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Carbon-Carbon Bond Forming Reactions with Oxiranyl Radicals

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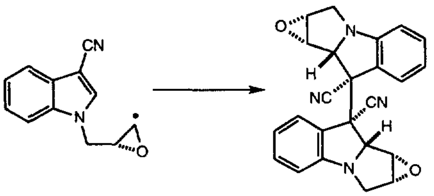
Abstract: Substituted oxiranyl radicals have been generated from glycidic acids. The cyclization of these species, the stereochemistry of the resultant products, and an intermolecular application of these reactive species is considered.

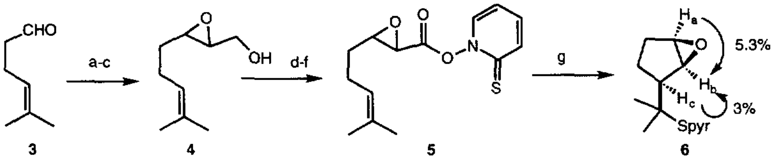
In a previous Letter we reported[1] that oxiranyl radicals can be generated by thiohydroxamate-initiated radical decarboxylation of glycidic acids and that the radical so generated cyclizes faster than it rearranges. The process occurred with high stereoselectivity; only an indole ring was employed as an acceptor (**1** ---> **2**). In this Letter we report on the application of oxiranyl radicals in both the intra- and intermolecular sense for carbon-carbon bond formation with isolated and conjugated olefins, and the stereochemical consequences of the intramolecular reaction.



1 **2**

The cyclization of three related oxiranyl radicals bearing different degrees of methyl substitution were studied because the rates of oxiranyl radical rearrangement had been reported[2] to increase with increased alkyl substitution of the epoxide ring. The glycidic acid from which the PTOC ester **5** was prepared[3] (Scheme 1) was synthesized from 5-methyl-4-hexenal (**3**)[4] via sequential Horner-Emmons reaction,[5] DIBALH reduction, Sharpless allylic epoxidation,[6] Swern[7,8] and Lindgren[9,10] oxidations. Visible light photolysis of PTOC ester **5**, which was not

Scheme 1



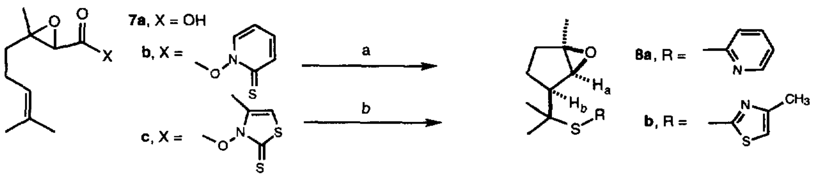
3 **4** **5** **6**

a) $(EtO)_2POCH_2CO_2Et$, LiCl, DBU, CH_3CN; 80%. b) DIBALH, Et_2O, -78 °C; 80%. c) TBHP, $VO(acac)_2$, PhH, reflux; 93%. d) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C; 70%. e) $NaClO_2$, NaH_2PO_4, aq. DMSO, 0 --> 25 °C; 75%. f) $ClCO_2$-i-Bu, N-methyl morpholine (NMM), THF, -20 °C; sodium N-hydroxy-2-thiopyridone; g) W-lamp (500W), 0.02M THF, 0 °C, 1.5 h; 52 % (two steps).

isolated, gave rise to epoxide **6** (52% yield) having the oxygen function and the alkyl group cis to one another. Less than 5% of the isobutyl glycidate, a ubiquitous by-product of these mixed anhydride thiohydroxamate activation, was isolated. The cis stereochemistry of epoxide **6** was confirmed by the NOEs of H_a, H_b, and H_c.

