THERMOLYSIS OF OXIME O-ALLYL ETHERS: A NEW METHOD FOR SYNTHESIS OF PYRIDINE DERIVATIVES

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Abstract —— A new method for constructing pyridine ring by thermolysis of oxime O-allyl ethers of several ketones in the presence of oxygen is described.

In 1973 Ranganathan and his co-workers reported the thermal rearrangement of oxime O-allyl ethers derived from some benzaldehydes to the corresponding nitrones according to the preferential [2,3] shift[1]. Following the report, Rogers and Eckersley indicated that the reaction proceeded by the homolysis-recombination manner at least in part by their e.s.r. investigation[2]. Our interest on the thermal rearrangement of oxime O-allyl ethers of cycloalkanones resulted in finding a new method for constructing pyridine ring.

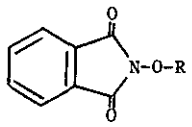
Treatment of N-hydroxyphthalimide with allyl chloride in the presence of potassium carbonate in dimethyl sulphoxide gave N-allyloxyphthalimide (1) in 95% yield. Hydrazinolysis of (1) gave O-allyl-hydroxylamine (2), which was isolated as its hydrochloride. O-methallyl- (3), O-crotyl- (4), and O-α-methyl-allyl-hydroxylamine hydrochloride (5) were also prepared by the same manner in good yield (> 85%). Treatment of cyclohexanone with these O-allyl-hydroxylamines in the usual way gave the respective oxime O-allyl ethers (6), (7), (8), and (9), quantitatively.

Cyclohexanone oxime O-allyl ether (6) thus obtained was heated in a sealed glass tube at 180-190°C (bath) under argon to give two products, which were separated by preparative thin layer chromatography on silica gel. The major one (isolated in 60% yield after compensating the starting material (20%)) was the isoxazolidine (10), the dimeric product of (6), i.r. ($CHCl_3$); 1645cm^{-1} (C=N), the molecular ion peak at m/e 306 corresponding to $C_{18}H_{30}N_2O_2$; ^{1}H-n.m.r. ($CDCl_3$), (δ); 6.27-5.83 (1H, m, CH_2-C<u>H</u>=CH_2), 5.31-5.04 (2H, m, C<u>H</u>$_2$=CH-), 3.33 (2H, t of d, J=1.5 and 6 Hz., CH_2-N), 4.09 and 4.10 (1H each, d, J=4 and 6 Hz., respectively, CH-C<u>H</u>$_2$-O), and 4.50-4.18 (1H, m, CH-O), ^{13}C-n.m.r. ($CDCl_3$), (ppm); 160.4 (s), 135.8 (d), and 116,3 (t) (sp^2 carbons), 75.4 (d) and 74.8 (t) (carbons bearing oxygen), and 67.0 (s) and 53.3 (t) (carbons bearing nitrogen), which was supposed to be produced by the cycloaddition of the 1,3-dipole species (11) with (6). The minor one, isolated in 3% yield, was 5,6,7,8-tetrahydroquinoline characterised as its picrate, m.p. 158

-159°C. On the other hand, when the thermolysis was carried out under air in place of argon, the tetrahydroquinoline was obtained in 50% yield along with water and very minute amount of the isoxazolidine (10). In order to extend the applicability of the cyclisation reaction of oxime O-allyl ethers, several cycloalkanone oxime O-allyl ethers were subjected to the thermolysis under the same conditions. The results, summarised in Table, show the cycloalkanone oxime O-allyl ethers gave respective cycloalkenopyridines in fair yield. Furthermore, the oxime O-allyl ethers of di-propyl- and di-butyl ketone furnished α-propyl-β-ethyl- and α-butyl-β-propyl-pyridine in 35 and 50% yield, respectively, by thermolysis under air, both of which were characterised as their picrate, m.p. 150°C and 154-155°C.

Cyclohexanone oxime O-methallyl ether (7) gave 3-methyl-5,6,7,8-tetrahydroquinoline as a sole product by heating, while crotyl- (8) and α-methyl-allyl ether (9) yielded a mixture of 2-methyl- and 4-methyl-5,6,7,8-tetrahydroquinoline in a ratio of 5:2, suggesting that the reaction proceeded by the way including the homolysis-recombination step in cage.

