Novel Electrochemical Reductive Amination of 4″-Oxo-5-*O*-(*tert*-butyldimethylsilyl)avermectin B_1

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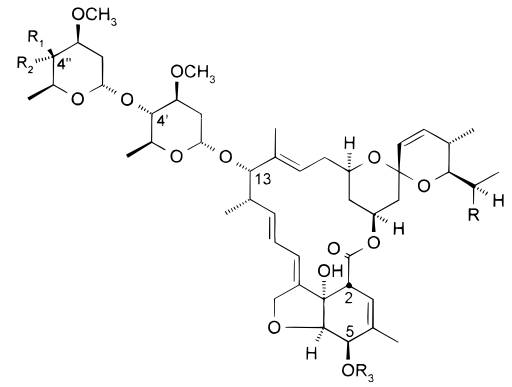
Cathodic reductive amination has been applied to ketones in aqueous ammoniacal solutions, but only to fairly simple substrates which allowed the use of aqueous conditions.[1,2] The scope of cathodic reductive amination is limited by the low solubility of complex substrates and the low concentration of imine in equilibrium with hindered ketones. The synthesis of 4″-aminoavermectins, members of a potent group of anthelmintic and insecticidal avermectin analogues, has been accomplished via reductive amination of the corresponding imines using sodium cyanoborohydride or sodium borohydride.[3] One important member of this class of 4″-aminoavermectins is emamectin benzoate (MK-244, **1**; Chart 1).[4] The hydrolytic sensitivity of ketone **2** toward acidic aqueous conditions and the sensitivity of the C-2 position toward base epimerization (pH >9) would complicate any prolonged electrochemical reductive amination under most standard conditions.[2] Development of conditions for cathodic reductive amination of sensitive ketones in the presence of a variety of functional groups could prove of value in expanding the use of electrochemical reductions.

Chart 1. MK-244 and Intermediates

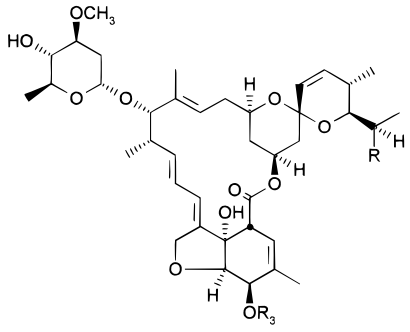


1: MK-244 (Emamectin Benzoate)

$R_1 = NHCH_3{\cdot}HO_2CPh$, $R_2 = H$, $R_3 = H$
2: $R_1 = R_2 = O$, $R_3 = TBDMS$
3: $R_1 = R_2 = NCH_3$, $R_3 = TBDMS$
4: $R_1 = NHCH_3$, $R_2 = H$, $R_3 = TBDMS$

B_{1a}: $R=CH_2CH_3$
B_{1b}: $R=CH_3$

Chart 2. Avermectin B_1 Monosaccharide



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Results and Discussion

Successful cathodic reductive amination of cyclic and acyclic ketones to secondary amines[2a,5] has been reported in divided cells with mercury cathodes and platinum anodes via *in situ* formation of imines in water or aqueous ethanol using a 10-fold excess of primary amines (adjusted to pH 10 with HCl). Attempts to utilize these conditions with ketone **2** (Chart 1) resulted in a low (<5%) yield of methylamine **4**. Significant acetal cleavage to produce monosaccharide **5** (Chart 2), epimerization at C-2, reduction of ketone **2**, and the destructive behavior of the electrode reaction products (i.e., Cl_2) produced at the counter electrode all contributed to the failure of this system.

To overcome these difficulties several experimental changes were made during the development of an acceptable electrochemical reductive amination. It was found that the saccharide acetal linkage in ketone **2** had a much higher susceptibility toward cleavage during electrochemical reduction than the saccharide acetal linkage in imine **3** or amine **4**. Using an H-divided cell (50 mL/cell), intermediate imine **3** was preformed in the cathode chamber prior to electrolysis by reaction of ketone **2** with methylamine/trifluoromethanesulfonic acid in anhydrous acetonitrile (Chart 1 and Scheme 1), in the presence of 4 Å molecular sieves. The methylammonium trifluoromethanesulfonate then continued to play a dual role by serving as the supporting catholyte. The use of methylammonium acetate in this role resulted in low current and large amounts of monosaccharide **5**, while the use of methylammonium trifluoroacetate produced excellent current but, as with methylammonium acetate, produced large amounts of monosaccharide **5**.

