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# Cyclization of 1,6-Heptadienes by α-Hydroxy Radicals

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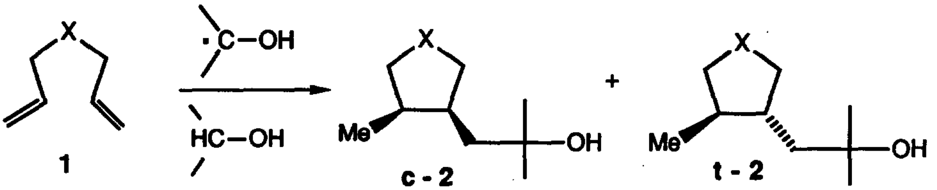
ABSTRACT. Addition of α-hydroxy isopropyl radicals, generated by γ irradiation of 2-propanol or photolysis of 2-propanol with acetone, to a variety of 1,6-heptadienes generates a 1-methyl-2-(2-hydroxyethyl)-cyclopentane or its heterocyclic equivalent. The cis-disubstituted cyclopentane predominates in these reactions.

The facile reactions which cyclize 5-hexenyl radicals to cyclopentylmethyl radicals have been the subject of numerous fruitful mechanistic[1] and synthetic[2] studies. We wish to report an efficient utilization of this reaction in which an α-hydroxyisopropyl radical, generated by γ irradiation of 2-propanol or photolysis of 2-propanol with acetone, is added to a 1,6-diene to generate a 1-methyl-2-(2-hydroxyethyl)-cyclopentane or its heterocyclic equivalent as illustrated in eq 1 and the following table.



(1)

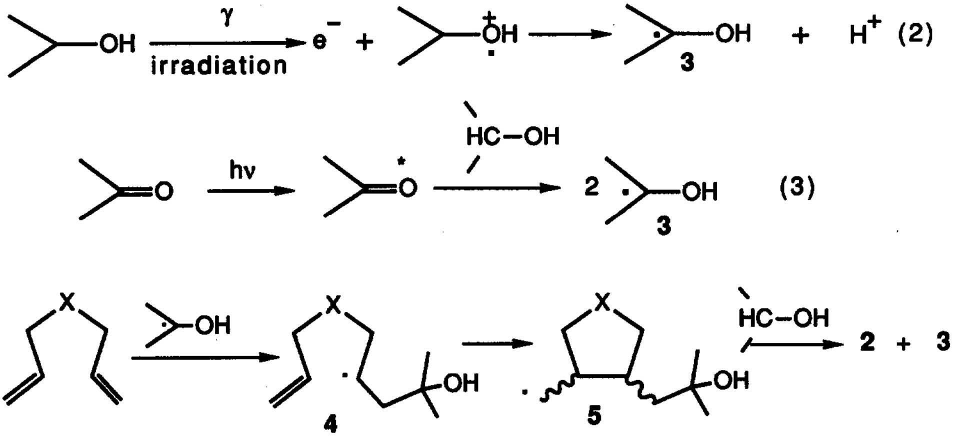
Table 1. Product Yields and *cis-trans* Ratios in the γ Irradiation Induced Addition of α-Hydroxy Isopropyl Radicals to 1,6-Heptadienes.

| Starting Material | X | R | % Yield | c-2:t-2 |
|---|---|---|---|---|
| **1a**[a] | O | | 97 (82)[a] | 4:1 (3.2:1) |
| **1b** | $CH_2$ | | 93 | 3.2:1 |
| **1c** | $CR_2$ | COOH | 83 | 5.7 |
| **1d** | CHR | COOH | 50 | - |
| **1e**[a] | NH | | 80 (80)[a] | 4.6 (4.6) |
| **1f**[a] | NR | $CH_3$ | 44[a](42) | 4.9 (4.9) |
| **1g** | NR | Allyl | 49 | 4.3 |
| **1h**[a,b] | $NR_2^+Cl^-$ | $CH_3$ | 80 (80)[a] | 4:1 (4:1) |

[a] Reaction also carried out by photolysis of 2-propanol-acetone solutions. [b] γ irradiation in 2-propanol-acetone.

