A Route to Chiral Epoxypyrroloindoles via Oxiranyl Radical Cyclization

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Abstract: An oxiranyl radical has been generated from a glycidic acid via the thiohydroxamic acid anhydride route. The radical has been shown to undergo cyclization, a process, which to our knowledge, has not been reported previously. The structure and the reactivity of the indole and dihydroindole products of the cyclization are discussed.

Oxiranyl radicals are intermediates in the radical chlorination of oxiranes (epoxides)[2], the reduction of halooxiranes with hydrostannanes,[3] and the decarbonylation of glycidaldehydes with *tert*-butoxy radical.[4] The rate of inversion[3a, 5] and the rearrangement to α-ketoalkyl radicals[2a, 5b] of these pyramidal species[6] have been determined. To our knowledge, the issue of whether or not an oxiranyl radical can undergo cyclization in competition with rearrangement has not been addressed. The realization that k_i for inversion of an unsubstituted oxiranyl radical center is $\sim 10^7$ s^{-1} at -100 °C and that k_r for rearrangement is $\sim 10^3$ s^{-1} at ambient temperature suggests that inversion would be sufficiently rapid to interconvert a trans-generated oxiranyl radical to its cis counterpart, a requirement for cyclization. Moreover, if the rate constant (k_c) for cyclization to form a five-membered ring were similar to k_c ($\sim 10^5$ s^{-1} at ambient temperature)[7] for the cyclization of 5-hexenyl radical, then cyclization would compete successfully with rearrangement. In this Letter we report the success of this process.

Ethyl (2S, 3R)-4-hydroxy-2,3-epoxybutyrate[8] **1** was converted to its triflate followed by the addition of the potassium salt of indole-3-carbonitrile (2 equiv.) to provide ester **2a** in 93% overall yield (Scheme 1). Efficient saponification of ester **2a** gave acid **2b**, which was activated *in situ* as the thiohydroxamic acid anhydrides (thiohydroxamate esters) **2c**[9a,b,d] and **2d** [9c] as described by Barton.

Scheme 1
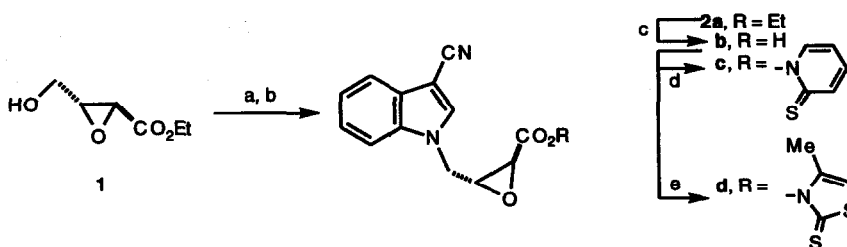
a) Tf$_2$O, pyr., CH$_2$Cl$_2$, -23 °C; b) Indole-3-carbonitrile, t-BuOK, THF, -23 °C --> rt, 93% (2 steps); c) LiOH, THF/H$_2$O, 10 °C, 95%; d) 2,2'-dithiobis(pyridine N-oxide), n-Bu$_3$P, THF, 0 °C; e) i-BuOC(O)Cl, N-methyl morpholine, THF, -15 °C; N-hydroxy-4-methylthiazole-2-thione, pyr., THF.