The anodic compartment was filled with acetonitrile saturated with anhydrous lithium chloride and was separated from the catholyte by a Nafion membrane.[6] This membrane allows only the lithium cations to migrate from the anode to the cathode chamber in order to maintain electrical neutrality. This effectively separated the cathode chamber containing imine solution from the anode process of chloride oxidation to chlorine. Although generally used in aqueous systems, Nafion 117 and 901

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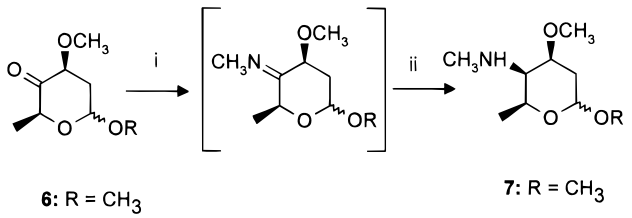
Scheme 1. Electrochemical Reduction of Imines in H-Cell with Platinum Anode and Mercury Cathode[a]



6: R = CH_3 **7**: R = CH_3

[a] (i) Cathode cell, CH_3NH_2, CF_3SO_3H, CH_3CN, 4 Å molecular sieves; (ii) anode cell, LiCl, CH_3CN: 150 mA electricity.

membranes were electrically conductive in this system, but Nafion 924 produced heat at the cathodic interface. The Nafion 117 membrane was utilized predominantly in our work and was found to be reusable under the reductive amination conditions employed.

The cathode compartment required a stirred mercury pool as the electrode, due to the high hydrogen overpotential. Other metals with high hydrogen overpotential, such as lead, tin, and cadmium, failed to produce amine **4**, and amalgamated lead produced only a trace of product. The anode was a smooth platinum flag (~6 cm^2) and produced a good current across the Nafion membrane.

An electric current was passed through the cells at a constant current of 150 mA at a current density of 25 mA/cm^2, which resulted in a 65% yield of methylamine **4**. This electrochemical reduction of relatively hindered imine **3** resulted in the predominant (>95%) formation of the all-cis (axial) amine, the same stereochemical result arising from reductive aminations using $NaBH_4$.[3] This is in contrast to aqueous electrochemical reductive amination of the relatively unhindered 2-substituted cyclohexyl ketones[2a] which produced predominantly trans amines. Stereochemical sensitivity to the choice of electrolyte in electrochemical reductions of 2-substituted cyclohexyl imines in aqueous systems has been reported,[5] but reductions in DMF produced predominantly the cis amines as in our system.

Application of this anhydrous cathodic reductive amination was extended to the simple keto oleandroside. Methyl 4-oxooleandroside **6** (Scheme 1) was cathodically reductively aminated to produce a 95% yield of axial methylamine **7**.

The method described herein for the successful anhydrous electrochemical reductive amination of sensitive and complex ketones should be a useful alternative to borohydride- or catalytic hydrogenation-based reductions.

Experimental Section

General. High-resolution mass spectroscopy studies were performed in the FAB mode. The following materials: 5-*O*-(*tert*-butyldimethylsilyl)-4″-oxoavermectin B_1 (**1**; mixture of B_{1a} and B_{1b}) and methyl 4-oxooleandroside (**6**), were prepared by literature methods.[3,7]