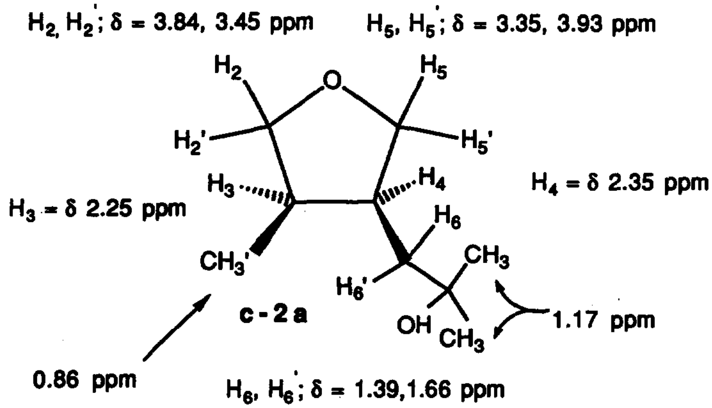
There is little doubt that the mechanism of these reactions involves generation of the α-hydroxy isopropyl radical, **3**, either by γ irradiation (eq 2)[3] or by UV photolysis of 2-propanol-acetone (eq 3).[4]

Subsequent addition of 3 to the diene generates a 1-substituted 5-hexenyl radical, 4, which cyclizes to the cyclopentyl methyl radical, 5. Abstraction of the 2-hydrogen of 2-propanol by 5 gives product along with another molecule of 3 to carry a chain reaction. A consideration of the $G_{radical}$ and $G_{product}$ for the radiation induced reaction indicates a chain reaction with a chain length of at least 5.4.[5] The appearance of two methyl doublets in the $^1H$ nmr spectra of the products demonstrates that the cyclizations give the expected *cis* and *trans* disubstituted cyclopentanes rather than cyclohexanes.



In a typical γ irradiation, diallyl ether (**1a**, 0.273 g, 2.79 mmol) was placed in a 25 mL bottle containing 2-propanol (9 mL, 0.310 M). The solution was purged with nitrogen for 20 minutes, sealed with a septum, and gamma irradiated with a $^{60}Co$ source for 48 hours at room temperature (dose rate =1.98 X $10^5$ RAD/h). The gas formed inside the reaction bottle was not analyzed. The product was isolated as a colorless oil (0.427 g, 97%) by evaporating the solvent from the irradiated solutions and drying under vacuum. The nmr spectrum of the oil showed evidence for a major and minor diastereomer and very little else. The major isomer was assigned the cis structure (vide infra): $^1H$ NMR ($CDCl_3$): δ 0.86 (d, 3 H, J=7.0 Hz, $-CH-CH_3$), 1.17 (S, 6 H, $CH_3$ $CCH_3OH$), 1.39 (dd, 1 H, J=8.9 Hz, $CH_2-CH-CHH$), 1.66 (dd, 1 H, J=4.15 Hz, $CH_2-CH-CHH$), 2.25 (m, 1 H, $CH_3-CH-CHHO$), 2.35 (m, 1 H, $CH_3-CH-CH$), 3.35 (dd, 1 H, J=8.46 Hz, $CH_2-CH-CHH-O$), 3.45 (dd, 1 H, J=2.80 Hz, $CH_3-CH-CHHO$), 3.84 (dd, 1 H, J=5.6 Hz, $CH_3-CH-CHHO$), 3.93 (t, 1 H, J=7.9 Hz, $CH_2-CH-CHH-O$). $^{13}C$ NMR ($CDCl_3$) δ 13.20 ($CH_3-CH$), 29.00 ($CH_3-C$), 30.10 ($CH_3-C$), 36.52 ($CH_2-C-OH$), 37.95 ($CH-CH_2-0$), 40.94 ($CH-CH_2-0$), 69.87 ($C(CH_3)_2-OH$), 71.98 ($CH_2-O$), 74.53 ($CH_2-O$). Gc/ms: m/e 158 ($M^+$, 17%), m/e 141 ($M^+$-OH, 100%). The gc/ms analysis also showed evidence for traces of a product in which **5** has added to another molecule of **1a** prior to H abstraction: m/e=239 ($M^+$-OH). In the photochemical reaction, **1a** (1.36 g, 13.9 mmol) was placed in a quartz vessel containing 2-propanol (37 mL, 488 mmol) and acetone (8.7 g, 150 mmol). The mixture was purged with nitrogen for 20 minutes and photolyzed for 6 hours at 280 nm. The solvents were evaporated to give 1.8 g (82%) of a colorless oil whose NMR and mass spectra were strikingly similar to those of the products prepared by γ irradiation.

