Pergamon

Tetrahedron Letters, Vol. 38, No. 23, pp. 4075-4078, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00827-7

Anodically Induced Cycloaddition of Vinylethylether to *N*-Cyanomethyl-Oxazolidine System. Stereoselective Synthesis of β-Amino Ketal Compounds.

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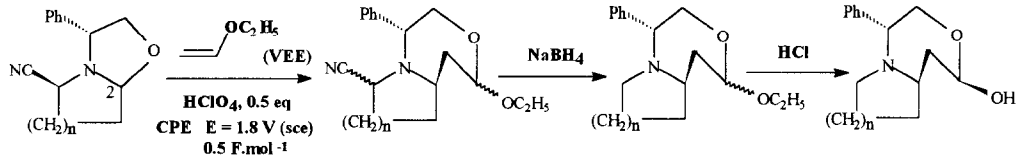
Abstract: The anodic oxidation of *N*-cyanomethyloxazolidine system **1** initiates an electrocatalytic cycloaddition of vinylethylether at the *N,O* acetal function and affords, after $NaBH_4$ reduction and acid hydrolysis, the corresponding enantiomeric pure bicyclic ketal **4**.

In recent papers[1,2] we have described the anodic oxidation of *N*-cyanomethyl-oxazolidine derivatives **1**. We postulated that an electrogenerated radical cation was a key intermediate in these reactions. In order to confirm this hypothesis and to develop electrochemical routes from **1**, based on the regioselective oxidation at the *N,O*-acetal function, we undertook the anodic oxidation of derivatives **1** in presence of vinylethylether (*VEE*). Indeed, it has been reported that *VEE* can undergo addition to radical species, generated by anodic oxidation of anions[3-5] or to iminium ion generated by electrooxidation of hydrazine compounds[6].

The controlled potential electrolysis (CPE) of **1** (E = 1.8 V vs s.c.e.), at a platinum electrode in acetonitrile, using *VEE* as reactant, perchloric acid as proton donor and lithium perchlorate as supporting electrolyte, led to the corresponding ketal **2** as a mixture of a number of diastereomers (four from **1a** and two from **1b** or **1c**). Upon sodium borohydrure reduction **2a** and **2b** furnished respectively **3a** and **3b** as a mixture of two diastereomers. The hydrolysis in hydrochloric acid of **3a** and **3b** afforded a single isomer **4a**[7] or **4b**[8] in 45% overall yield from **1a** or **1b**. With **2c**[9] reduction and hydrolysis treatment provided only tarry materials.



1a (n = 2, 2R)
1b (n = 1, 2S)
1c (n = 0, 2R)

2a (4 isomers), 75%
2b (2 isomers), 75%
2c (2 isomers), 52%

3a (2 isomers), 90%
3b (2 isomers), 90%

4a (1 isomer), 70%
4b (1 isomer), 70%
$[\alpha]_D$ -52.6 ($CHCl_3$, c 0.83)

Scheme 1

The new carbon-carbon bond formation, which took place during the electrochemical step, was highly stereoselective, since the ketal **2a** (or **2b**) was isolated as a mixture of four (or two) diastereomers but the elimination of the cyanide group halfed the number of isomers and hydrolysis of acetal centre led to a single isomer **4a** (or **4b**) (Scheme 1).

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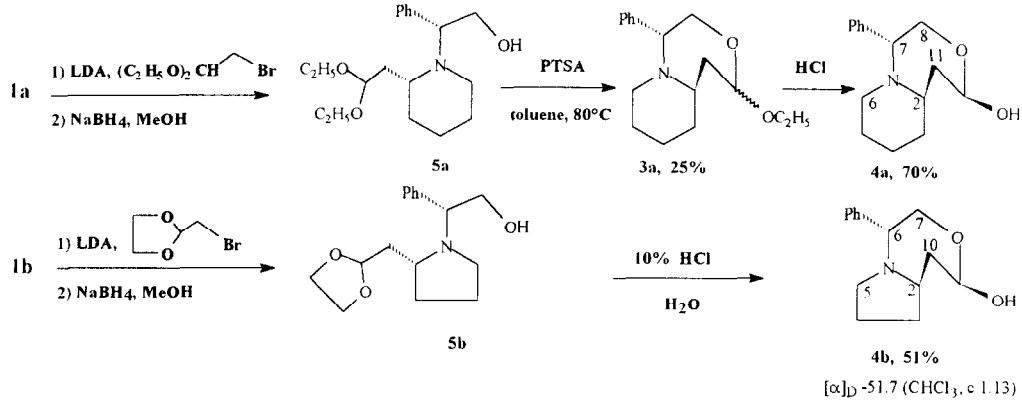
The absolute configuration at the newly created chiral centre of **4a** (and **4b**) was assessed by chemical correlation. We recently reported[10] the preparation of enantiomerically pure (2R)-ketal **5a** (and (2R)-ketal **5b**) from **1a** (and **1b**) *via* an alkylation/reduction sequence. These ketals were easily transformed to **4a** and **4b** identical in all aspects to the compounds obtained *via* the electrochemical route[11].



