

CONTROLLING FACTORS FOR THE FORMATION OF PYRROLE, PYRIDINE, AND
AZEPINE IN THERMAL REARRANGEMENT OF 2H-AZIRINES[†]

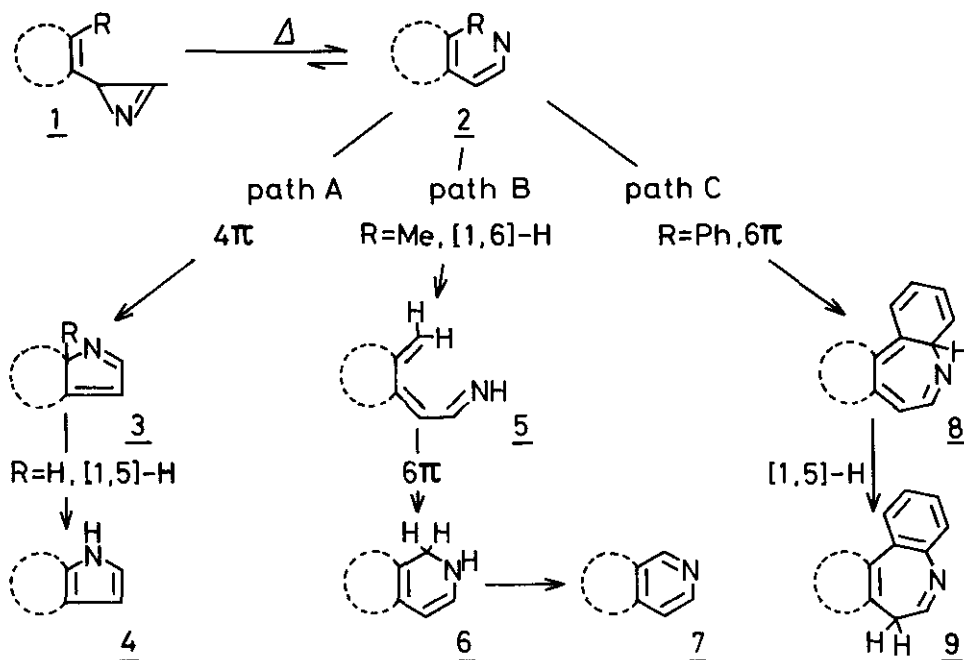
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Abstract—Thermal rearrangement of 2-(cyclohexen-1-yl)- and 2-(cyclopenten-1-yl)-2H-azirines, bearing a methyl or a phenyl group at the 2-position of cycloalkenes, was compared with those of corresponding acyclic and benzofuranylazirines. Suppression of the cyclization into pyrrole in favor of pyridine and azepine formations from the azirines having cyclic unsaturation is explained by the strain of fused 2H-pyrrole and the electronic character of vinyl nitrene intermediates.

Thermal rearrangement of azirines into 5-membered ring compounds, such as indole, pyrrole, isoxazole, and pyrazole, has been well established.¹ As these reactions proceed in high yields by heating azirines in inert media, azirines can be considered as versatile starting material for the synthesis of these heterocycles. Our recent investigations revealed that thermal rearrangement of azirines also gave 6- and 7-membered nitrogen containing heterocycles.² It was further shown that these reactions could be recognized by electrocyclic reaction and hydrogen shift from vinyl nitrene,³⁻⁵ as shown in Scheme 1. These three types of reactions forming pyrrole (path A), pyridine (path B), and azepine rings (path C) proceeded selectively when the unsaturated groups at 2-position of the azirine were benzofuran nuclei and substituent R was hydrogen, methyl, or phenyl group, respectively. However, in the cases of acyclic unsaturated group, 3-phenyl-2-(Z-propenyl)-2H-azirine gave a mixture of pyrrole and pyridine derivatives⁶ but 3-phenyl-2-(Z-styryl)-2H-azirine gave 2,5-diphenylpyrrole selectively.^{1b} Here, we

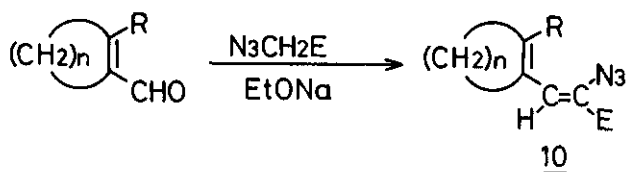
[†] This communication is dedicated to late Professor Tetsuji Kametani in honor of his great achievement in the field of heterocyclic chemistry.



Scheme 1.

describe our investigation to elucidate the factors controlling in the partition between paths A and B and also between paths A and C.

