FLASH VACUUM PYROLYSIS OF PYRIDINE *N*-OXIDES

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Abstract-Pyridine *N*-oxide was pyrolysed under flash vacuum pyrolysis conditions to afford pyridine, pyrrole, 2-pyridone, 2-cyanomethylpyridine, and bipyridyls. Phenylpyridine *N*-oxides gave cyanonaphthalenes and naphthalene other than the above mentioned products. Pyrolysis of 2,6-disubstituted pyridine *N*-oxides provided the products which were supposed to be derived from the intramolecular oxygen migration.

The chemistry of pyridine *N*-oxides **1** has been one of the most extensively studied fields in heterocyclic compounds, and the thorough investigations have been done for the reactivity of **1** in solution.[1] Under the photoreaction conditions, it was proposed that **1** transformed to the oxaziridine intermediates, which resulted in ring expansion and sequential reactions.[2] On the other hand, vapor phase chemistry of pyridine *N*-oxides are seldom reported. We have studied the flash vacuum pyrolysis (FVP)[3] of pyridine *N*-oxides which have active methylene groups at their α-positions.[4] Picolyl radicals were the primary intermediates in the reaction, therefore the reactivities of pyridine *N*-oxide moiety itself could not be clarified. In this paper we wish to report the FVP of pyridine *N*-oxides and the reaction mechanisms.

In the typical experiment,[5] 10 mmol of pyridine *N*-oxide was distilled into a quartz pyrolysis tube (15 cm X 1 cm) from a flask heated by surrounding it with a Nichrome wire. FVP was carried out at 750-850°C under 0.01-0.001 mmHg. Products were collected in a cold trap (liquid N_2). Collected reaction mixture was distilled to seperate into a residual part and a distillable part. The former was chromatographed. The latter was analyzed and identified with the authentic samples by nmr and gcms. Pyridine *N*-oxide **1a** was pyrolysed to afford pyridine **2**, pyrrole **3**, 2-pyridone **4**, 2-cyanomethylpyridine **5**, and bipyridyls **6** (mainly 2,2'-isomer) (Table). Their formation can be interpreted by a plausible mechanism as shown in Scheme 1.

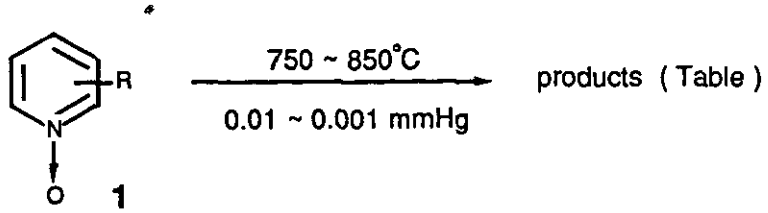

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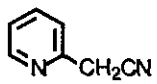
Table **Flash Vacuum Pyrolysis of Pyridine *N*-Oxides**

entry	substrate 1	products 2	3	4	others
1	R=H	31 %	trace	4 %	**5** 6 % **6** 7 %
2	R=2-Ph	22 %	11 %[6]	2 %	**7** 11 % **8** 20 % **9** 20 %
3	R=3-Ph	23 %	3 %[6]	1 %[9]	**7** 11 % **8** 16 % **9** 9 %
4	R=4-Ph	26 %	7 %[6]	2 %	**7** 17 % **8** 21 % **9** 9 %
5	R=2,6-diPh	12 %	14 %[7]	-	**10** 21 % **11** 18 %
6	R=2-CN,6-Ph	7 %	15 %[8]	-	**12** 1 % **13** 17 % **14** 9 %



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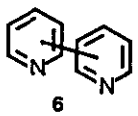

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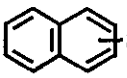
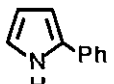


7 R=1-CN
8 R=2-CN
9 R=H



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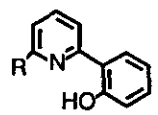
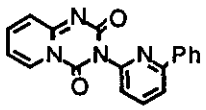


11 R=Ph **13** R=CN



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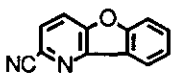

