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Preparation of β-hydroxyesters from isoxazolines. A selective Ni^0bpy-catalyzed electrochemical method

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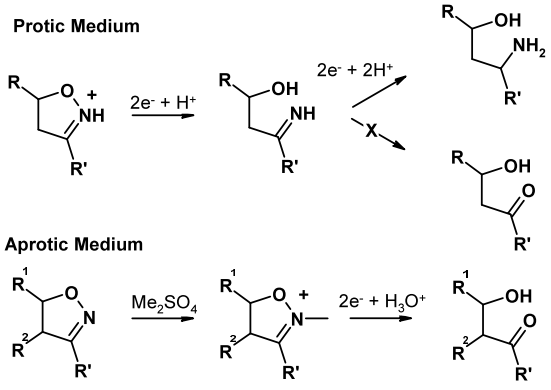
Abstract—An electrocatalytic method for the reductive *N–O* cleavage of isoxazolines is described. Ni^0bpy, generated in situ, was used to promote selective ring opening of 3-methoxy-5-phenylisoxazoline (**1a**) and 3-methoxy-[4,5]cyclohexylisoxazoline (**1b**). DMF and NaI were used as solvent and supporting electrolyte, and β-hydroxyesters **2a** and **2b** were obtained in high yields respectively, after acid hydrolysis. β-Hydroxynitriles **3a** and **3b** were also identified as side products.

Isoxazolines have been used as key intermediates in the synthesis of bioactive molecules.[1–4] Heterocyclic ring opening gives access to many important functional groups, especially β-hydroxynitriles,[2] -ketones[3,7,8] and -esters.[4] These occur in many natural products of interest, and are usually obtained by aldol condensation of ketones and aldehydes often compromising selectivity however.

Torsell[5] has developed a synthetic route to β-hydroxyketones via isoxazolines expanding the method to other β-hydroxycarbonyl compounds as well. Cycloaddition reactions between readily available olefins and nitrile oxides furnish excellent yields of the requisite isoxazolines under very mild conditions.[4,6] Tri-substituted olefins can be used routinely. The major disadvantage of this approach is the sensitivity of other functionalities to the catalytic hydrogenolysis typically employed for the subsequent reductive cleavage of the isoxazolines.[3,4,7,8] In spite of these disadvantages, isoxazolines are routinely employed as precursors in natural product synthesis. Furthermore alternative methods have been employed for isoxazoline *N–O* bond cleavage, using transition metal complexes, for example.[7,8]

Surov and Lund[9,10] described the electrochemical reduction of isoxazolines (Scheme 1) and isoxazoles. In protic solvents, *N–O* bond cleavage is observed, followed by reduction of the intermediate azomethine, giving β-hydroxyamines as the principal products. β-Hydroxyketones, on the other hand, were obtained in aprotic solvents by prior quaternization of the isoxazolines, followed by electrochemical reductive cleavage. Although attractive as an alternative to hydrogenolysis, this direct electrochemical process has some potential disadvantages such as: elevated reduction potential, lack of selectivity in the presence of reducible groups and the use of a two-compartment cell making the procedure cumbersome.



Scheme 1. Electrochemical *N–O* bond cleavage of isoxazolines in protic and aprotic media.[9,10]

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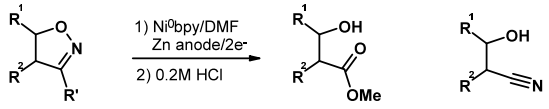
The Ni^0–bipyridine complex (Ni^0bpy) has been employed as a catalyst in homo- or heterocoupling reactions of aryl halides.[11,12] The process involves a catalytic cycle with successive reductions of intermediates,[13] which may be performed by using an electrochemical system,[11] or an easily oxidizable transition metal,[14] as a source of electrons. A reductive cleavage of the Ar–*X* bond (*X*=Cl or Br) occurs in the first step involving the Ni^0bpy complex:

$$Ni^0bpy + Ar\text{-}X \rightarrow Ni^{II}bpyArX$$

We reasoned that application of such a rationale, in which a nickel complex acts as the actual electron source, to the electrochemical reduction of isoxazolines could result in a much milder protocol, which would obviate the problems of high reduction potential and over-reduction to β-hydroxyamines. In the event, the electrocatalytic isoxazoline *N–O* bond cleavage was successfully carried out using Ni^0bpy in DMF with 0.1 M NaI as supporting electrolyte and a zinc rod as sacrificial anode in an undivided cell. The reduction, occurring at around 2.5 V cell potential (–0.4/–0.6V versus Ag/AgCl cathodic potential), completely avoided the direct electrochemical reduction of the (presumed) azomethine intermediate.