Four ethyl α -azidoacrylates 10a - 10d having 2-methyl- or 2-phenylcycloalkenyl group at the β -position were prepared by base catalyzed condensation of the corresponding aldehydes with ethyl azidoacetate.⁷



	n	R
a	4	Me
b	3	Me
c	4	Ph
d	3	Ph

E=CO₂Et

As it has been established that thermolyses of vinyl azides generally proceed via azirines,⁸ thermal reactions of 10a-10d were performed to study the reactions of corresponding azirines 1a-1d. Decomposition of 10a, having a 2-methylcyclohexen-1-yl group, was carried out in heptane under reflux for 30 min. Separation of the resulting product mixture by column chromatography on silica gel gave an oily product and colorless crystalline compound, mp 52 - 53°C, in a ratio of 41 : 59. The nmr spectrum of the minor product showed the presence of one olefinic proton (δ 6.38) and methyl protons (3H singlet at δ 1.30).⁹ On the other hand, the

major product did not show the methyl singlet but two aromatic signals (δ 7.81 and 8.37), each as singlet.⁹ On the basis of ir and nmr spectra,⁹ these products were assigned as ethyl 7a-methyl-5,6,7,7a-tetrahydro-4H-indole-2-carboxylate 3a and ethyl 5,6,7,8,-tetrahydroisoquinoline-3-carboxylate 7a formed by paths A and B, respectively.

By the same way, the cyclopentenyl derivative 10b gave also the mixture of ethyl 6a-methyl-4,5,6,6a-tetrahydrocyclopenta[b]pyrrole-2-carboxylate 3b⁹ and ethyl 6,7-dihydro-5H-cyclopenta[c]pyridine-3-carboxylate 7b.⁹ But compared to the reaction of 10a the ratio of 3b to 7b changed drastically to 14 : 86.

When the vinyl azides 10c having 2-phenylcyclohexen-1-yl group was decomposed under the same conditions as above, a single product, mp 123 - 124°C, was obtained, quantitatively. This compound was assigned as ethyl 7a-phenyl-5,6,7,7a-tetrahydro-4H-indole-2-carboxylate 3c on the basis of nmr spectrum showing the presence of one olefinic proton (δ 6.53) and aromatic protons (5H singlet at δ 7.31) and ir spectrum.⁹

However, in the case of 2-phenylcyclopenten-1-yl derivative 10d, two compounds were obtained. The major product, mp 64 - 65°C, having the same spectral properties as 3c, was assigned as ethyl 6a-phenyl-4,5,6,6a-tetrahydrocyclopenta[b]pyrrole-2-carboxylate 3d. The minor product, mp 76 - 77°C, showing only 4 aromatic protons, and a singlet corresponding to the methylene of azepine ring at

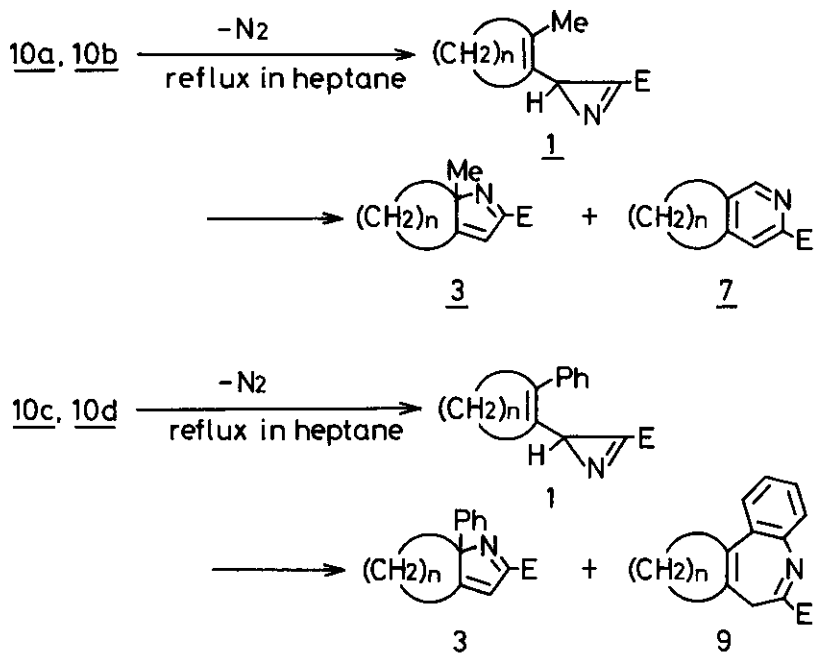
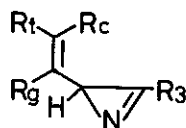


Table. Fraction of the partition to each path depending on the substituents.