Scheme 2

Concerning the mechanistic pathway of the electrochemical step different experimental facts should be underlined:

(a) the small amount of electricity (0.5 electron per mole), required for this reaction, suggests a chain process initiated by a single electron transfer.

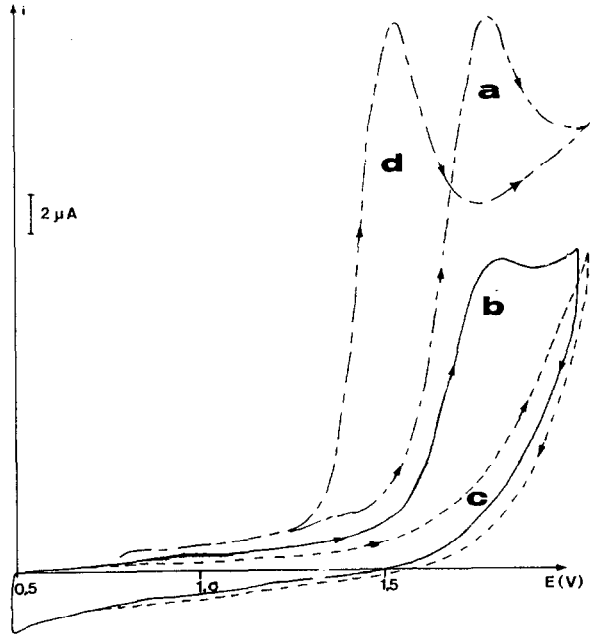


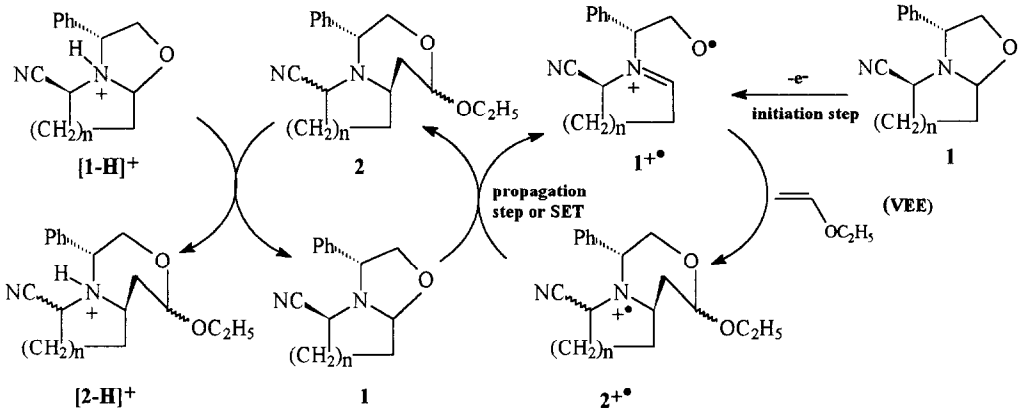
Figure: Cyclic voltammograms at a 0.14 $V.s^{-1}$ potential scan rate in CH_3CN containing $LiClO_4$ ($5x10^{-2}$ mol L^{-1}) of: a solution of **1a** ($2.5x10^{-3}$ mol L^{-1}) (curve a — - —), a mixture of **1a** ($2.5x10^{-3}$ mol L^{-1}) and $HClO_4$ ($1.25x10^{-3}$ mol L^{-1}) (curve b ——), the electrolysis mixture at the end of the oxidation (0.5 electron per mole) (curve c - - - -), and electrolysis mixture after addition of pyridine ($2.5x10^{-3}$ mol L^{-1}) (curve d — - - —).

(b) although **2** was not an authentic oxidation product *versus* **1**, the electrochemical step was essential to its formation since in the absence of anodic oxidation compound **1** did not react with *VEE* under various acidic conditions.