Table 1 shows the results obtained from electrocatalytic *N–O* bond cleavage[16] of 3-methoxy-5-phenylisoxazoline (**1a**), 3-methoxy-[4,5]cyclohexylisoxazoline (**1b**) and 3-bromo-5-phenylisoxazoline (**1c**).

Several Ni^0bpy concentrations (7–100%) were tested and uniformly high reduction yields were obtained.



1a: R^1 = Ph, R^2 = H, R' = OMe
1b: R^1/R^2 = -$(CH_2)_4$-, R' = OMe
1c: R^1 = Ph, R^2 = H, R' = Br

2a,b **3a,b**

Table 1. Electrocatalytic isoxazoline *N–O* bond cleavage using Ni^{II}bpy, DMF, 0.1 M NaI and a sacrificial Zn anode.[16] A constant current of 100 mA was applied[a]

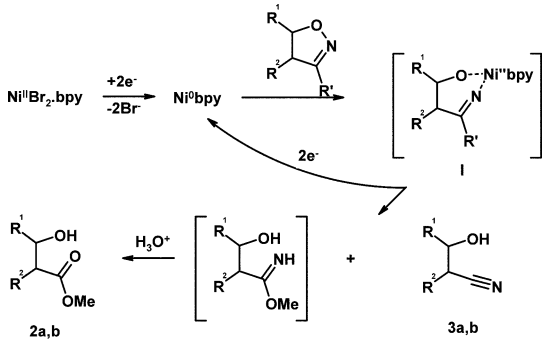
Entry	Isoxazoline (56.5 mM)	Ni^{II}bpy (%)	Yield (%)[d,e]	**2**:**3**[e]
1	**1a**	7	90	4:1
2	**1a**	15	99	1.9:1
3	**1a**	30	90	2.2:1
4	**1a**	100	99	13:1
5	**1b**	7	98	1.7:1
6	**1b**	100	99	9:1
7	**1c**	7	100	0:1
8[b]	**1a**	7	100	3:1
9[c]	**1a**	7	23	2.3:1

[a] The reaction was conducted under N_2.
[b] Acetonitrile was used as solvent.
[c] An iron bar was used as sacrificial anode.
[d] Isolated yields were uniformly >90%.
[e] Determined by GC analysis.

Although appreciable amounts of β-hydroxynitrile **3a**/**3b** were formed in the catalytic procedures (entries 1–3, 5), the yields of desired β-hydroxyesters **2a** and **2b** were very good compared to the yields of theses products obtained by Ra–Ni hydrogenolysis[4] (62–72% versus 76%-**2a** and 62% versus 32%-**2b**). The exclusive formation of nitrile **3a** (entry 7) from the bromoisoxazoline precursor **1c** can be attributed to the better leaving group ability of bromide as compared to methoxy. Hence elimination of bromide (R′=Br) from the proposed Ni^{II}–chelate intermediate **I** forms **3a**, (see below).

If the Ni^0bpy complex is indeed the electron source for the reductive *N–O* cleavage, a reaction employing a stoichiometric equivalent of the complex in the absence of current should also work. This is indeed the case, although the yields are slightly lower (**2a**, 82%). However, when one equivalent of the $Ni^{II}Br_2$·bpy complex and the substrate were subjected concurrently to 2 F/mol in the same way as in the catalytic procedures (entries 4 and 6), not only did we obtain excellent yields of reduced products, but the proportions of desired β-hydroxyesters were much higher.

A possible mechanism is suggested in Scheme 2. A nickel complex chelate intermediate **I** is formed by oxidative insertion of Ni^0bpy (formed from the employed Ni^{II}(bpy)Br_2 by two-electron reduction) into the *N–O* bond. This stabilizes the oxy-azomethine formed after reductive ring cleavage. The continuous passage of electrons however regenerates Ni^0bpy for the catalytic cycle. A charge of 1.1 to 2.0 F mol^{-1} was passed, until complete consumption of the substrate. The β-OH-esters **2a**/**b** are obtained at the end, after acid hydrolysis during work-up. We believe that the ratio of β-OH-ester to β-OH-nitrile products (**2**:**3**) for a given isoxazoline is related to the solvent and the stability of the hydroxy-azomethine intermediate in the reaction medium. This may explain why the best results were obtained when 1 equiv. of Ni^0bpy was used as reductant (entries 4 and 6). In this case the stabilized nickel–oxyazomethine chelate is not deprived of nickel entering back into the catalytic cycle. Some reactions were carried out in acetonitrile (entry 8) and the yield of β-OH-ester was the same as in DMF. Iron was also tested as a sacrificial anode (entry 9). In this case the reaction did not go to completion, stopping at about 25% consumption of starting material and giving a



Scheme 2. Electrocatalytic reductive *N–O* bond cleavage of isoxazolines using Ni^0bpy as catalyst.

lower proportion of β-OH-ester. Probably iron forms a stable complex with the isoxazoline impeaching the Ni^0bpy catalytic effect.

