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THE THERMAL REACTIONS OF 2H-AZIRINES

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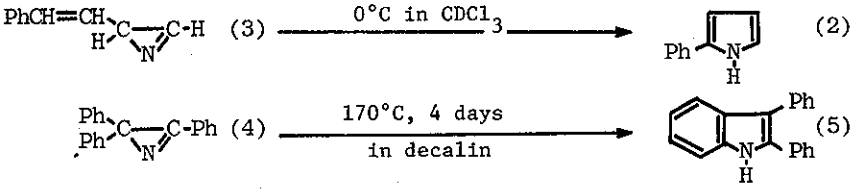
Since the developement of the synthetic methods for various 2H-azirines the chemistry of the highly strained heterocycle has come to be extensively studied and many reactions of 2H-azirines with a variety of both nucleophiles and electrophiles have been performed. Padwa's and Schmid's groups studied the photo-induced reactions of 2H-azirines and found that C-C bond fission takes place to give nitrile ylides which further undergo intra- and intermolecular cycloaddition reactions giving a wide variety of heterocycles.

We were particularly interested in the effects of strain of 2H-azirines on their thermal reactions. We have found that C-N bond fission occurs to give a vinyl nitrene intermediate which is further transformed to 1) nitriles via C-3 H migration in the cases of 3-unsubstituted 2H-azirines and to 2) five-membered rings by recyclization in the cases of 2H-azirines bearing unsaturated group at 2-position.[1] We would like to discuss the thermal reactions of 2H-azirines in this paper.

Thermal Reactivity of 2H-Azirines Depending on Substituents

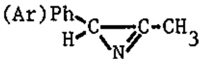
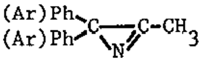
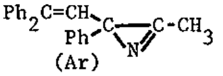
Thermal decomposition of 1-azido-4-phenylbuta-1,3-diene (1) in hexane under reflux gave 2-phenylpyrrole (2) exclusively. Photodecomposition of (1) at -82°C gave 2-styryl-2H-azirine (3), which gave the same pyrrole (2) when the solution was warmed to 0°C.[2] In contrast to high reactivity of (3), 2,2,3-triphenyl-2H-azirine (4) gave 2,3-diphenylindole (5) by heating at 170°C for 4 days.



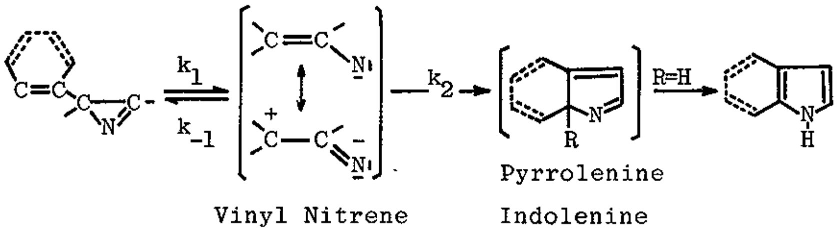
Why was such a large difference in reactivity observed depending on the substituents?

1) **Effect of the Substituents at 2-Position of 2H-Azirine**

Table 1. Activation parameters in thermal isomerization forming five-membered rings.

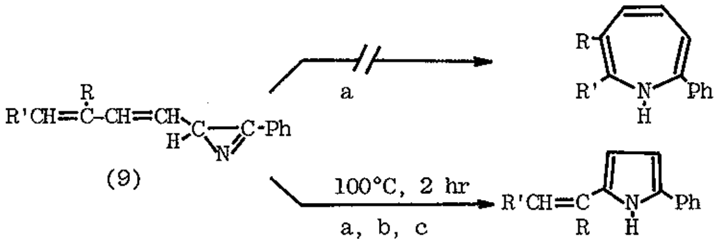
Azirine	Solv.	Temp. (°C)	10^4k (s^{-1})	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (e.u.)
 (6)	decalin	185.0	1.13	35	-1.3
 (7)	decalin	170.0	2.16	28	-13
 (8)	heptane	64.2	4.11	32	19

Based on the results in Table 1 and the investigation on the substituent effects on the rate, the course of thermal ring expansion of 2H-azirines was considered as follows.



Sluggish indole formation may be attributed mainly to the slow k_2-step owing to disruption of aromaticity in the formation of indolenine intermediates.

