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1,4-Dihydropicolinic acid derivatives: novel NADH analogues with an altered connectivity pattern

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Abstract—Sodium dithionite reduction of α-substituted *N*-alkylpyridinium salts (derived from picolinic acid derivatives) afforded the corresponding 1,4-dihydropyridines with a new substitution pattern, in which the electron-withdrawing group is at the α-position. These compounds promote biomimetic reductions and are hence considered functional NADH analogues.

NADH is the cofactor used by many reductases in metabolism, and its reactive moiety is a 1,4-dihydropyridine (DHP) unit. Compounds based on this heterocycle play key roles in medicinal chemistry (as calcium channel blockers), organic synthesis (versatile intermediates) and bioorganic chemistry (NADH analogues), and have inspired several lines of research.[1] Considerable efforts have been devoted to the preparation of diversely substituted DHP derivatives, yet some substitution patterns with potential applications in the aforementioned fields remain elusive or simply unknown. This fact probably reflects the complexity of the factors that control the stability and the reactivity of these heterocyclic systems. The classic sodium dithionite reduction of *N*-alkylpyridinium salts is perhaps the most simple and reliable method for the regioselective formation of the corresponding 1,4-DHP derivatives.[2] These reactions are often conducted in basic medium, whereby the key step involves the nucleophilic attack of the sulfinic species upon the γ-position of the activated pyridinium salt.[3] For this reason, the process is restricted almost entirely to pyridinium salts bearing electron-withdrawing substituents at the β-position, as these salts are more electrophilic at C-4, and the resulting DHPs benefit from the conjugation of the nitrogen atom and the β-substituent.[4] However, this situation may not be a sine qua non requirement, and results of the reduction of pyridinium salts with stabilizing electron-withdrawing groups at the α-position are herein reported (Fig. 1). Albeit simple, the variation strongly affects the electronic properties of the heterocyclic system, consequently changing the structural and reactivity parameters of the new DHPs.[5]

The first experiments involved the reactivity of the *N*-methyl-2-methoxycarbonylpyridinium iodide (**1a**), which was readily prepared by interaction of MeI with methyl picolinate. The reduction of this compound under standard conditions (excess of $Na_2S_2O_4$ and $NaHCO_3$, CH_2Cl_2–H_2O, room temperature, 12 h) afforded a mixture of the DHP **2a** together with the piperidine derivative **3a** and unreacted salt. Modifications of stoichiometry and reaction time ultimately provided optimized protocols for the clean partial and total reductions of the heterocyclic system. Thus, upon

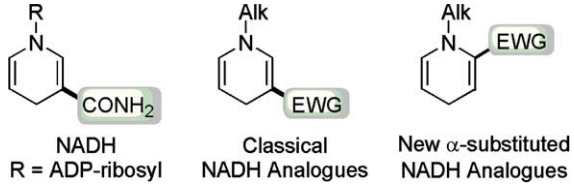

Figure 1.

Keywords: Dihydropyridines; Piperidines; NADH; Reduction; Sodium dithionite.
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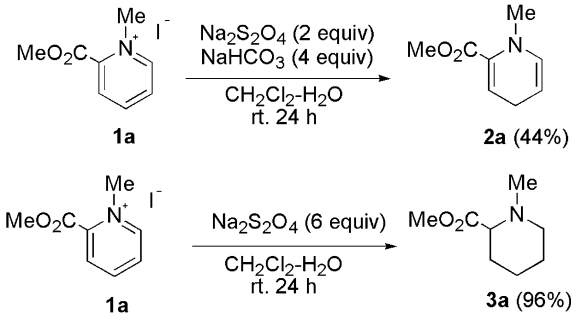


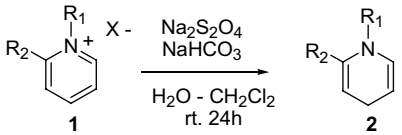
Scheme 1. Sodium dithionite reduction of pyridinium salt **1a**.

treatment with reduced amounts of sodium dithionite (2 equiv) for 24 h, the dihydropyridine **2a** (44%) was selectively obtained, whereas with a larger excess of the reducing agent, in the absence of $NaHCO_3$, piperidine **3a** (96%) was isolated as the only product (Scheme 1).

The α-substituted DHP **2a** was characterized spectroscopically. This compound is more prone to oxidation and acid-catalyzed decomposition than the well known β-substituted NADH analogues, nevertheless it could be conveniently stored under inert atmosphere at low temperature.[6] Although the reduction works well with different *N*-alkyl (methyl and benzyl) substituents at the nitrogen, it seems to be highly dependent on the nature of the substituent at the α-position of the pyridine ring. Thus, reduction under the usual conditions works with α-CO_2Me and $CONH_2$ groups (Table 1, entries 1 and 2), but not with α-H, Cl or alkyl groups. This is in agreement with the known requirements for the $Na_2S_2O_4$ of β-substituted pyridinium salts, however a CHO group fails to yield detectable amounts of DHP (Table 1, entry 3), probably due to its extended hydration under the reaction conditions.[7] Pralidoxime (**1d**, Table 1, entry 4) did not react under the same conditions.[8]

The transformation of salt **1e** under the usual conditions afforded a more complex mixture, hence the corresponding DHP (**2e**) was isolated in moderate yield (entry 5). The reactivity of the cyano derivatives merits separate commentary (vide infra).