When thiohydroxamate ester **2c** was irradiated (12 min., rt) with UV light (Scheme 2), symmetrical dimer **3** (33%), unsymmetrical dimer **4** (7%), epoxyindole **5** (6%),[10] and 2,2'-dipyridyl disulfide were isolated. Dimer **3**, whose structure was secured by single crystal x-ray analysis,[11] displayed 11 of the expected 12 signals in its ^{13}C NMR spectrum. The ^{1}H NMR spectrum was unique in that the coupled oxirane protons were not coupled to the other three aliphatic protons. During the formation of **3**, the oxiranyl radical cyclizes through a transition state that places the oxygen atom syn to the aromatic ring. No products having the anti relationship were detected. The resultant stabilized radicals undergo dimerization on their respective exo faces.[12] Dimer **4**, which displays 24 resonances in its ^{13}C NMR spectrum, differs from dimer **3** only in the facial selectivity of the dimerization (i.e.; endo-exo). The stereochemical assignment of dimer **4** is considered below.
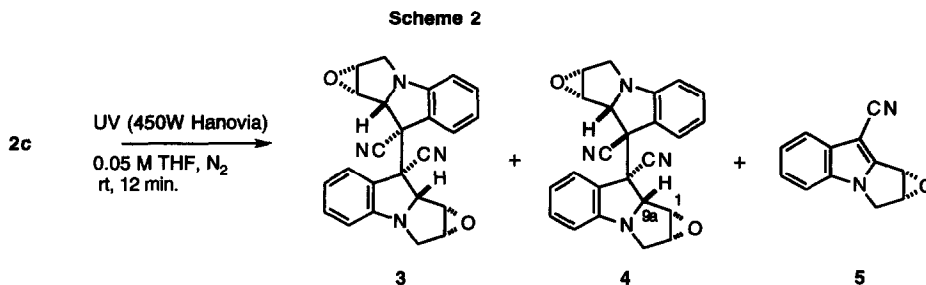
Scheme 2

Prolonged irradiation (8 h, rt) of dimer **3** effected dissociation and disproportionation to a 1.7:1 mixture of dihydroindoles **6** and **7** (52%), respectively, and cyclopentanone **8** (26%) (Scheme 3). The anticipated, oxidized product of disproportionation, epoxide **5**, was shown independently to produce ketone **8** cleanly (35% conversion after 1.5 h) under similar conditions. The stereochemistry of dihydroindoles **6** and **7** was assigned based upon NOE measurements.

Scheme 3
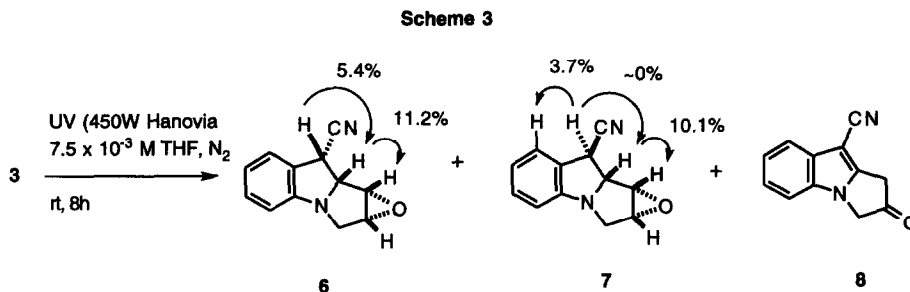
The stereochemistry of unsymmetrical dimer **4** was inferred from the following experiment. Irradiation of **4** (UV, 7.5 x 10^{-3} M THF, rt, 4h) was conducted in the presence of n-Bu$_3$SnH (4 equiv.). The ^{1}H NMR spectrum of the reaction mixture revealed complete consumption of **4**, the appearance of a 2:1 mixture of dihydroindoles **6** and **7**, and *the presence of symmetrical dimer 3*. None of the uncyclized epoxide **12** (see Scheme 4) was detected. These results demonstrate that dimer **3**, and presumably dimer **4**, are formed kinetically in the photolysis of **2c**. Moreover, dissociation of dimer **4** and recombination to dimer **3** is faster than reduction of the intermediate radical. The absence of uncyclized epoxide **12** suggests, but does not prove, that cleavage of the C$_1$-C$_{9a}$ bond does not

occur prior to formation of the symmetrical dimer. Based upon these observations and assumptions, the stereochemistry of dimer **4** differs from **3** at the C_9-$C_{9'}$ bond and not at the C_1-C_{9a} bond.