(c) the anodic oxidation of **1a** has been followed by cyclic voltammetry (CV) as shown in Figure. In an acetonitrile solution and presence of lithium perchlorate, **1a** exhibited an oxidation peak at 1.8 V(sce) (curve a). After addition of 0.5 equivalent of perchloric acid the anodic peak decreased by half since 50% of **1a** was in a non-oxidizible protonated form **[1a-H]**$^+$ (curve b). At the end of the reaction no more product could be detected (curve c) but after addition of 1 equivalent of pyridine a new peak was recorded at 1.5 V(sce) (curve d). This signal corresponded to the oxidation of compound **2a** as indicated by CV of a solution of this compound after isolation and purification. This means that after exhaustive electrolysis of **1a**, in presence of *VEE* and perchloric acid, the cyclic adduct **2a** obtained was in a protonated form **[2a-H]**$^+$.

Scheme 3 shows a postulated electrocatalytic mechanism for the formation of ketal **2** based on numerous reported examples[12-16]. The different steps can be detailed as follows: the initially formed radical cation $1^{+\bullet}$ (**initiation step** of the process) reacts with *VEE* to form a new cyclic radical cation $2^{+\bullet}$ which then accepts an electron from **1** to initiate a new cycle (**propagation step** or SET). On the other hand, a proton exchange between **[1-H]**$^+$and **2**, which is more basic than **1**, afforded the final protonated product **[2-H]**$^+$.

Although the anodic oxidation of **2** occurs at a lower potential than **1** (Figure), the thermodynamically unfavourable electron exchange between $2^{+\bullet}$ and **1** was then rendered possible due to a fast protonation step that followed the SET. This latter step constituted the driving force of the reaction and prevented the overoxidation of **2**. Besides the amount of acid (0.5eq) introduced at the beginning of the electrolysis (Figure, curve b), the same amount (0.5eq) was electrogenerated by oxidation of residual water, solvent or electrolyte support which then permited the quantitative protonation of **2** (Figure, curve c). Indeed this proton electrogeneration would be mainly responsible for the observed consumption of electricity (0.5 electron per mole), thus a very small quantity of electricity was used for the oxidative process of **1** in accordance with the proposed catalytic mechanism.



Scheme 3

The occurrence of this electrolytic oxidative coupling is consistent with the previously reported[2] hypothesis which postulated the formation of a radical cation species during the anodic oxidation of *N,O*-acetal function of synthon **1**. In addition this stereoselective addition of *VEE* to anodically generated radical constituted an alternative route *versus* chemical method to afford ketal compounds which are useful intermediates in the synthesis of piperidine or pyrrolidine alkaloids[10]. However, it should be mentioned that the electrochemical route preserves the α-aminonitrile function which might be used for subsequent alkylation or oxidation reactions[17].

Acknowledgements: The authors wish to thank Professors M.-B. Fleury and H.-P. Husson for their interest in this work and valuable discussions.