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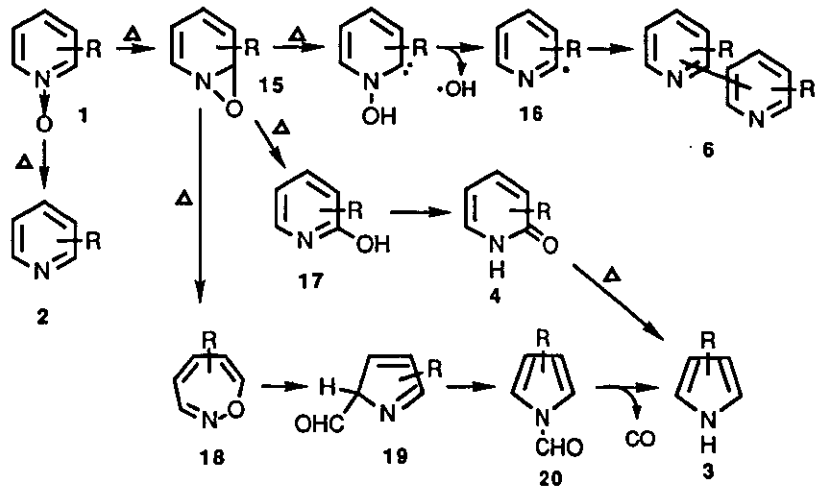
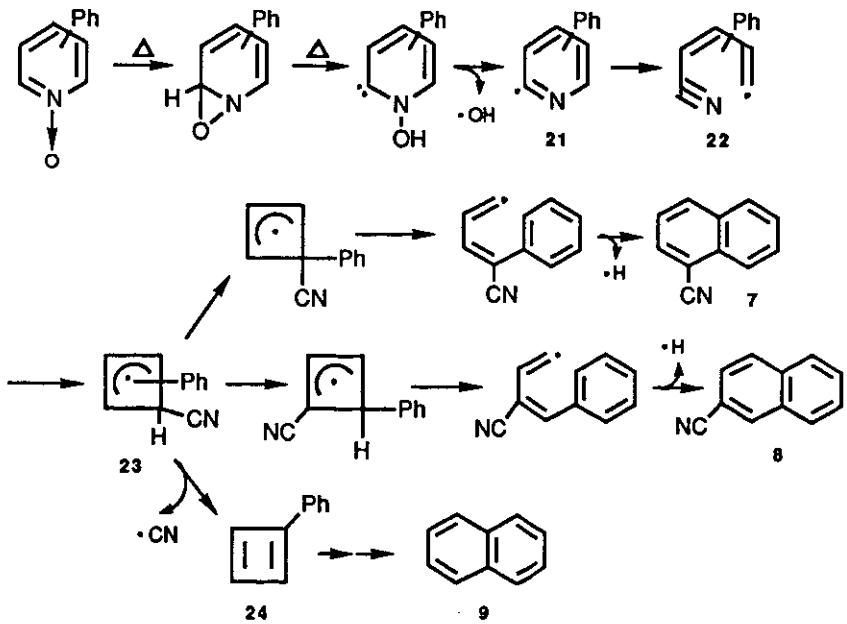
Pyridine was obtained from the heterolytic cleavage of the N-O bond. Pyrrole, 2-pyridone, and bipyridyls were suggested to be formed via the common intermediate oxaziridine **15**. Elimination of hydroxyl radical from **15** caused the formation of pyridyl radical **16**, which attacked pyridine to produce bipyridyls **6**. Oxygen insertion to α-C-H bond gave 2-hydroxypyridine **17**, which isomerized to 2-pyridone **4**. Compound **4** was stable under our FVP conditions although decarbonylation of **4** to pyrrole by FVP was reported.[10] Ring expansion of **15** afforded 1,2-oxazepine **18**, which was transformed to 2*H*-pyrrole-2-carbaldehyde **19** followed by decarbonylation to give pyrrole **3**. The formation mechanism of 2-cyanomethylpyridine was remained uncomprehensible, but might be explicable by the existence of CHCN unit which was derived from the ring fission of pyridine. The differences in the reaction products from the photoreaction ones were suggested to owe the high temperature of FVP conditions.



