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Productive trapping of NAD-type radicals. Non-biomimetic reduction of pyridinium salts†

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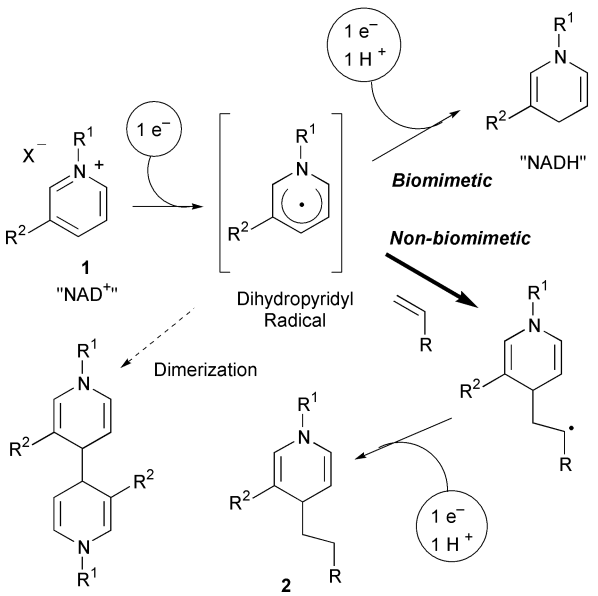
One-electron reduction of pyridinium salts (NAD+ analogues) generates dihydropyridyl radicals which may then be engaged in radical addition processes to regioselectively form γ-substituted dihydropyridines.

The NAD+–NADH interconversion plays a vital role in metabolism, promoting many enzyme mediated redox processes. This has stimulated several lines of research, which have dealt mainly with mechanistic aspects of this transformation, synthetic analogues of the cofactors, and the biological chemistry of oxidoreductases. Although evolution has selected these compounds almost exclusively for electron transfer purposes, the rich chemistry of pyridinium salts and dihydropyridines suggests there are alternative transformations with potential use in organic synthesis.[1]

In recent years, we have developed what we call the *non-biomimetic* oxidation of dihydropyridines.[2] In these reactions, the oxidation of the heterocyclic system takes place through bonding with electronegative atoms (by-passing the usual hydride transfer) and a wide variety of functionalized tetrahydropyridines are now available using this technique.

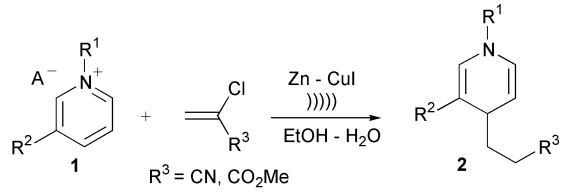
Following a complementary approach, we envisaged the *non-biomimetic* reduction of pyridinium salts **1**, which would involve the interception of the intermediate radical, formed by SET, through addition to activated alkenes to yield the substituted dihydropyridines **2** (Scheme 1).[3]



Scheme 1

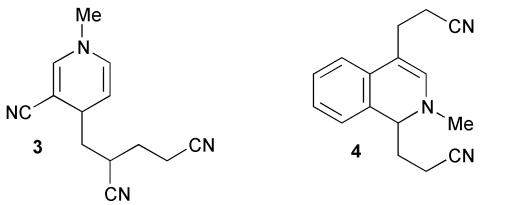
Although the reductive generation of dihydropyridyl radicals by chemical or electrochemical methods has been described, to our knowledge the formal dimerization of these reactive intermediates was the exclusive outcome of such processes.[4,5] After much experimentation—involving a combination of different reducing agents (Mg, Cu, Cu+, In,[6] Fe, Zn), solvents, buffers, additives, azinium salts and activated alkenes— the only successful processes were achieved by interaction of the NAD+ analogues (salts **1**) with chloroacrylonitrile (acrylates being unreactive, and fumarates being reduced to succinates), in the presence of a Zn–CuI couple in a EtOH–H_2O medium under sonochemical activation (Scheme 2).

Thus pyridinium salt **1a** reacted with chloroacrylonitrile under the above conditions to regioselectively produce 1,4-dihydropyridine **2a** as a slightly unstable oil in 60% yield (based on consumed pyridinium salt) together with mixtures of dihydropyridine dimers.[4] The mechanism probably involves the expected one-electron reduction of the salt, and the addition of the nucleophilic dihydropyridyl radical to the electrophilic alkene. Reduction of the resulting radical, proton abstraction (from the solvent) and Zn-promoted cleavage of the C–Cl bond, complete the transformation.[7] The isolation of byproduct **3** (5%) lends additional support to this hypothesis. The presence of the chlorine atom at the α-position of the π-acceptor may facilitate the addition step by activation of the olefin and/or stabilization of the newly-formed radical through the captodative effect; on the other hand, the regioselectivity of the reaction, affording γ-addition products‡ may deal with the higher spin density of the dihydropyridyl radicals at position 4.[8] The reaction seems to be quite general, tolerating different electron-withdrawing groups at the β-position and methyl or benzyl substituents at the heterocyclic nitrogen. Methyl chlor-



a R^1 = Me R^2 = CN
b R^1 = Me R^2 = CO_2Me
c R^1 = Bn R^2 = $CONH_2$
d R^1 = Me R^2 = COMe

a R^1 = Me R^2 and R^3 = CN
b R^1 = Me R^2 = CO_2Me R^3 = CN
c R^1 = Me R^2 and R^3 = CO_2Me
d R^1 = Bn R^2 = $CONH_2$ R^3 = CN
e R^1 = Me R^2 = COMe R^3 = CN



