Synthesis of 5,6,7,8-Tetrahydroquinolines by Thermolysis of Oxime *O*-Allyl Ethers in the Presence of Boron Trifluoride Etherate

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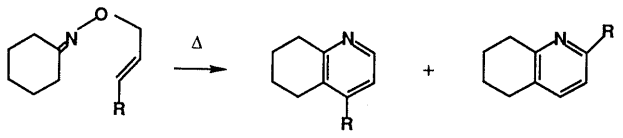
Thermolysis of cyclohexanone oxime *O*-crotyl and *O*-cinnamyl ether in the presence of BF_3-etherate regioselectively gave 4-methyl- and 4-phenyl-5,6,7,8-tetrahydroquinoline, while the addition of organic bases such as triethylamine and pyridine inhibited the rearrangement. These findings suggested that the addition of the acid made [1,2] shift the predominant one of the two possible transformations, [1,2] and [2,3] shift, of the *O*-allyl ethers.

Keywords thermal rearrangement; oxime *O*-crotyl ether; 6,7-dimethoxyonychine; oxime *O*-cinnamyl ether; 4-methyl-5,6,7,8-tetrahydroquinoline; 4-phenyl-5,6,7,8-tetrahydroquinoline

We have reported the thermal rearrangement of cycloalkanone oxime *O*-allyl ethers to cycloalkenopyridines. For example, thermolysis of cyclohexanone oxime *O*-crotyl ether (**1**) gave a mixture of 4-methyl- (**2**) and 2-methyl-5,6,7,8-tetrahydroquinoline (**3**) in the ratio of 17:40,[1] though the mechanism of this reaction has not been established. Now, we have investigated the effect of Lewis acids on the reaction. We report here some experimental results obtained by conducting the rearrangement reaction of oxime *O*-allyl ethers, in the presence of BF_3-etherate.

The results of thermolysis of cyclohexanone oxime *O*-crotyl ether (**1**) in benzene in the presence of some Lewis acids are summarized in Table I. The rearrangement of cyclohexanone oxime *O*-crotyl ether in benzene in the presence of BF_3-etherate resulted in formation of **2** in a highly regioselective manner. We also ran the reaction in several other solvents, and the use of benzene as a solvent gave the best result [tetrahydrofuran, ethyl acetate, acetonitrile—**2**:**3**=4:1 (yield 20—30%); chloroform, methanol, dimethyl sulfoxide, dimethylformamide, hexane, dioxane, dichlorobenzene—**2**:**3**=1:1 (1—5%)]. The rearrangement of cyclohexanone oxime *O*-α-methylallyl ether under the same conditions gave a mixture of **2** and **3** in the ratio of 4:5, whereas the ratio of the two isomeric products was approximately 2:7[1] in the case of no addition of Lewis acid. On the other hand, addition of bases such as dimethylamine, triethylamine, and pyridine prevented the rearrangement, resulting in the recovery of the starting material, though the reason for this is unknown.



1: R=Me **2**: R=Me **3**: R=Me

4: R=Ph **5**: R=Ph **6**: R=Ph

Chart 1

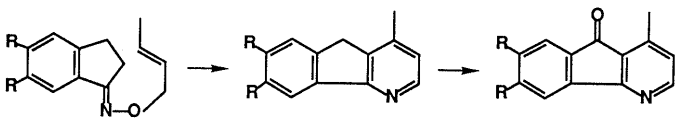
TABLE I. Yields of the Rearrangement Product and Ratio of 4-Methyl- and 2-Methyltetrahydroquinoline

Lewis acid 0.1 eq	Yield (**2**+**3**)	**2**:**3**
— (neat)	57%	1:2
— (in benzene)	50%	1:1
$AlCl_3$	25%	5:4
$ZnCl_2$	10%+**1** (50%)	5:3
$CeCl_3$	5%+**1** (70%)	5:3
$PdCl_2$	7%	1:1
$SbCl_3$	18%	5:3
$SnCl_4$	5%+**1** (20%)	1:1
$ZrCl_4$	10%+**1** (50%)	5:4
BF_3-etherate	55%	25:1

Thermolysis of the oxime *O*-cinnamyl ether (**4**) in the presence of BF_3-etherate gave 4-phenyl-5,6,7,8-tetrahydroquinoline (**5**) as a sole product, though a mixture of two regioisomeric products, 4-phenyl- (**5**) and 2-phenyl-5,6,7,8-tetrahydroquinoline (**6**) was produced from the same starting material when no acid was used.[2]

These findings imply that addition of BF_3-etherate to the rearrangement reaction makes [1,2] shift predominant and also has the effect of trapping the cycloalkenopyridine initially produced by the rearrangement as a salt.