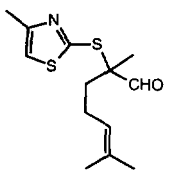
Racemic geraniol epoxide[6,11] (Scheme 2) was converted into the carboxylic acid **7a** in 56% overall yield as described for glycidol **4**. Two thiohydroxamate activating groups were investigated. PTOC ester **7b**, prepared by the mixed anhydride procedure, afforded the cis-substituted cyclopentane **8a** upon photolysis, the stereochemistry of which was also established by NOE studies (H_a---> H_b; 4.5%).[12] Similarly, N-hydroxy-4-methylthiazole-2-thione derivative **7c** gave rise to epoxide **8b** (50%) along with 8% of a mixture of aldehyde **9** and epoxides **10**.

Scheme 2

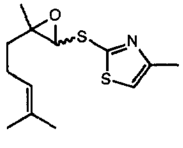


a) 0.02M THF, W-lamp (500W), 0 °C, 1.5 h, 48% (from **7a**). b) 0.05M CH_2Cl_2, 450W-Hanovia Hg lamp, U glass filter, 25 °C, 6h.

The formation of thiohydroxamate ester **7c** proved troublesome with the mixed anhydride method[3] and other protocols employed in this area.[13,14] The use of the BOP reagent [benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate] for esterification[15] gave **7c** in 50% isolated yield. The yields of activated glycidate esters are less than those obtained with less complex carboxylic acids. Thus, the N-hydroxy-4-methylthiazole-2-thione derivative of hydrocinnamic acid was prepared in 77% isolated yield by the BOP procedure.



9

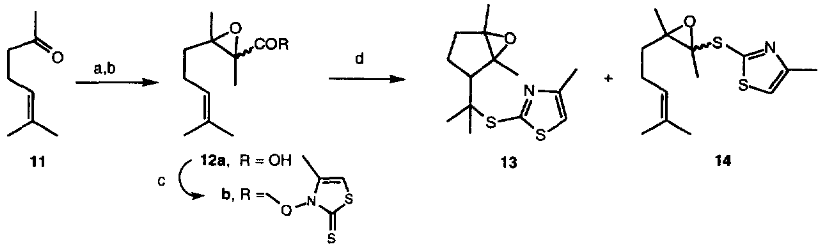


10

The trisubstituted glycidic acid **12a** was prepared efficiently as an ~1:1 mixture via a Darzens condensation (Scheme 3). Although the PTOC ester was difficult to form using standard esterification conditions[3,13], the N-hydroxy-4-methylthiazole-2-thione esters **12b** could be isolated in 50% yield when the BOP reagent was employed.[16] UV photolysis of thiohydroxamate **12b** produced cyclized epoxide **13** (35%) and the uncyclized epoxides **14** (9%). Epoxide **13** is a single stereoisomer and is presumed to have the same relative stereochemistry as its less substituted congeners **6**, **8a**, and **8b**. Although the yield of **13** is lower than that of its less substituted analogs, the formation of **13** and **14** indicates that intra- and intermolecular reactions of highly substituted oxiranyl radicals are competitive with rearrangement.

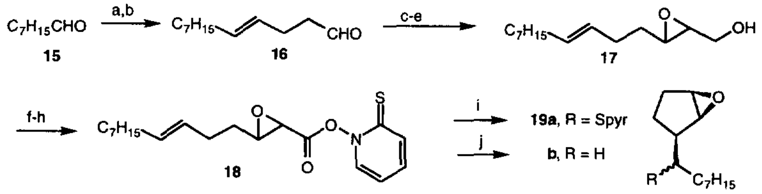
Scheme 4 demonstrates that geminal olefin substitution is not required for successful cyclization to occur. Moreover, the presence of n-Bu_3SnH during the photolysis of PTOC ester **18** permits formation of the sulfur-free epoxide **19b** as a 4:1 (cis:trans) mixture of diastereomers. Although a mixture could not be detected in the formation of **19a**, it may be inferred. Minor amounts of trans products may be present in the reaction mixtures of Schemes 1 and 2. The stereochemistry of epoxide **19b** was confirmed by synthesis from the known[17] iodolactone **21** as described in Scheme 5.