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7. a typical procedure is as follows: 2-cyano-6-oxazolopiperidine **1a** (0.114g; 0.5 mmol) was dissolved in dry acetonitrile (200 mL) containing lithium perchlorate (1.06g; 10 mmol) as supporting electrolyte and perchloric acid (0.5 mL of a solution 0.5 mol L^{-1} in acetonitrile; 0.25 mmol). The resulting solution was oxidized, at a platinum electrode, under nitrogen, at 5°C using a two compartments cell while vinylethylether (1 mL; 10 mmol) was added slowly to the electrolysis mixture. After exhaustive electrolysis, the solvent was distilled off and the residue was diluted in CH_2Cl_2 (50 mL) and washed with water (2x20 mL). The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The crude product obtained was then dissolved in ethanol (10 mL) and $NaBH_4$ (200mg; 5.3 mmol) added. The reaction mixture was stirred at room temperature for 15h, H_2O (20 mL) was added, and the mixture extracted with CH_2Cl_2. The combined extracts were concentrated and the residue was treated with hydrochloric acid (5 mL of a 5 mol L^{-1} solution) for 20h at room temperature. After neutralization with solid Na_2CO_3, extraction with ethyl acetate and evaporation of organic layers, the crude product was purified by flash chromatography (ethyl acetate:cyclohexane; 3:7) to give the bicyclic ketal **4a** (55mg; 45% overall yield from **1a**) as white crystals: mp 96 °C; $[\alpha]_D^{20}$ -30.3° (CH_2Cl_2, c 1.0); MS m/z 248 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.1-1.7 (m, 6H, C<u>H</u>$_2$-3, C<u>H</u>$_2$-4, C<u>H</u>$_2$-5); 1.8-2.0 (m, 2H, C<u>H</u>$_{(ax)}$-6, C<u>H</u>$_{(eq)}$-11); 2.3-2.5 (m, 2H, C<u>H</u>$_{(ax)}$-11, C<u>H</u>-2); 2.65 (d, 1H, J = 12.0 Hz, C<u>H</u>$_{(eq)}$-6); 3.25-3.40 (m, 3H, C<u>H</u>$_{(eq)}$-8, C<u>H</u>$_{(ax)}$-7, OH); 4.15 (dd, 1H, J = 15.0, 11.0 Hz, C<u>H</u>$_{(ax)}$-8); 5.25 (dd, 1H, J = 10.0, 5.0 Hz, C<u>H</u>-10); 7.2 (m, 5H, Ar-7); ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm): 24.6 (<u>C</u>H$_2$-4 or <u>C</u>H$_2$-5); 25.6 (<u>C</u>H$_2$-4 or <u>C</u>H$_2$-5); 36.0 (<u>C</u>H$_2$-3); 43.1 (<u>C</u>H$_2$-11); 54.9 (<u>C</u>H$_2$-6); 57.0 (<u>C</u>H-2); 65.8 (<u>C</u>H$_2$-8); 73.6 (<u>C</u>H-7); 94.7 (<u>C</u>H-10); 127.1-128.4 (<u>C</u>H-Ar); 142.2 (<u>C</u>q-Ar). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.55; N, 5.66; Found: C, 72.88; H, 8.37; N, 5.68.
8. **4b**:52 mg (45% overall yield from **1b**) as a colorless oil: $[\alpha]_D^{20}$ -52.6 ($CHCl_3$, c 0.83); MS m/z 234 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.6 (m, 3H, C<u>H</u>$_2$-4, C<u>H</u>-3); 1.9-2.4 (m, 4H, C<u>H</u>$_2$-10, C<u>H</u>-3, C<u>H</u>-5); 2.6 (m, 1H, C<u>H</u>-2), 2.8 (m, 1H, C<u>H</u>-5); 3.35 (dd, 1H, J = 10.0, 2.0 Hz, C<u>H</u>-6); 3.39 (dd, 1H, J = 13.0, 2.0 Hz, C<u>H</u>-7); 4.2 (dd, 1H, J = 13.0, 10.0 Hz, C<u>H</u>-7); 5.3 (dd, 1H, J = 9.0, 6.0 Hz, C<u>H</u>-9); ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm): 21.1 (<u>C</u>H$_2$-4 or <u>C</u>H$_2$-3); 32.4 (<u>C</u>H$_2$-4 or <u>C</u>H$_2$-3); 40.9 (<u>C</u>H$_2$-10); 55.1 (<u>C</u>H$_2$-5); 58.5 (<u>C</u>H-2); 66.4 (<u>C</u>H$_2$-7); 71.0 (<u>C</u>H-6); 94.8 (<u>C</u>H-9); 127.2-128.3 (<u>C</u>H-Ar); 141.1 (<u>C</u>q-Ar).
9. **2c**: 58 mg, 42% two epimers, separated by flash chromatography (ether:cyclohexane, 3:7, rf 0.5 and 0.35). Major epimer rf 0.35 (38 mg, 28%) as a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.20 (t, 3H, OCH$_2$C<u>H</u>$_3$); 1.45 (d, 3H, C<u>H</u>$_3$-7); 2.30 (m, 2H, C<u>H</u>$_2$-6); 3.3-3.5 (m, 5H, C<u>H</u>$_2$-CN, C<u>H</u>-2, C<u>H</u>-3, C<u>H</u>-7); 3.7 (m, 1H, C<u>H</u>-3); 4.1 (q, 2H, OC<u>H</u>$_2$CH$_3$); 4.9 (dd, 1H, J = 9.0, 6.0 Hz, C<u>H</u>-5); 7.35 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm): 11.3 (OCH$_2$<u>C</u>H$_3$); 15.1 (<u>C</u>H$_3$-7); 40.8 (<u>C</u>H$_2$-6); 41.9 (<u>C</u>H$_2$-CN); 55.8 (<u>C</u>H-7); 62.7 (O<u>C</u>H$_2$CH$_3$); 64.5 (<u>C</u>H-2); 65.8 (<u>C</u>H$_2$-3); 98.5 (<u>C</u>H-5); 117.2 (<u>C</u>N); 127.6-128.9 (<u>C</u>H-Ar); 138.9 (<u>C</u>q-Ar).
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11. Unexpectedly, while **5b** was easily transformed to **4b** in an aqueous acidic medium, compound **5a** was not transformed under the same conditions and required a non-aqueous treatment to give transacetalization in poor yield.
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(*Received in France* 2 *April* 1997; *accepted* 29 *April* 1997)