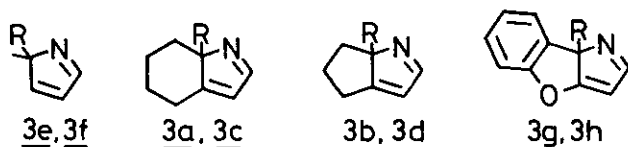


No	Substituent				Yield(%)	Fraction (%)	
	R _c	R _t	R _g	R ₃		path A	path B
<u>1e</u>	Me	H	H	Ph	quant.	85	15
<u>1a</u>	Me	-(CH ₂) ₄ -		CO ₂ Et	26	41	59
<u>1b</u>	Me	-(CH ₂) ₃ -		CO ₂ Et	60	14	86
<u>1g</u>	Me	benzofuran		CO ₂ Et	quant.	0	100
No	Substituent				Yield(%)	Fraction (%)	
	R _c	R _t	R _g	R ₃		path A	path C
<u>1f</u>	Ph	H	H	Ph	quant.	100	0
<u>1c</u>	Ph	-(CH ₂) ₄ -		CO ₂ Et	quant.	100	0
<u>1d</u>	Ph	-(CH ₂) ₃ -		CO ₂ Et	82	60	40
<u>1h</u>	Ph	benzofuran		CO ₂ Et	quant.	0	100

5 3.11, was assigned as ethyl 7,8,9,10-tetrahydrocyclopenta[d][1]benzazepine-7-carboxylate 9d, formed by cyclization of vinyl nitrene at the ortho-position of benzene ring and following 1,5-hydrogen shift.

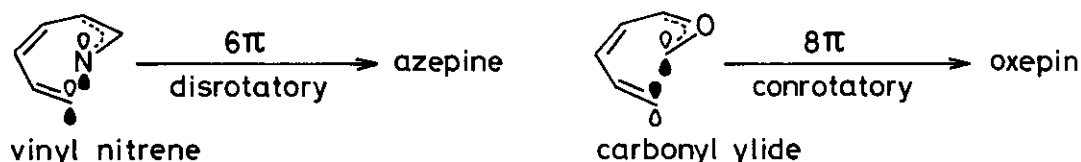
The results obtained in thermal decomposition of these four vinyl azides were summarized in Table, with the data of thermal reactions of acyclic azirines 1e⁶ and 1f^{1b} as well as the benzofuranylazirines 1g and 1h,² for comparison.

Considering that the vinyl nitrenes 2 are the common intermediates in paths A, B, and C, partition between these reactions are determined by the steps forming 3, 5, and 8. Suppression of path A in favor of path B in the order, acyclic < cyclohexenyl < cyclopentenyl < benzofuranyl, would be explained in terms of ring strain of 2H-pyrroles 3. The benzofuran system 3g is considered to have the highest strain, because of fusion of additional benzene ring. Thus, as the strain of the



2H-pyrrole 3 increases, path A is suppressed making path B important. Although data were absent concerning the strain energy of these types of 2H-pyrrole ring system, the strain energy of bicyclo[3.3.0]nonane and bicyclo[4.3.0]octane were reported to be 41 and 52 kJ/mol,¹⁰ respectively.

The same would be the reason for the partition between path A and path C. The fact that azepine formation is not observed in cyclohexenyl azirine 1c, suggesting path C is the least favored process, would be explained by the disadvantage destroying the aromatic stability of benzene ring in 8. Another important factor would be the electronic character of the vinyl nitrene intermediate 2. Eberbach and his co-workers reported that thermal reaction of vinyl oxirans usually gave dihydrofuran via carbonyl ylide intermediates, but even acyclic vinyl oxirans having a phenyl group cis to the oxiran ring gave benzoxepin exclusively.¹¹ Marked difference between the carbonyl ylide and vinyl nitrene intermediate could be explained in terms of the number of the π -electrons participating in the cy-



Scheme 2.

clization processes. To attain 1,7-cyclization the molecules must have an all-cis configuration in which the terminal atoms are forced to overlap, as shown in Scheme 2. For the oxepin formation from styryl substituted carbonyl ylide, this helical configuration is favorable. On the other hand, as the vinyl nitrene is considered as a 2π -component,⁵ styryl substituted vinyl nitrene has 6π -electrons. Therefore, in 1,7-cyclization of vinyl nitrene into azepines, disrotatory cyclization requires large deformation making path C difficult.