Table 1. Reduction of α-substituted pyridinium salts **1**



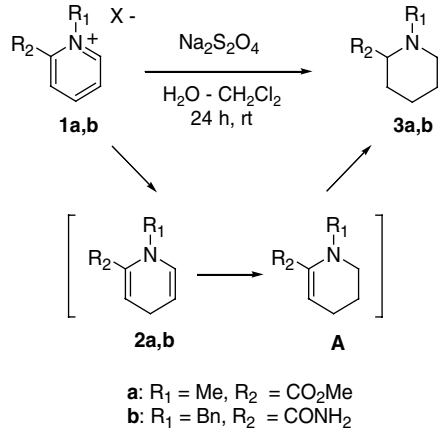
Entry	Pyridinium salt	R^1	R^2	Product	Yield[a] (%)
1	**1a**	Me	CO_2Me	**2a**	44
2	**1b**	Bn	$CONH_2$	**2b**	97
3	**1c**	Me	CHO	—	—
4	**1d**	Me	CH=NOH	—	—
5	**1e**	Me	CN	**2e**	58

[a] Isolated yield.

In some experiments of the previous series, the formation of small amounts of the corresponding piperidines **3** was observed when extended reaction times were used.[9] The full reduction of the starting heterocyclic systems was found to proceed more efficiently in the absence of $NaHCO_3$. In this way, piperidines **3a** (96%) and **3b** (45%) were prepared and positively identified.[10] We may consider, as a reasonable mechanistic hypothesis, that under these conditions, the initially formed DHPs (**2**) may undergo protonation from the increasingly acidic reaction medium to generate iminium ions, which would be reduced by the dithionite, to yield the reactive tetrahydropyridine intermediates, for instance **A**. These species, which could not be detected or isolated, would in turn undergo further reduction via conjugate dithionite addition to the activated double bond and subsequent protonolysis (see Scheme 2).

The reduction of the cyanopyridinium salt **1e** under these conditions surprisingly afforded the 2,6-dicyanopiperidine **4** (35%),[11] as a 7:1 mixture of *cis*/*trans* stereoisomers (see Fig. 2). Although no rigorous mechanistic studies were performed, a plausible explanation for this result might involve the formation of the expected α-cyanopiperidine, which, being an iminium ion precursor,[12] could expel a cyanide anion capable of adding to the protonated form of a DHP intermediate (type **2**, Scheme 2). Reduction of the resulting species would yield the dicyano structure **4**.

Interestingly, water acts as the hydrogen source in these reductive processes, which apart from environmental considerations,[13] enables the deuteration of the DHPs **2** and the piperidines **3**, simply by using D_2O. In this



Scheme 2. Pyridinium salt reduction to piperidines **3**.

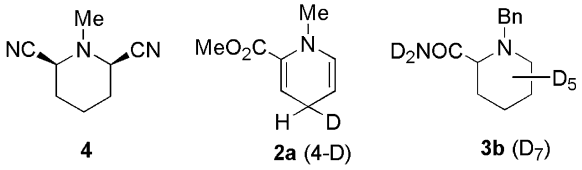
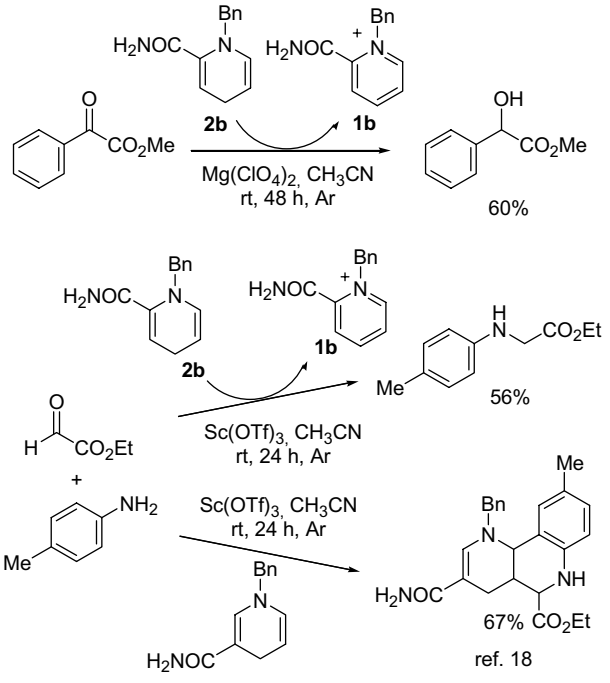


Figure 2.

way the deuterated analogues of **2a**[14,15] and **3b**[16] were efficiently prepared (Fig. 2). Remarkably, the last reaction allows the simultaneous incorporation of up to seven deuterium atoms (five C–D and two N–D bonds).