Scheme 2

† Electronic supplementary information (ESI) available: experimental procedure and characterization data. See: http://www.rsc.org/suppdata/cc/b2/b201813f/

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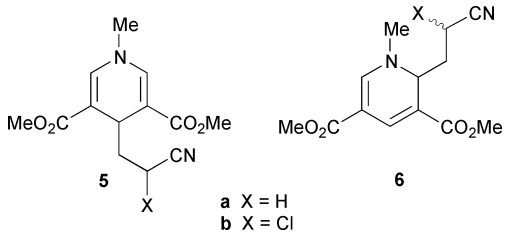
oacrylate was also a good substrate for this kind of addition. Therefore **2b** (62%, based on consumed pyridinium salt),§ **2c** (47%), **2d** (57%) and **2e** (65%) were prepared using the same protocol. Non-activated pyridinium cations (for instance 1-methylpyridinium iodide) failed to react under these conditions. However, *N*-methylquinolinium iodide afforded a complex mixture of unstable enamines which could not be purified, while *N*-methylisoquinolinium iodide gave the dihydroisoquinoline **4** (58%) which incorporates two acrylonitrile units. The one located at C-1 arises from the expected radical addition, while the second (at C-4) is probably the result of an electrophilic addition of acrylonitrile taking place upon the enamine moiety of the initially-formed dihydroisoquinoline.¶

Some features of these reactions deserve additional comment. The isolation of the resulting dihydropyridines **2** (minor losses were observed during chromatography) did not constitute a serious problem, as they are much more stable than other substrates lacking the β-electron-withdrawing substituents.[3b,c] The efficiency of the process, from a preparative point of view, remains somewhat limited. Attempts to improve it by using excesses of Zn–CuI and/or olefin, longer reaction times, and/or slow co-addition of the alkene and the salt to the reaction vessel were unsuccessful. In all these conditions, the unreacted pyridinium salt accounted for 60% to 75% of the initial amount. An attempt was also made to carry out the reaction under electrochemical conditions,‖ rather than by using a chemical reducing agent, but no defined products were extracted from the resulting solution after exhaustive electrolysis. Assays to promote intramolecular addition processes (Zn-mediated reactions of *N*-allyl- or *N*-homoallylnicotinium salts, and β-allyloxycarbonylpyridinium halides) resulted in failure: the desired reductive cyclization was not observed and only dihydropyridine dimers were produced.[6]

On the other hand, the overall yield in the transformation of 1-methyl-3,5-dimethoxycarbonylpyridinium salt was higher (80%), although with lower regiocontrol, affording nearly equal amounts of the γ- and α-addition products (**5a**, 38% and **6a**, 36% respectively). In this reaction, the halogenated precursors **5b** (6%) and **6b** were also detected (Scheme 3).



Scheme 3

The results described above demonstrate the feasibility of trapping the dihydropyridyl radical intermediates through the addition to electron-deficient olefins. This new *non-biomimetic* reduction constitutes an *umpolung* procedure, reversing the natural electrophilicity of pyridinium salts at the γ-position, and allows nucleophilic (radical in nature) reactions at this point to be carried out in a polar (aqueous) environment.**

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Notes and references

‡ Traces of the regioisomeric α-substituted-1,2-dihydropyridines were detected by NMR in the crude reaction mixtures.

§ Determined by UV spectrophotometry by absorption of salt solutions (monitored at the peak located at λ_{max} around 220 nm) in a linear response concentration range.

¶ This compound [1-(2-cyanoethyl)-2-methyl-1,2-dihydroisoquinoline] was isolated in minute amounts ($\approx 1\%$). ^{1}H NMR ($CDCl_3$) δ 7.18 (m, 2H), 6.93 (m, 2H), 6.06 (d, J = 6.6 Hz, 1H), 5.21 (d, J = 6.6 Hz, 1H), 4.45 (m, 1H), 2.99 (s, 3H), 2.35 (m, 1H), 2.18 (m, 2H), 1.86 (m, 1H); MS (EI) *m/z* (%) 198 (M+, 10), 197 (30), 146 (100).

‖ A controlled-potential electrolysis of salt **1c** in a DMF–H_2O (1 : 1, v/v) with olefin (inert) and 0.1 M Na_2SO_4 (background electrolyte) was carried out in a three-compartment cell containing a Pt cathode, a Pt anode and a SCE as a reference electrode. The solution was deoxygenated with Ar and maintained under magnetic stirring. The reduction potential applied to the cathode was −1.30 V *vs*. SCE, a value slightly more negative than the cathodic peak potential of −1.03 V *vs*. SCE determined for the irreversible peak of **1c** in the same medium by cyclic voltammetry at a scan rate of 50 mV s^{-1}.

** The classical approach involves organometallic additions to the γ-position of the pyridinium salts, with the well-known restrictions in terms of solvent and functional group incompatibilities.

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7 The reaction must closely resemble the sonochemical additions of alkyl halides to conjugated carbonyls, developed by Luche: C. Einhorn, J. Einhorn and J.-L. Luche, *Synthesis*, 1989, 787; P. Cintas and J.-L. Luche in *Synthetic Organic Sonochemistry*, ed. J.-L. Luche, Plenum Press, New York, 1998, chapter 5; J.-L. Luche and L. A. Sarandeses in *Organozinc Reagents*, eds. P. Knochel and P. Jones, Oxford University Press, Oxford, 1999, chapter 15. For the reductive cleavage of carbon-halide bonds, see: P. Knochel, in *Encyclopedia of Reagents for Organic Synthesis*, ed. L. A. Paquette, Wiley, Chichester, 1995, vol. 8, p 5526.

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