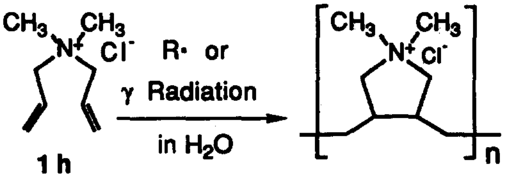
It is thought that both the regiochemistry and the stereochemistry of the cyclization of 5-hexenyl radicals are dictated by a stereoelectronic effect associated with the FMO interaction between the radical SOMO and the LUMO of the π-bond.[6] Cyclization of 1-substituted-5-hexenyl radicals generally yields a preponderance of the *cis*-2-substituted cyclopentylmethyl radical.[7] A stereoelectronic effect, in which the transition state leading to the cis product is stabilized by an interaction of the p-$\pi CH_2$ SOMO of the radical with the π* orbital of the olefin, has been invoked to explain this preference.[7,8] The nmr spectra of products of our reactions all show two diastereomers and we assume the major isomer to be the *cis*. In the case of *cis* and *trans*-3-methyl-4-(2-hydroxy-2-methylpropyl) tetrahydrofuran, **c-2a** and **t-2a**, a detailed examination of the nmr spectra bears out this assumption. A series of selective decoupling experiments and an $^1H$-$^1H$ COSY allow an assignment of the $^1H$ chemical shifts in the predominate isomer:



**c-2a**

A MM2 calculation predicts dihedral angles between $H_3$ and $H_4$ of 40° and 168° in **c-2a** and **t-2a** respectively indicating minimal coupling between these hydrogens in **c-2a**. A 2D $^1H$-$^1H$ COSY of the major isomer from the reaction of **1a** showed no off diagonal peaks to indicate coupling between $H_3$ and $H_4$ confirming that this isomer was **c-2a**. The *cis-trans* ratios in table 1 were obtained by assuming a predominance of the *cis* isomer and measuring the integrated area under the peaks for the newly created methyl groups of both diastereomers in the $^1H$ nmr spectra.

The behavior of diallyldimethylammonium chloride, **1h**, in this reaction is interesting. It is well known that aqueous solutions of diallyldimethyl ammonium salts undergo the efficient cyclopolymerization reaction shown in eq 4 when exposed to radicals in aqueous solution.[9] We observe that γ irriadiation of a 65% aqueous solution of **1h** also brings about this polymerization. In contrast, irradiation of a 65% aqueous solution of **1h** (1.34 mL, 0.54 mmol) in the cobalt source in a 2-propanol (12 g, 2 mol) acetone (5.8 g, 1 M) mixture or UV irradiation in this solvent mixture generates the monomeric cycloaddition product in 80% yield. It is probable that the availability of the abstractable hydrogens in isopropanol



(4)

prevents the addition of radical **5** to another molecule of **1h** and the consequent polymerization.

It appears that radicals derived from other secondary alcohols will also participate in this reaction. Preliminary spectral data indicate that the α-hydroxy radicals from 2-butanol and cyclohexanol undergo a cycloaddition reaction with diallyl ether upon γ irradiation.

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