Pergamon

*Tetrahedron Letters*, Vol. 36, No. 23, pp. 3993-3996, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00696-6

# The Behavior of Indene Oxide in the Ritter Reaction: A Simple Route to *cis*-Aminoindanol.

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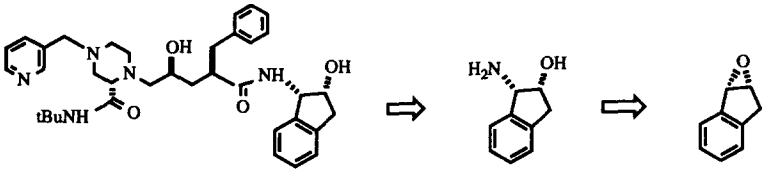
***Abstract:*** *A regio- and stereoselective synthesis of cis-1-aminoindan-2-ol via a Ritter reaction is described.*

The HIV protease inhibitor L-735,524 is currently being tested for its effectiveness against AIDS.[1] This orally active inhibitor contains (-)-*cis*-(*1S,2R*)-1-aminoindan-2-ol (**1**) as a key component; the structure-activity relationship suggests that this moiety serves as a phenylglycine surrogate.[2] Furthermore, the substrate has served as the key *inducer of the asymmetry* in the synthesis of these aminoindanol-derived protease inhibitors.[3] Herein, we describe a practical chiral synthesis of *cis*-aminoindanol.[4]




L-735, 524 **1** **2**

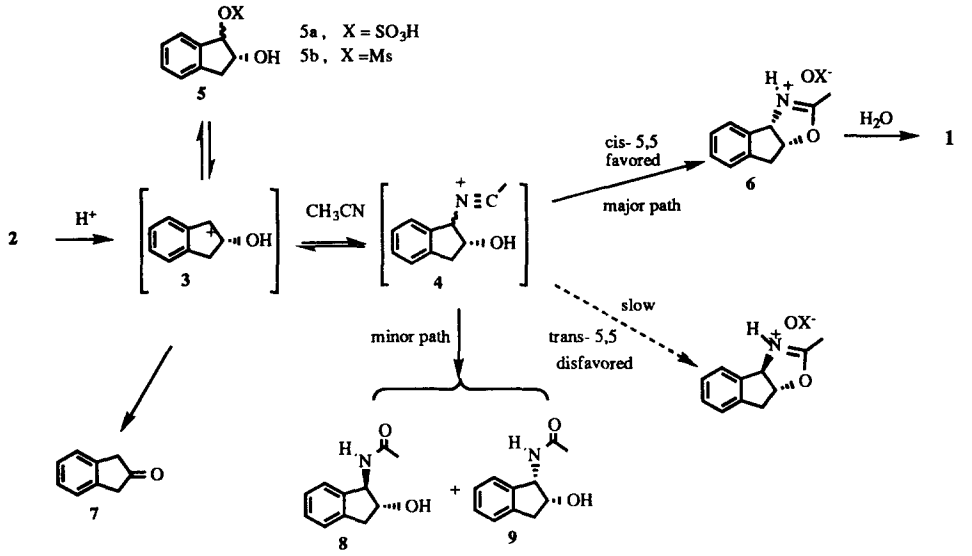
Epoxides have been reported to give poor yields of regioisomeric oxazolines when subjected to the conditions of the Ritter reaction,[5] especially with sulfuric acid.[6] However, when racemic indene oxide, prepared by the reaction of indene with hydrogen peroxide in acetonitrile,[7] was treated with sulfuric acid in acetonitrile, the methyl oxazoline **6** was formed directly as the major product. Hydrolysis with water yielded *cis*-1-aminoindan-2-ol.[8]

Low temperature NMR studies indicated that with 2.0 equivalents of 97% sulfuric acid in acetonitrile at -40 °C the epoxide formed a 1:1 mixture of the methyl oxazoline **6** and intermediate **5a** as the major products, along with **7**, **8** and **9** as minor products. While warming the reaction to room temperature, the sulfate intermediate **5a** converted to **6**. The proposed mechanism for this interesting reaction involves trapping the highly reactive carbenium ion **3** by acetonitrile to provide the nitrilium intermediate **4**; conformationally biased *cis*-5,5-ring formation then affords the desired compound **6** (Scheme 1). Typically, 10-12% of 2-indanone (**7**) was formed in this reaction.[9] Addition of water to the reaction and heating provided the *cis/trans* aminoindanols in a ratio of 95:5.[10]

The choice of the acid was critical to the success of the selective amination. Hydrochloric or trifluoroacetic acid gave the 1-chloro- or the 1-trifluoroacetoxy-2-hydroxyindane,[11] respectively. In contrast, less nucleophilic acids, such as 97% $H_2SO_4$ and methanesulfonic acid (Scheme 1, **5a, b**) provided the methyl

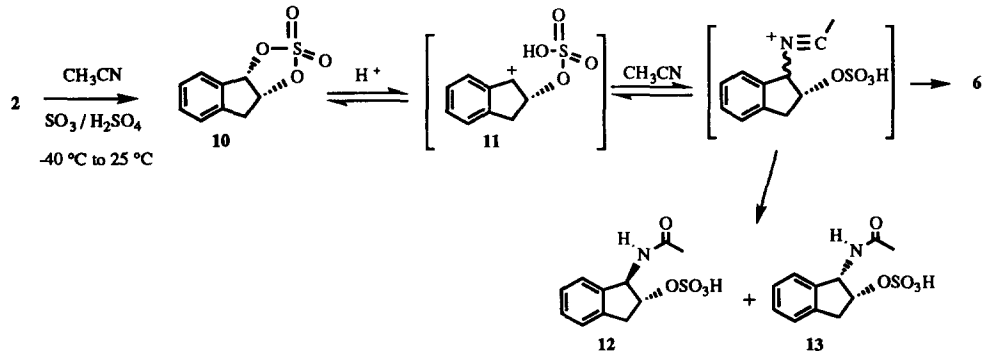
oxazoline as the major product, but still generated significant amounts of 2-indanone and unidentified polymeric material. Yields were in the range 60-65%.