A complete mechanistic study and determination of ideal reaction parameters for this reaction is under way.

3-Methoxy-5-phenylisoxazoline (**1a**):[4] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23–7.32 (m, 5H), 5.54 (dd, $J=10.9$ Hz, 1H), 3.88 (s, 3H), 3.24 (dd, $J=16.10$ Hz, 1H), 2.91 (dd, $J=16.9$ Hz, 1H). MS: *m*/*e* 177 (39), 132 (100), 105 (36), 77 (30).

3-Methoxy-[4,5]cyclohexylisoxazoline (**1b**):[4] ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.54 (dt, $J=11$, 9 Hz, 1H), 3.86 (s, 3H), 2.87 (dt, $J=11.9$ Hz, 1H), 1.9–1.2 (m, 8H). MS: *m*/*e* 155 (6), 124 (10), 69 (68), 43 (100).

3-Bromo-5-phenylisoxazoline (**1c**):[4] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.46 (m, 5H), 5.7 (dd, $J=11$, 9 Hz, 1H), 3.66 (dd, $J=17$, 11 Hz, 1H), 3.25 (dd, $J=17$, 9 Hz, 1H). MS: *m*/*e* 225/227 (58), 128 (39), 115 (32), 105 (100).

Methyl 3-phenyl-3-hydroxypropanoate (**2a**):[17] oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24–7.18 (m, 5H), 4.98 (dd, $J=4$, 9 Hz, 1H), 3.69 (s, 1H), 3.50 (s, 3H), 2.56 (ddd, $J=4$, 9, 16 Hz, 2H). MS: *m*/*e* 180 (27), 163 (28), 120 (25), 107 (100), 79 (85), 77 (61).

Methyl hexahydrosalicylate (**2b**):[18] oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.18 (dt, $J=11$ Hz, 1H), 3.68 (s, 3H), 2.52 (dt, $J=11$ Hz, 1H), 1.9–1.2 (m, 8H). MS: *m*/*e* 158 (1), 127 (7), 130 (30), 87 (100), 81 (31), 55 (36).

3-Phenyl-3-hydroxypropanecarbonitrile (**3a**):[19] oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26–7.20 (m, 5H), 4.80 (t, $J=6$, 3 Hz, 1H), 3.60 (s, 1H), 2.54 (d, $J=6$ Hz, 2H). MS: *m*/*e* 148 (16), 130 (6), 118 (9), 107 (68), 79 (100), 51 (34).

2-Cyanocyclohexanol (**3b**):[20] oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.10 (dt, $J=10$ Hz, 1H), 2.51 (dt, $J=10$ Hz, 1H), 1.9–1.2 (m, 8H). MS: *m*/*e* 125 (10), 99 (9), 85 (40), 71 (72), 57 (67), 43 (100).

Acknowledgements

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16. The controlled current preparative electrolyses were carried out in undivided cells of 15 mL capacity. A zinc rod of 0.8 cm diameter and nickel foam (10 cm×4 cm, Nitech) were used as sacrificial anode (immersed >1 cm in solution) and working electrode, respectively (Ni foil or bar can also be used). The Ni electrode can be reused about 20 times, after cleaning with a 6 M HCl solution after each application. The same solution was used to clean the anode. For experiments involving Ni^0bpy as catalyst, the precursor $Ni^{II}(bpy)Br_2$ was prepared separately according to the literature.[15] The electrolytic cell was charged under nitrogen with 15 mL DMF containing 100 mM NaI. The isoxazoline (56.5 mM) was mixed with $Ni^{II}(bpy)Br_2$ in 5 mL of solvent and then added to the cell. A constant current (100 mA) was applied until full consumption of the starting reagent ($Q=175$). (In experiments using 1 equiv. of Ni complex a charge of 320 C was passed, and stirring continued for 2 h before work-up). The solvent was removed at reduced pressure and the residue was dissolved in diethyl ether, washed thoroughly with five portions of 0.2 M HCl solution, dried with Na_2SO_4,

filtered and concentrated in vacuo. The product ratios were determined by GC analysis using a Varian 3380 chromatograph, fitted with a 30 m capillary CP-SPL5CB Chrompack column, using a 60–200°C temperature ramp (20°C min^{-1}). The mixture of products was purified by silica gel column chromatography using hexane/ethyl acetate (3:2).

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