Facility of pyrrole formation is exhibited by the following examples.



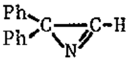
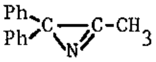
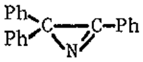
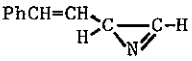
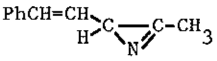
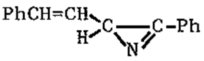
(9) (10) (11)

a; $R=H$, $R'=CH_3$: b; $R=CH_3$, $R'=H$: c; $R=H$, $R'=CO_2CH_3$

In these cases formation of seven-membered rings (10) may be possible and claimed to be the case by Padwa et al.[3] but our investigation made clear that the reported assignment was incorrect and five-membered rings (11) were exclusively formed.[4]

2) Effect of the Substituents at 3-Position of 2H-Azirine

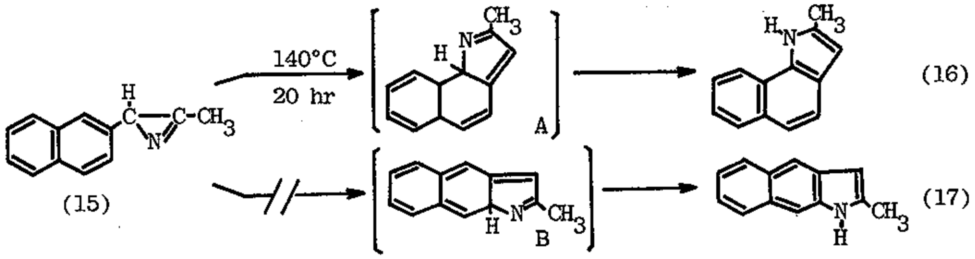
Table 2. Dependence of the reactivity on the substituent at 3-position

Indole formation			
Azirine	 (12)	 (7)	 (4)
Temp. (°C)	80	170	170
$t_{1/2}$ (min)	18	53	720
Pyrrole formation			
Azirine	 (3)	 (13)	 (14)
Temp. (°C)	0	room temp.	80

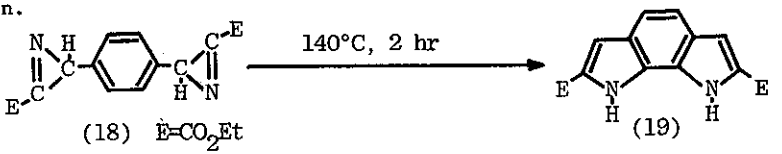
The reactivity is decreased by the change of the substituent in the order $H > CH_3 > Ph$. Extremely high reactivity of 3-unsubstituted 2H-azirines may be ascribed to the difference of mass. The difference of the reactivity between 3-methyl- and 3-phenyl-2H-azirines can be accounted for by conjugative elongation of C=N bond releasing the ring strain.

Selective Recyclization of Vinyl Nitrene

The thermal reaction of 3-methyl-2-(naphth-2-yl)-2H-azirine (15) afforded 2-methylbenz[g]indole (16) exclusively. This selective reaction will be ascribed to the higher energy of the intermediate (B) to form the alternative benz[f]indole (17) compared with intermediate (A) to form (16).

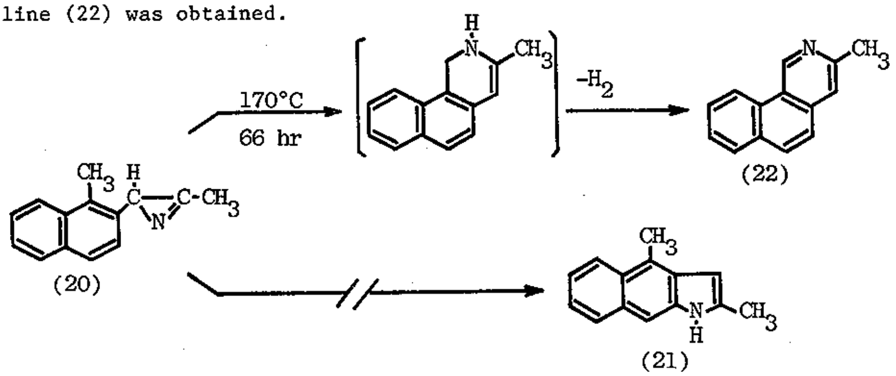


The selective formation of benz[2,1-b, 3,4-b']dipyrrole (19) from *p*-bis(3-carbethoxy-2H-azirin-2-yl)benzene (18) is recognized by the same reason.