In conclusion, we could make clear that the formation of pyrrole, pyridine, and azepine rings are mainly controlled by the ring strain of the 2H-pyrrole. And furthermore azepine formation proceeds in compelled situation owing to the sterically difficult 6-electron-1,7-cyclization.

REFERENCES

1. a) K. Isomura, T. Tanaka, and H. Taniguchi, Chemistry Lett., 1977, 397. and references cited therein.
 b) A. Padwa, J. Smolanoff, and A. Tremper, J. Org. Chem., 1976, 41, 543.
2. K. Isomura, H. Taguchi, T. Tanaka, and H. Taniguchi, Chemistry Lett., 1977, 401.
3. K. Isomura, S. Noguchi, M. Saruwatari, S. Hatano, and H. Taniguchi, Tetrahedron Lett., 1980, 21, 3879.

4. K. Isomura, G. Ayabe, S. Hatano, and H. Taniguchi, J. C. S. Chem. Comm., 1980, 1252.
5. M. Sakurai, G. Ayabe, S. Teramoto, K. Isomura, and H. Taniguchi, presented at the 7th. IUPAC Conference on Physical Organic Chemistry, Auckland, New Zealand, 1984, Abstract No. A7.
6. Thermal rearrangement of 3-phenyl-2-(Z-propenyl)-2H-azirine at 140°C for 40 h gave 2-methyl-5-phenylpyrrole and 2-phenylpyridine in 85 and 15 % yields, respectively.
7. H. Hemetsberger, D. Knitel, and H. Weidmann, Monatsh. Chem., 1969, 100, 1599.
8. K. Isomura, Y. Hirose, H. Shuyama, S. Abe, G. Ayabe, and H. Taniguchi, Hetrocycles, 1987, 9, 1207.
9. Ir and nmr spectra of 3, 7, and 9.
 - 3a Ir (liq. film, cm^{-1}) 1720. Nmr (δ in CDCl_3) 0.50-3.10 (8H, m), 1.30 (3H, s), 1.42 (3H, t, $J=7\text{ Hz}$), 4.40 (2H, q, $J=7\text{ Hz}$), 6.38 (1H, m).
 - 7b Ir (liq. film, cm^{-1}) 1718. Nmr (δ in CDCl_3) 1.40 (3H, t, $J=7\text{ Hz}$), 1.60-2.10 (4H, m), 2.50-3.00 (4H, m), 4.40 (2H, q, $J=7\text{ Hz}$), 7.81 (1H, s), 8.37 (1H, s).
 - 3b Ir (liq. film, cm^{-1}) 1738, 1725. Nmr (δ in CDCl_3) 1.38 (3H, t, $J=7\text{ Hz}$), 1.38 (3H, s), 1.00-2.70 (5H, m), 6.30 (1H, m).
 - 7b Ir (liq. film, cm^{-1}) 1738, 1712. Nmr (δ in CDCl_3) 1.41 (3H, t, $J=7\text{ Hz}$), 1.85-2.5 (2H, m), 2.80-3.20 (4H, m), 4.45 (2H, q, $J=7\text{ Hz}$), 7.98 (1H, s), 8.56 (1H, s).
 - 3c Ir (nujol, cm^{-1}) 1710, 760, 705. Nmr (δ in CDCl_3) 0.9-3.3 (8H, m), 1.33 (3H, t, $J=7\text{ Hz}$), 4.22 (2H, q, $J=7\text{ Hz}$), 6.49 (1H, m), 7.13 (5H, s).
 - 3d Ir (nujol, cm^{-1}) 1722, 758, 695. Nmr (δ in CDCl_3) 1.34 (3H, t, $J=7\text{ Hz}$), 1.50-2.80 (6H, m), 4.34 (2H, q, $J=7\text{ Hz}$), 6.53 (1H, m), 7.30 (5H, s).
 - 9d Ir (nujol, cm^{-1}) 1712. Nmr (δ in CDCl_3) 1.39 (3H, t, $J=7\text{ Hz}$), 1.80-2.40 (2H, m), 2.50-3.10 (4H, m), 2.90 (2H, s), 4.36 (2H, q, $J=7\text{ Hz}$), 7.10-7.70 (4H, m).
10. E. M. Engler, D. J. Andose, and P. v. R. Schleyer, J. Am. Chem. Soc., 1973, 95, 8005.
11. W. Eberbach, B. Burchardt, and U. Trostmann, Tetrahedron Lett., 1979, 4049.

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