Scheme 1

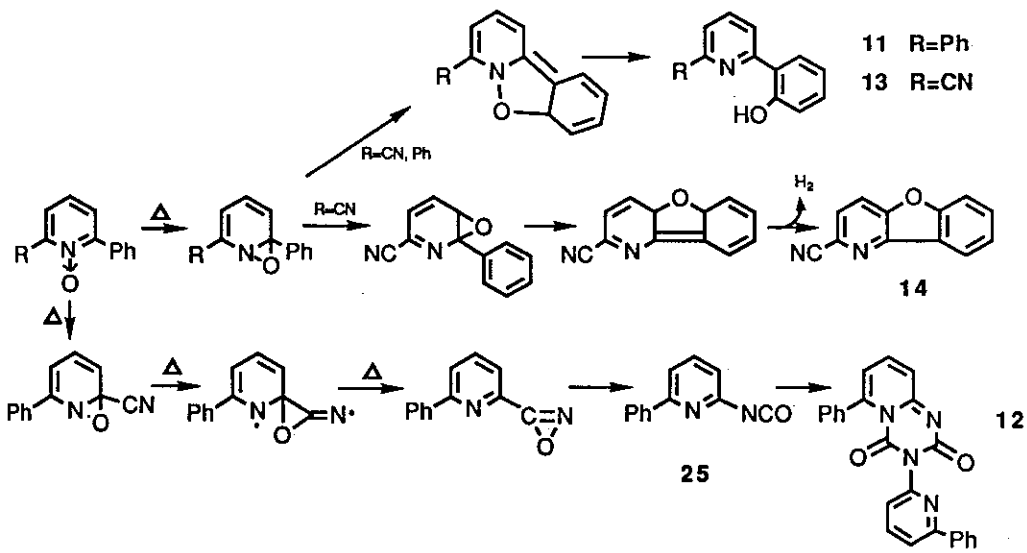
Next, phenylpyridine *N*-oxides were pyrolysed under the same conditions. Cyanomethylpyridines were not obtained in these cases, but instead cyanonaphthalenes **7**, **8** and naphthalene **9** were produced (Table). The formation mechanisms of naphthalenes were considered as shown in Scheme 2. The pyridyl radical **21** underwent the C-N bond cleavage, and **22** re-closed to cyclobutenyl radical **23**, which underwent phenyl and/or hydrogen shift followed by ring opening and ring closure to form cyanonaphthalenes (**7** and **8**). Elimination of CN radical gave phenylcyclobutadiene **24**, which isomerized to naphthalene **9**.



Scheme 2

The character of postulated intermediary oxaziridine was supposed to be greatly affected by the α-substituent on the pyridine ring. Hence 2,6-diphenylpyridine *N*-oxide was selected as a substrate in order to investigate the influence of α-substituent. As a result, 2-(2-hydroxyphenyl)-6-phenylpyridine **11** (R=Ph) was obtained besides 2,6-diphenylpyridine and pyrroles. Compound **11** was suggested to be produced via the sequential intramolecular oxygen migration (Scheme 3). Similar phenomenon was observed in the case of 2-cyano-6-phenylpyridine *N*-oxide. The oxygen migration to the phenyl group formed 2-cyano-6-(2-hydroxyphenyl)pyridine (**13** R=CN) and 3-cyano-4-azadibenzofuran **14**. The oxygen migration to the other side gave 2-isocyanato-6-phenylpyridine **25**, which dimerized to **12**.

In summary, pyridine *N*-oxides were activated at their N-O bond by thermal energy. The heterolytic cleavage of N-O bond gave the deoxygenated pyridines. Formations of the other products were rationally accounted for by the intermediacy of oxaziridines. The sequential oxygen migration of the α-substituted pyridine *N*-oxides also suggested the oxaziridine as an intermediate.



Scheme 3

REFERENCES AND NOTES

1. a) E. Ochiai, "Aromatic Amine Oxides," Elsevier, New York, 1967.
   b) A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic N-Oxides," Academic Press, New York, 1971.
2. C. Kaneko, S. Yamada, I. Yokoe, and T. Kubota, *Tetrahedron Lett.*, **1970**, 2333.
3. R. F. C. Brown," Pyrolytic Methods in Organic Chemistry," Academic Press, New York, 1980.
4. a) A. Ohsawa, T. Kawaguchi, and H. Igeta, *Chem. Pharm. Bull.*, 1981, **29**, 1481.
   b) idem, *Chemistry Lett.*, **1981**, 1737. c) idem, *J. Org. Chem.*, 1982, **47**, 3497.
   d) idem, *Synthesis*, **1983**, 1037.
5. A. Ohsawa, T. Itoh, and H. Igeta, *Heterocycles*, 1987, **26**, 2677.
6. Mixtures of 2- and 3-phenylpyrroles. Substituents of pyrroles migrated under FVP conditions.
7. Mixtures of diphenylpyrroles. Migration was supposed to occur at structure **18**.
8. Mixtures of cyanophenylpyrroles.
9. 3-Phenyl-2-pyridone. 5-Phenyl-2-pyridone was not detected.
10. D.A. Brent, J.D. Hribar, and D.C. DeJongh, *J. Org. Chem.*, 1970, **35**, 135.

Received, 6th February, 1990