Compelled Six- and Seven-Membered Ring Formation[5]

Even if a methyl group was introduced at the selective cyclization position of (15), no benz[f]indole (21) was obtained but 3-methylbenz[h]isoquinoline (22) was obtained.



Thermal reaction of three 2-(benzofuran-2-yl)-2H-azirines (23a, 23b, 23c) in which the 3-position was substituted by hydrogen, methyl and phenyl group were performed and the results are shown in Figure. Formations of pyridine (25) and azepine ring (26) were explained by the intramolecular insertion of vinyl nitrene intermediates, which were more facile reaction paths than formation of unstable five-membered ring.

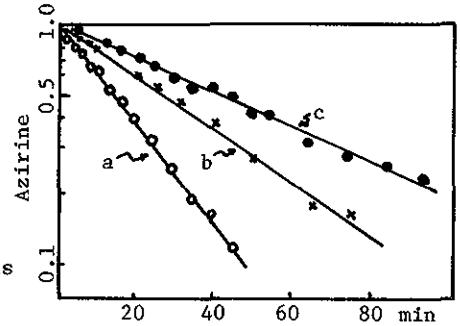
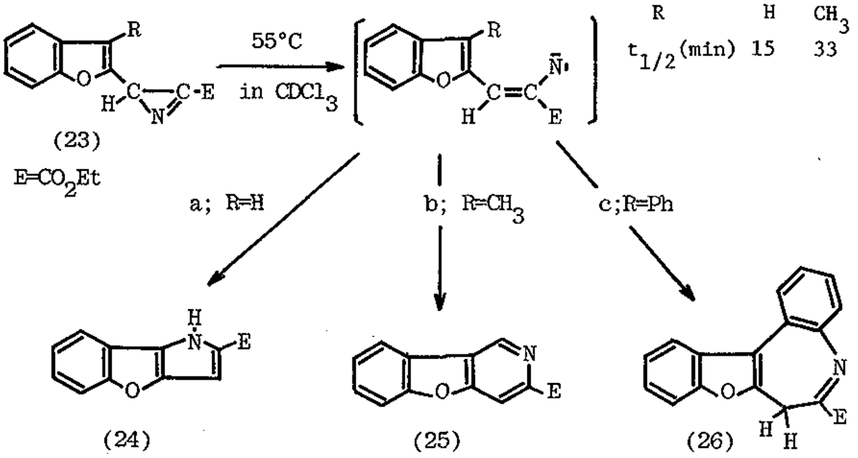


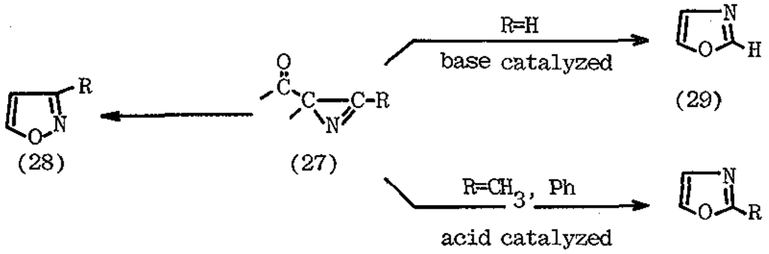
Figure. Thermal reaction of 23a, 23b, and 23c at 55°C in $CDCl_3$

	23a	23b	23c
R	H	CH_3	Ph
$t_{1/2}$(min)	15	33	44



C-C Bond Fission in Thermal Reaction of 2H-Azirines

Thermal reactions of 2-acyl-2H-azirines (27) were reported to give



isoxazoles (28) by C-N bond fission,[6] but we noticed that oxazoles (29) were always accompanied. Formation of oxazoles was found to be catalytically accelerated by bases or acids.

Thermal reactions of 2H-azirines were found to occur in the way that vinyl nitrenes stabilized intramolecularly. If there is no hydrogen at 3-position or unsaturated group at 2-position, C-C bond fission is compelled at elevated temperatures.[7]

Although the intermolecular reaction of vinyl nitrene has not been observed, its intramolecular cyclization would be of great utility because of giving N-heterocyclic compounds selectively and in high yields.

References

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