Electrochemical Reductive Amination, General Procedure. Into the cathodic chamber of a 50 mL H-cell fitted with a Nafion 117 film (which was boiled in water for 15 min prior to use), a mercury cathode, and a platinum anode (each with a surface area of ~6 cm^2) were added methylamine in acetonitrile (2 N, 30 mL), 4 Å molecular sieves (1.5 g), trifluoromethanesulfonic acid (2 mL), and ketone (0.5 mmol) at 0 °C, and the resulting slurry was stirred at 22 °C for 2 h. The anodic chamber was then filled with acetonitrile (30 mL) saturated with anhydrous lithium chloride. The H-cell was connected to an Electrosynthesis 412 controller equipped with an Electrosynthesis 640 digital coulometer and then cooled in an external water bath at 20 °C. A constant current of 150 mA at a current density of 25 mA/cm^2 was applied through the cell until 4 Faradays/mol of electricity was passed. After the removal of mercury, the catholyte was filtered to remove the molecular sieves and then partitioned between water (50 mL) and ethyl acetate (60 mL). The organic phase was dried over $MgSO_4$, concentrated *in vacuo*, and purified by chromatography on silica gel.

4″-*epi*-(Methylamino)-5-*O*-(*tert*-butyldimethylsilyl)-4″-deoxyavermectin B_1 (4). Ketone **2** was subjected to the general procedure above, and amine **4** was isolated in 65% yield by column chromatography (E. Merck silica gel 60, 230−400 mesh ASTM) using ethyl acetate:hexanes mixtures. ^1H NMR (400.13 MHz, $CDCl_3$): δ 5.83 (m, 1H), 5.77−5.70 (om, 3H), 5.54 (dd, J = 9.8, 2.5 Hz, 1H), 5.42−5.31 (om, 3H), 5.00 (m, 1H), 4.76 (br d, J = 4.8 Hz, 1H), 4.67 (dd, J = 14.4, 2.1 Hz, 1H), 4.58 (dd, J = 14.5, 2.1 Hz, 1H), 4.44 (m, 1H), 4.12 (br s, 1H), 3.98−3.78 (om, 5H), 3.67 (dt, J = 11.6, 4.2 Hz, 1H), 3.59 (ddd, J = 8.4, 6.4, 4.0 Hz, 1H), 3.48 (d, J = 9.4 Hz, 1H), 3.42 (s, 3H), 3.41 (om, 1H), 3.38 (s, 3H), 3.23 (t, J = 8.9 Hz, 1H), 2.68 (br d, J = 3.2 Hz, 1H), 2.58 (s, 3H), 2.51 (m, 1H), 2.34−2.23 (om, 3H), 2.20 (dd, J = 13.1, 4.8 Hz, 1H), 2.03 (dd, J = 11.5, 3.0 Hz, 1H), 1.92 (dd, J = 13.1, 4.8 Hz, 1H), 1.86−1.73 (om, 2H), 1.79 (s, 3H), 1.65−1.43 (om, 6H), 1.50 (s, 3H), 1.27 (d, J = 6.7 Hz, 3H), 1.24 (d, J = 6.2 Hz, 3H), 1.15 (d, J = 6.9 Hz, 3H), 0.96−0.86 (om, 10H), 0.93 (s, 9H), 0.13 (s, 6H). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 174.1, 140.2, 137.6, 137.5, 136.2, 135.2, 127.8, 124.8, 119.3, 118.3, 117.2, 98.6, 95.5, 95.0, 82.0, 80.5, 80.2, 80.1, 79.2, 75.4, 74.9, 69.5, 68.4, 68.3, 67.9, 67.3 (2C), 60.1, 56.7, 55.5, 45.8, 40.4, 39.7, 38.4, 36.5, 35.2, 34.5, 34.3, 31.0, 30.6, 27.5, 25.9 (3C), 20.2, 20.0, 18.4, 18.2, 18.1, 16.4, 15.1, 13.0, 12.0, −4.6, −4.8. HRMS ($C_{55}H_{89}NO_{13}Si$): $[MH]^+$ = 1000.6210 (calcd = 1000.6181); [M + Na] = 1022.5962 (calcd = 1022.6001).

Methyl 4-*epi*-(Methylamino)-4-deoxyoleandroside (7). Ketone **6** was subjected to the general procedure above, and the amine **7** was isolated in 98% yield, which was identical to amine prepared by the $NaBH_4$ reduction previously reported.[7b]

Acknowledgment. We are grateful to Ms. D. Zink for providing us with the high-resolution mass spectra.

Supporting Information Available: ^1H and ^{13}C NMR spectra for compound **4** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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