Scheme 3



a) methyl α-bromopropionate, 1.6 equiv. LDA, THF, -78 °C; 95%. b) LiOH, aq. THF; 86%.
c) i-$Pr_2NC_2H_5$, N-hydroxy-4-methylthiazole-2-thione, BOP, CH_2Cl_2, -23 °C; 50%.
d) 0.05M CH_2Cl_2, 450W-Hanovia lamp, U glass filter, 25 °C, 7h; 35%.

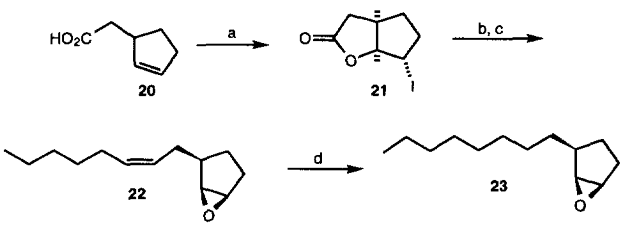
Scheme 4



a) CH_2=CHMgBr, THF; 75%. b) CH_2=CHOEt, $Hg(OAc)_2$, PhH, Δ; 66%. c) $(EtO)_2POCH_2CO_2Et$, LiCl, DBU, CH_3CN; 95%.
d) DIBALH, Et_2O, -78 °C; 94%. e) TBHP, $VO(acac)_2$, PhH, reflux; 85%. f) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C. g) $NaClO_2$, NaH_2PO_4, aq. DMSO, 0 --> 25 °C; 76% (2 steps). h) $ClCO_2$-i-Bu, N-methyl morpholine (NMM), THF, -20 °C; sodium N-hydroxy-2-thiopyridone; i) W-lamp (500W), 0.02M THF, 0 °C, 1.5 h; 42%. j) W-lamp (500W), 0.02M THF, 1.5 equiv. n-Bu_3SnH, 0 °C, 1h; 47%.

The preference for 1,2-cis stereochemistry is in accord with the paradigm established by Beckwith[18,19] and refined by Houk[20] for the cyclization of 6-hepten-2-yl radical although it is uncertain how the ring strain and hybridization of the oxiranyl radical would accommodate the simpler model.

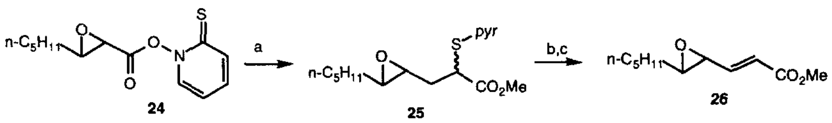
Scheme 5



a) KI, $KHCO_3$, I_2, aq. THF; b) DIBALH, Et_2O; 80%. c) $Ph_3PC_6H_{13}Br$, DMSO', DMSO; 74%.
d) H_2, PtO_2, EtOH; 85%.

Oxiranyl radicals may be applied in an intermolecular reaction as well as the intramolecular examples presented thus far. PTOC ester **24**, prepared from (E)-2-octen-1-ol by the Sharpless-Swern-Lindgren route described above, afforded unsaturated epoxy ester **26** as a 9:1 mixture (trans:cis) about the epoxide ring. The use of the Sharpless asymmetric epoxidation (SAE),[21] as opposed to the Sharpless vanadium/t-BuOOH route, coupled with the Swern and Lindgren oxidations would lead to the formation of enantiomerically-pure glycidic acids. Consequently, several of the epoxides described in this Letter could be prepared in enantiomerically-pure form.

Scheme 6



a) 500W W-lamp, 0.05M THF, 5 equiv. methyl acrylate, 40 min., 0-10 °C, 48 % (from the glycidic acid). b) m-CPBA, CH_2Cl_2. c) benzene, Δ; 64% (2 steps).

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