Finally, the ability of the new DHPs **2** to promote biomimetic reductions was preliminarily tested. Thus under standard conditions [Mg(II), CH_3CN][14a] **2b** was capable of reducing methyl benzoylformate to form methyl mandelate. Additionally, a reductive amination,[17] (*p*-methylaniline, ethyl glyoxalate) was carried out with DHP **2b** in the presence of $Sc(OTf)_3$ (Scheme 3). Interestingly these compounds seem to be comparatively more efficient reducing agents than the classic β-susbtituted 1,4-DHPs, as the latter behave as enamine derivatives leading to multicomponent reactions under the aforementioned conditions (see Scheme 3).[18] These results illustrate the dramatic influence of the substituent location at the DHP ring on its reactivity. The overall yield of these processes is moderate (≈60%) presumably because of the fragility of the DHPs and their tendency to spontaneously oxidize.[19] To the best of our knowledge, this is the first non-Hantzsch dihydropyridine, which promotes the biomimetic reductive amination.

In conclusion, access to a novel class of stable DHPs with an altered substitution pattern has been described. The synthetic process is simple, employs a cheap reducing agent and uses water as the proton source. In addition, modification of the reaction conditions permits the straightforward preparation of the corresponding piperidines and deuterated derivatives. The DHPs thus prepared can be considered as functional NADH analogues, as they promote the same type of biomimetic carbonyl and imine reductions as NADH. Further applications of these DHPs are currently under investigation.



Scheme 3. Biomimetic reductions promoted by the new DHPs **2**.

Acknowledgements

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Supplementary data

A supplementary data section is provided, which includes the experimental procedures and characterization data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.03.069.

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4. Some exceptions, however, are reported in the literature, although the DHPs lacking electron-withdrawing groups are very unstable. See Marazano's approach to chiral dihydropyridines: Wong, Y.-S.; Marazano, C.; Gnecco, D.; Génisson, Y.; Chiaroni, A.; Das, B. C. *J. Org. Chem.* **1997**, *62*, 729; For a Birch-type approach, see: De Konig, A. J.; Budzelaar, P. H. M.; Brandsma, L.; De Bie, M. J. A.; Boersma, J. *Tetrahedron Lett.* **1980**, *21*, 2105.
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6. DFT calculations (B3LYP; basis set 6-31G*) show that **2a** is about 8.7 kcal/mol less stable than the corresponding β-substituted isomer. Remarkably, the steric interaction between the *N*-methyl and the methoxycarbonyl groups seems to force a nonplanar alignment of the enamine moieties of the heterocyclic ring, resulting in a significant loss of conjugation.
7. The ^{1}H NMR spectrum in DMSO-d_6 of the 2-formyl-1-methylpyridinium iodide shows a 1:1 equilibrium between the carbonyl and the hydrate forms, which should presumably be totally shifted towards the *gem*-diol in water, thus deactivating the pyridinium salt.
8. Although a lenghty route for a putative 1,6-dihydropralidoxime has been described, the 1,4-dihydro derivative is

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12. The dithionite reduction of this iminium ion would afford the *N*-methylpiperidine, which was detected.
13. Catalytic (Pd, PtO_2, etc.) hydrogenation is the standard procedure for reduction of pyridinium salts to piperidines.
14. The use of deuterated NADH analogues is useful for studying the hydride transfer mechanism. See, for instance: (a) He, G.-X.; Blaskó, A.; Bruice, T. *Bioorg. Chem.* **1993**, *21*, 423; (b) Zhu, X.-Q.; Cao, L.; Liu, Y.; Yang, Y.; Lu, J.-Y.; Wang, J.-S.; Cheng, J.-P. *Chem. Eur. J.* **2003**, *9*, 3937.
15. Incidentally, the spontaneous (oxygen promoted) oxidation of the deuterated DHP **2a** (4-D), afforded a nearly quantitative yield of the corresponding pyridinium salt, bearing a deuterium atom at the γ-position [**1a** (4-D)], which could be considered as a labeled NAD^+ analogue.
16. Presumably as a mixture of isotopomers. For the deuterium transfer reduction of pyridines using deuterated ammonium formate, see: Derkau, V. *Tetrahedron Lett.* **2004**, *45*, 8889.
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19. Although DHPs **2** rapidly decompose in open air, the NMR spectrum of a DMSO-d_6 solution of **2a** remains unchanged after 7 days at rt.