**Scheme 1**




Fuming sulfuric acid (21% $SO_3$), on the other hand, completely eliminated ketone formation (Scheme 2).[12] Sulfur trioxide captured the epoxide **2** to form the novel cyclic sulfate **10**, which was observed by low temperature NMR. When the reaction was conducted at -40 °C in acetonitrile with 2.0 equivalents of $H_2SO_4/SO_3$, several species **6**, **10**, **12**, and **13** were observed. After the reaction was warmed to room temperature **10** had completely reacted. Upon refluxing in water **6**, **12**, and **13** hydrolyzed to aminoindanols, yielding *cis*-1-aminoindan-2-ol in 78-80% yield.

**Scheme 2**



By taking advantage of the stereochemical integrity of the carbon-oxygen bond at C-2 in this reaction a chiral synthesis of **1** was feasible. When non-racemic indene oxide[13] was converted to the aminoindanol the % e.e. was unchanged. Similarly, either *cis* or *trans*-indane diol afforded *cis*-aminoindanol with the same optical purity as the starting diol.[14]

Through understanding the behavior of the acid employed in the Ritter reaction a novel sulfur trioxide-mediated Ritter reaction has been developed that has led to a practical, high-yielding preparation of chiral *cis*-aminoindanol from chiral indene epoxide **2.** Stabilization of the carbocation intermediate has eliminated the yield-lowering ketone formation. This procedure also offers a general method to other important chiral aminoalcohols from the corresponding chiral epoxides. These results will be reported shortly.

**References and notes**

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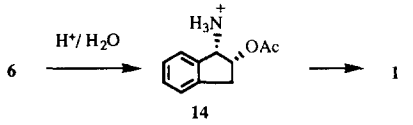
(8) Other nitriles are comparable to acetonitrile in this reaction. However due to the expense (nitrile is used as the solvent) and the high toxicity of some of the nitriles, acetonitrile was deemed optimal.

(9) 2-Indanone is formed via a 1,2-hydrogen shift of carbenium ion **3.** Low temperature NMR studies indicated that exposure of indene oxide to $CH_2Cl_2$/$MeSO_3H$ without acetonitrile generated the indanone and mesylate **5b** as the major compounds, along with several other by-products.

(10) Compounds **6, 8** and **9** were individually subjected to reflux in aqueous sulfuric acid. The corresponding aminoindanol was obtained with no detectable epimerization at the C-1 position. NMR study indicated that cis aminoindanol is obtained mainly via the acetate intermediate **14** by further hydrolysis as shown below.

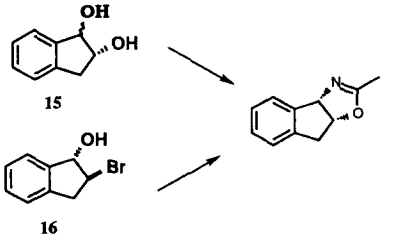



(11) The 1-chloro- and 1-trifluroacetoxy -2-hydroxyindanes are stable products and do not ionize to the corresponding carbenium ion to provide compound **6**. Increasing the temperature of the reaction media resulted in decomposition.

(12) Support of this argument comes from varying the amount of $SO_3$ present in the $H_2SO_4$ solution. When the Ritter reaction was carried out using 3% $SO_3$ in $H_2SO_4$, 4% of ketone was observed. When the percentage of $SO_3$ was increased to 10%, the Ritter reaction yielded 2% of 2-indanone. Further increasing the amount of $SO_3$ to 21%, no ketone formation was observed. These results support the argument that the more cyclic sulfate formed the less 2-indanone is formed. From these results, it is apparent that the percentage of $SO_3$ is critical in order to avoid ketone formation.

(13) For the preparation of chiral indene oxide via asymmetric metal catalysis, see (a) Jacobsen, E.N Asymmetric Catalytic Epoxidation of Unfunctionalized Olefins in *Catalytic Asymmetric Synthesis*, Iwao Ojima, VCH; New York, **1994**, Chapter 4.2, 159. (b) Chiral indene oxide is obtained in >86% ee via the Jacobsen epoxidation method, see reference: Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063. (c) Halterman, R. L.; Jan, S. *J. Org. Chem.* **1991**, *56*, 5254. For the preparation of chiral indene oxide via microbiological transformation, see: (d) Zeffer, H.; Imuta, M. *J. Org. Chem.* **1978**, *43*, 4540. (e) Boyd, R. D.; Sharma, D.N.; Smith, E. A. *J. Chem. Soc., Perkin Trans. I* **1982**, 2767. (f) *1S, 2R* indene oxide was prepared in >99% ee from the racemic epoxide with epoxide hydrolase; Zhang, J.; Chartrain, M.; Greasham, R.; Senanayake, C.H. manuscript in preparation. (g) Zeffer, H.; Imuta, M. *J. Am. Chem. Soc.* **1979**, *101*, 3990.

(14) Both *cis*- and *trans*- indandiol (**15**) with the correct stereochemistry at C-2 serve as sources of methyl oxazoline. Racemic 2-bromo-indan-1-ol (**16**) also provides racemic methyl oxazoline when the intermediate Ritter product, *trans* -1-acetamido-2-bromo indane, is heated.




(*Received in USA* 21 *February* 1995; *revised* 4 *April* 1995; *accepted* 11 *April* 1995)