A brief investigation concerning the reaction mechanism was made: (a) re-heating of the isoxazolidine (10) did not give the tetrahydroquinoline, (b) the thermolysis of (6) in the presence of 2,6-di-t-butyl-p-cresol as a radical scavenger did not affect the yield of the tetrahydroquinoline. These results suggest that oxygen participates after nitrone formation and in an ionic manner. One of the plausible mechanisms was shown in Chart I[3, 4].



(1) R= $CH_2-CH=CH_2$

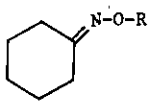
NH_2-O-R

(2) R= $CH_2-CH=CH_2$

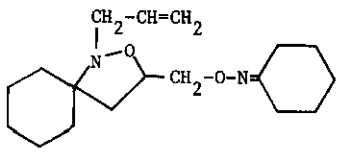
(3) R= $CH_2-C(Me)=CH_2$

(4) R= $CH_2-CH=CH-Me$

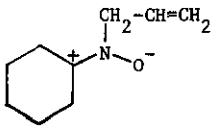
(5) R= $CH(Me)-CH=CH_2$



R of (6), (7), (8), and (9) correspond to (2), (3), (4), and (5), respectively



(10)



(11)

Chart I

Table

oxime O-allyl ether	alkenopyridine	heating time hr	yield %
cyclopentanone	2,3-cyclopentenopyridine	30	30
cyclohexanone	5,6,7,8-tetrahydroquinoline	70	50
cycloheptanone	2,3-cycloheptenopyridine	50	55
cyclooctanone	2,3-cyclooctenopyridine	48	65
cyclododecanone	2,3-cyclododecenopyridine	48	60
2-methyl-cyclohexanone	8-methyl-5,6,7,8-tetrahydro-quinoline	35	35
3-methyl-cyclohexanone	5-, and 7-methyl-5,6,7,8-tetra-hydroquinoline	40	40
4-methyl-cyclohexanone	6-methyl-5,6,7,8-tetrahydro-quinoline	40	40

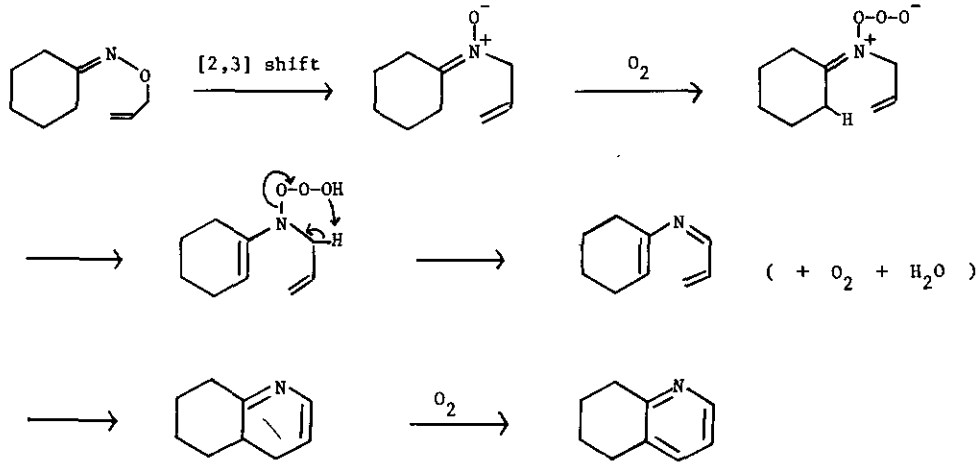


Chart II

References

1) S. Ranganathan, D. Ranganathan, R. S. Sidhu, and A. K. Mehrotra, Tetrahedron Lett., 1973, 3577.

2) A. Eckersley, and N. A. J. Rogers, Tetrahedron Lett., 1974, 1661.

3) We express our appreciation to Dr. A. Nishinaga (Department of Synthetic Chemistry, Kyoto University) for useful discussion of the reaction mechanism.

4) Photooxidation of 2,4,4-trimethyl-Δ^1-pyrroline-N-oxide with singlet oxygen has been reported as an "ene" reaction or a 1,3-dipolar cycloaddition. T. -Y. Ching and C. S. Foote, Tetrahedron Lett., 1975, 3771.

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