Scheme 4
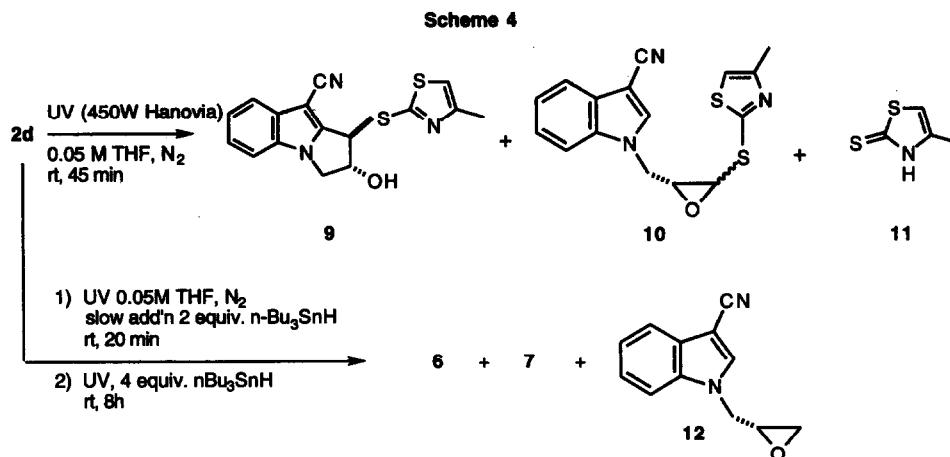
In contrast to the behavior of **2c**, irradiation of N-hydroxy-4-methylthiazole-2-thione ester **2d** provided cyclized indole **9** (33%),[13] uncyclized epoxythiazoles **10** [16%, 3:1, trans (J = 1.7 Hz):cis (J = 5.3 Hz)], 4-methylthiazole-(2,3H)-thione (**11**), and trace amounts of dimer **3** (Scheme 4). When epoxide **5** was treated with thiazolethione **11** (1 equiv.) in THF at room temperature for 1h, compound **9** was formed to the extent of 25% without the formation of by-products. The formation of **5** and **10** from **2d** under these photolytic conditions may indicate a chain process or, in the case of **5**, the propensity for the thiazolethiyl radical to abstract a hydrogen atom from C_{9a} of the stabilized, cyclized radical. Lastly, the decomposition of **2d** can be altered to give principally dimeric products by the slow addition of 2 equiv. of nBuSn3H during the first 20 min. of irradiation. Continued photolysis (8h) in the presence of additional nBu3SnH (4 equiv.) provides dihydroindoles **6** and **7** in a 1:1.3 ratio (53%)[14] and epoxyindole **12** (5%).

This study has demonstrated that an oxiranyl radical can be produced from a glycidic acid and that the radical can undergo cyclization faster than, or in competition with, rearrangement. Moreover, the method provides an alternative to traditional methods for the incorporation of epoxides into organic structures.

References and Notes:

1 Recipient of a Bristol-Myers Squibb Fellowship, 1993.
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10 Yields refer to isolated products after silica gel (flash) chromatography. All new compounds exhibited satisfactory NMR data and HRMS and/or combustion analysis data.
11 Dimer 3 ($C_{24}H_{18}O_2N_4$) grew as thin plates. A crystal of approximate dimensions 0.25 mm x 0.18 mm x 0.06 mm was cleaved from a conglomerate of crystals and mounted in a random orientation on a glass fiber. Diffraction measurements were made on a four-circle Rigaku AFC5S fully automated diffractometer using graphite monochromatic CuKα ($\lambda = 1.54178$ Å). The cell constants and orientation matrix for data were obtained from a least-squares refinement using the setting angles of 20 carefully centered reflections in the range $40.61 \le 2\Theta \le 56.67^\circ$ and corresponded to an orthorhombic cell with dimensions: a = 12.937(5) Å, b = 15.277(3) Å , and c = 9.688(1) Å. The space group was determined to be $P2_12_12_1$ (No. 19), Z = 4, with one molecule of 3 forming the asymmetric unit. The volume is 1914.8(9) Å^3 and the calculated density is 1.368 g/cm^3.
12 For a related study employing dioxolanyl radicals, see Ziegler, F. E.; Harran, P. G. *J. Org. Chem.* **1993**, *58*, 2768.
13 The stereochemistry of 9 has not been determined with certainty. Coupling constants ($J_{1,2} = 4.9$ Hz, $J_{2,3'} = 6.4$ Hz, and $J_{2,3''} = 7.6$ Hz) appear to be in accord with a cis configuration for C_1-thio/C_2-amino analogues.[15a] However, this analysis depends upon a preferred conformation for the cyclopentane ring.[15b] The acetate, 2,4-dinitrobenzoate, and p-bromophenylisocyanate derivatives of 9 failed to give crystals suitable for x-ray diffraction.
14 The disparity of the ratio of dihydroindoles 6 and 7 in different experiments is not clear. Both diastereomers are stable to photolysis in the presence of nBu3SnH.
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