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A Highly Diastereoselective Electrochemical Epoxidation

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Abstract: *The electrochemical epoxidation of 3 gives the Merck HIV-protease inhibitor, Indinavir Sulfate, intermediate 1 in high yield and diastereoselectivity in an operationally simple procedure.*
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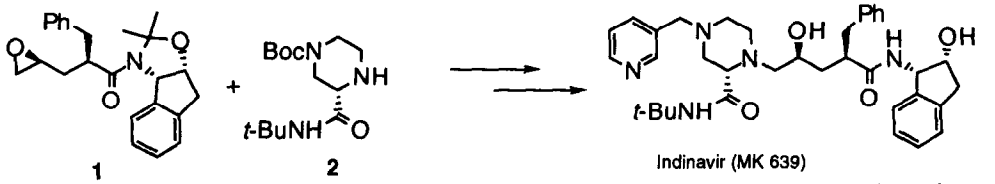
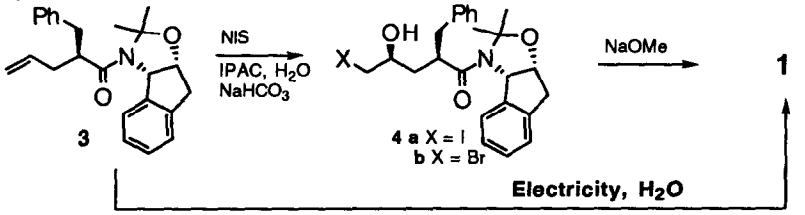
Electrochemical processes are the basis for the large scale production of many bulk commodity chemicals. There are few applications for the electrochemical production of complex molecules, such as pharmaceutical intermediates with chiral centers, despite the potential advantages that electrochemical processes have in terms of ease of operation and minimal environmental impact.[1]

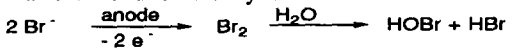
The Merck HIV-protease inhibitor, Crixivan® (Indinavir Sulfate, MK 639, L-735,524),[2] is currently prepared by a convergent route that requires coupling of the chiral non-racemic epoxide **1** and piperazine **2**[3] subunits. This communication describes an efficient, diastereoselective electrochemical process for the preparation of **1** from the allyl acetonide precursor **3**.



The epoxide **1** is currently prepared from olefin **3** by a conventional two step procedure involving formation of the iodohydrin **4a** with NIS (N-iodosuccinimide) or NCS (N-chlorosuccinimide) and NaI in a biphasic reaction mixture (EtOAc or isopropylacetate (IPAC) and $NaHCO_3$ buffered H_2O).[4] While the reaction proceeds in high yield (92%) and diastereoselectivity (97:3) the resulting iodohydrin **4a** must be converted to the epoxide **1** with a strong base (NaOMe) in a separate step.



The epoxidation of **3** to **1** was achieved by constant current electrolysis of **3** in the presence of NaBr in an undivided electrochemical cell with graphite felt electrodes in a MeCN/H_2O 3/2 solvent system.[5] Epoxide **1** was formed cleanly and crystallized directly from the solution (86% yield after a simple filtration).[6] The diastereoselectivity in the electrochemical formation (94:6) is comparable to that observed in the conventional NIS transformation and the reaction is operationally very simple to perform. The epoxidation is made possible by the different local environments provided by the anode and cathode in the reaction vessel. At the anode the hypohalous acid HOBr is generated and adds efficiently to the olefin **3** to form the bromohydrin **4b**.[7]



At the cathode the formation of base allows for the closure of **4b** to the epoxide **1** with the concomitant regeneration of the halide.

$$2\,H_2O \xrightarrow[+\,2\,e^-]{\text{cathode}} H_2 + 2\,OH^-$$

Since NaBr is regenerated in the closure of **4b** to **1**, the electrochemical epoxidation is expected to be catalytic in NaBr and this is indeed the case: 0.5 equivalent of NaBr effects complete conversion.[8] The overall process produces as much base at the cathode as acid at the anode, and the overall pH of the bulk solution remains close to neutral (pH = 6).

The use of NaI in the CH_3CN/H_2O system does not lead to the formation of any epoxide, presumably because of the facile disproportionation of the positive iodine species to the iodate.[9] Interestingly, it is also possible to prepare halohydrins **4a** and **4b** in the electrochemical cell by simply switching the solvent system to a biphasic IPAC/H_2O system. In contrast to the trend observed for epoxide formation in CH_3CN/H_2O, in IPAC/H_2O the iodohydrin **4a** is formed cleanly and can be isolated by chromatography in 69% yield, while the reaction to the corresponding bromohydrin **4b** is inefficient and low yielding. Partitioning of positive halogen, presumably the hypohalous acid HOX, into the organic phase is a prerequisite for the formation of **4a** and **4b** and HOI is expected to be more soluble in IPAC than HOBr.

In summary, an operationally simple and highly efficient procedure allows the epoxidation of **3** to give the Indinavir Sulfate intermediate **1** in an undivided electrochemical cell in excellent diastereoselectivity and yield.

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6. **Experimental:** The reactions were performed in a 250 mL jacketed beaker covered with a rubber stopper and two 20 cm^3 graphite felt electrodes connected to a graphite rod (Electrosynthesis Company, Lancaster, NY, Lancaster, NY 14086-9779). The electrical current was kept constant using a DC power supply (Electrosynthesis Company). A constant current of 0.75 A was applied to a slurry of the olefin **3** (5.00 g, 13.53 mmol and NaBr (1.42 g, 13.5 mmol) in 90 mL of CH_3CN and 60 mL H_2O which was stirred with a cross shaped Spinplus (Aldrich) 2.5 x 2.5 cm stirring bar at ca. 900 rpm.. The reaction was complete after 3 h, when a total of 8700 C (31 % electrical yield) were consumed. The reaction mixture was warmed to 70°C to dissolve any precipitated product, and on cooling to 10°C **1** precipitated. It was filtered, washed (H_2O and H_2O/MeOH 50/50) and dried to give 4.47g (86% yield) of **1**. The product was identical in all respects to material described in ref. 4. The HPLC method described in ref. 4 did not separate **4b** from **1**, but this was accomplished on a Zorbax RX 8 column (25cm X 4.6 mm)wi CH_3CN/0.1% H_3PO_4 in H_2O 40/60 assay, 1mL/min, RT **1** 12.4 min, RT **4b** 13.5 min.
7. HOBr generated from Br_2 and HgO reacts with **3** to give **4b** in 84 % yield.
8. An interesting dependence of the diastereoselectivity and isolated yield on the stoichiometry of the NaBr was noted:
   0.5 equiv. NaBr, 89% yield, 93:7 de
   1.0 equiv. NaBr, 86% yield, 94:6 de
   2.0 equiv. NaBr, 80% yield, 97:3 de
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