2. A. Reductive amination of benzaldehyde and aniline using DHP **1c** under stoichiometric amounts of BF_3OEt_2 to produce amine **3a**. *one-pot, two-step procedure: under rt, benzaldehyde and aniline were mixed with 1 mL of CH_2Cl_2. The mixture was kept under stirring for 24 h. DHP **1c** and BF_3OEt_2 were then added. The resulting mixture was kept for further 24 h. **one-step procedure: under room temperature, benzaldehyde, aniline, DHP **1c** and BF_3OEt_2 were mixed in 1 mL and kept for 24 h. B. Attempted reduction of benzaldehyde to produce benzyl alcohol.

reacts with a mild oxidizing agent, namely, a catalyzed one-step hydride transfer.

The applicability of DHP **1c** was also evaluated under reductive amination conditions, specifically through one-pot, two-step and one-step procedures (Scheme 2A), which gave **3a** with 72% and 60% yield, respectively. A reaction conducted in the absence of aniline (Scheme 2B) was additionally performed, where benzyl alcohol (expected product) could not be detected, with the benzaldehyde utilized persisting after 24 h of reaction time. This result suggested that the selective reduction towards imine **2a**, with benzaldehyde remaining unreactive, was an important factor during the course of the one-pot reductive amination.

In conclusion, the present study was devoted to the comparison of four DHPs (**1a**–**1d**), which were employed as reducing agents of *N*-benzylideneaniline (imine **2a**). The DHPs evaluated presented distinct substitution with phenyl group at N-1 and C-4 positions of the DHP ring. Reduction reactions were based on the combination of each of the DHPs and BF_3OEt_2. The C-4-substituted DHPs (**1a** and **1b**) presented lower efficacies in promoting imine **2a** reduction in comparison with DHPs **1c** and **1d** (C-4 unsubstituted derivatives). By evaluating the amount of added BF_3OEt_2, we have found that DHP **1c** (substituted at the N-1) showed its best result when associated with stoichiometric amounts BF_3OEt_2, while the N1, C4-unsubstituted Hantzsch ester analogue (**1d**) was more effective with catalytic quantities of the Lewis acid. The reaction system constituted of stoichiometric amounts of BF_3OEt_2 combined with DHP **1c** could be also utilized for reduction of the *N*-benzylideneaniline analogues, imines **2c**–**2e**, and under reductive amination conditions.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151129.

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[23] Compound 1c: A mixture of methyl acetoacetate (2.15 g, 2.0 mL, 18.5 mmol), aniline (1.67 g, 1.7 mL, 18.5 mmol) and l-proline (0.4 g, 3.5 mmol) was stirred with 2 mL of methanol as solvent for 2 h in 55 °C. Then, paraformaldehyde (0.564 g, 18.5 mmol) and methyl acetoacetate were added (2.15 g, 2.0 mL, 18.5 mmol). The temperature of the reaction was raised to 70 °C under inert atmosphere. The reaction was kept under these conditions for 12 h. Afterwards, 7 mL of methanol was added and the reaction was refrigerated overnight to allow precipitation. The precipitate was filtered and washed with cold methanol. The final yield was 35%. 1H NMR (200MHz, CDCl3) δ (ppm) 7.43–7.12 (m, 5H); 3.72 (s, 6H); 3.38 (s, 2H); 1.92 (s, 6H). 13C NMR (101 MHz, CDCl3) δ (ppm) 168.8, 148.6, 141.0, 130.7, 129.50, 128.6, 125.1, 124.6, 101.6, 51.3, 25.0, 18.5. ESI-Q-TOF m/z calc, for [M+Na]+ C17H19NNaO4+ 324.1206; found 324.1215. IR: v max 2902 cm-1 (C-H), 1683 cm-1 (C=O), 1192 cm-1 (C-N).
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[31] In an appropriate flask imine was added (0.1 mmol), as well as the dihydropyridine 1c (30.1 mg, 0.1 mmol) and BF3Et2O (12 μL, 0.1 mmol). The reaction was stirred for 24 hours in room temperature. Afterwards, 5 mL of dichloromethane and 5 mL of NH4OH 10% were added and stirred. The organic phase was collected and filtered in anhydrous sodium sulfate. The solvent was completely removed under reduced pressure. The product was isolated using chromatographic plates with hexane/ethyl acetate 9:1 as eluent. The plates were observed under ultraviolet light and the region with the product was marked and collected. The product was extracted washing the collected silica with 50 mL of methanol. Finally, the solvent was removed under reduced pressure, isolating the corresponding product.
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