Isolation of **2** as a major product as mentioned above provided an improved synthesis of the alkaloid, onychine (**8**),[3,4] in the sense of overall yield. Application of the modified method to 5,6-dimethoxyindan-1-one oxime *O*-crotyl ether (**9**) gave 6,7-dimethoxy-1-methyl-4-azafluorene (**10**) as a major product in 45% yield. Oxidation of **10** with potassium permanganate gave 6,7-dimethoxyonychine (**11**) in good yield, and its spectroscopic data showed good agreement with those described in the literature,[5] indicating the accomplishment of the first synthesis of this simple alkaloid.



7: R=H **8**: R=H

9: R=OMe **10**: R=OMe **11**: R=OMe

Chart 2

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Infrared (IR) spectra were measured on a

Hitachi 270-30 spectrophotometer. ^{1}H-NMR spectra were determined in $CDCl_3$ with Me_4Si as an internal reference on a NEVA NV-21 instrument. Mass spectra were recorded on a JEOL JMS-O1SG spectrometer. Preparative thin layer chromatography (PTLC) was carried out on Kiesel gel $60F_{254}$ (Merck) with appropriate solvents.

General Method for the Thermolysis of the Oximes Heating an oxime (100 mg) in a sealed glass tube in the presence of Lewis acid or base in benzene or another solvent (0.3 ml) at 180—190 °C (bath temperature) for 24—48 h gave a brown oil. The crude product was separated by preparative thin layer chromatography ($CHCl_3$: MeOH = 50 : 1) to give the corresponding pyridine derivative.

Cyclohexanone Oxime *O*-Cinnamyl Ether (4) IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640, 1600, 1580. ^{1}H-NMR ($CDCl_3$) δ: 4.73 (2H, d, J=5 Hz, OCH_2), 6.41 (1H, m, –CH=), 6.67 (1H, d, J=15 Hz, =CH–C_6H_5), 7.22—7.52 (5H, m, C_6H_5). MS *m/z*: 229.1457 (M^+, Calcd for $C_{15}H_{19}NO$, 229.1465).

4-Phenyl-5,6,7,8-tetrahydroquinoline (5) IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1595. ^{1}H-NMR ($CDCl_3$) δ: 1.65—1.98 (4H, m, 6, 7-H_2), 2.64 (2H, t, J=6 Hz, 5-H_2), 3.02 (2H, t, J=6 Hz, 8-H_2), 6.98 (1H, d, J=5 Hz, 3-H), 7.26—7.48 (5H, m), 8.41 (1H, d, J=5 Hz, 2-H). MS *m/z*: 209.1209 (M^+, Calcd for $C_{15}H_{15}N$, 209.1204).

5,6-Dimethoxyindan-1-one Oxime *O*-Crotyl Ether (9) A solution of 5,6-dimethoxyindanone (1 g), *O*-crotylhydroxylamine hydrochloride (1 g), and sodium acetate (1 g) in EtOH (15 ml) was heated under reflux for 2 h. After evaporation of the solvent, the residue was suspended in water and this solution was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water, dried ($MgSO_4$), and evaporated to dryness to give the oxime (**9**) as white crystals. Yield: 1.29 g (95%). mp 91—93 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680. ^{1}H-NMR ($CDCl_3$) δ: 1.75 (3H, d, J=5 Hz, CH_3), 2.93 (4H, m, $CH_2 \times 2$), 3.90, 3.92 (3H each, s, OCH_3), 4.61 (2H, m, OCH_2), 5.78 (2H, m, CH=CH), 6.79 (1H, s, 4-H), 7.15 (1H, s, 7-H). MS *m/z*: 261.1364 (M^+, Calcd for $C_{15}H_{19}NO_3$, 261.1368).

6,7-Dimethoxy-1-methyl-4-azafluorene (10) IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1600, 1570. ^{1}H-NMR ($CDCl_3$) δ: 2.42 (3H, s, CH_3), 3.71 (2H, s, CH_2), 3.97, 4.00 (3H each, s, OCH_3), 6.95 (1H, d, J=5 Hz, 2-H), 7.11 (1H, s, 8-H), 7.61 (1H, s, 5-H), 8.42 (1H, d, J=5 Hz, 3-H). MS *m/z*: 241.1102 (M^+, Calcd for $C_{15}H_{15}NO_2$, 241.1112).

6,7-Dimethoxyonychine (11) A solution of azafluorene (**10**) (100 mg) and $KMnO_4$ (300 mg) in acetone (5 ml) was stirred at room temperature for 5 h then diluted with EtOH (0.5 ml), and the whole was filtered. The filtrate was concentrated under reduced pressure to leave a residue, which crystallized from EtOH to give dimethoxyonychine (**11**) (95 mg, 90%). mp 188—189 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700, 1600, 1565. ^{1}H-NMR ($CDCl_3$) δ: 2.60 (3H, s, CH_3), 3.96, 4.03 (3H each, s, OCH_3), 6.87 (1H, d, J=5 Hz, 2-H), 7.22 (1H, s, 5-H), 7.35 (1H, s, 8-H), 8.31 (1H, d, J=5 Hz, 3-H). MS *m/z*: 255.0894 (M^+, Calcd for $C_{15}H_{13}NO_3$, 255.0894).

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