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NEW THERMAL REARRANGEMENT OF 2H-AZIRINES: FORMATION OF ENAMINES AND THEIR CYCLIZATION INTO PYRIDINES

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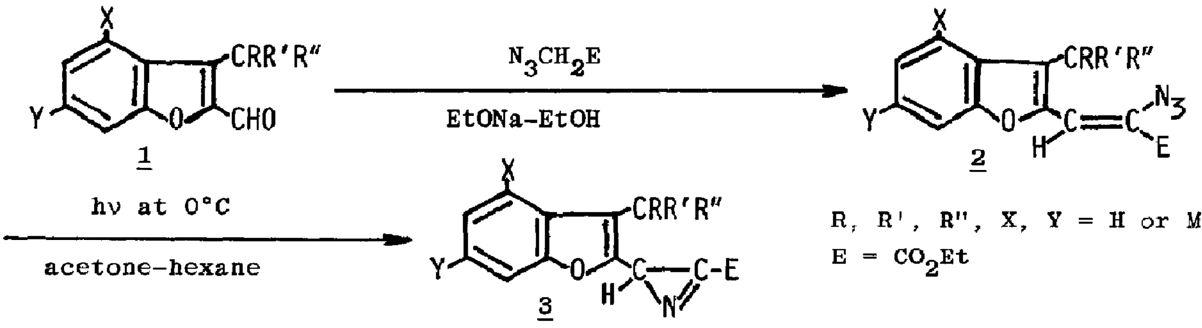
Abstract; Intermediary formation of enamines in the course of cyclization of vinyl nitrenes into 6-membered ring compounds showed that this reaction proceeded not by insertion but by consecutive hydrogen shift and electrocyclic reaction.

It has been established that thermal reaction of 2H-azirines, bearing unsaturated group at the 2-position, gives 5-membered heterocyclic compounds via vinyl nitrene intermediates.[1] Recently, it has been revealed that 6-membered cyclic compounds can also be formed from 2H-azirines, if the cyclization position to form 5-membered ring was blocked by a methyl group.[2-5] This reaction might b explained by insertion reaction of vinyl nitrene into the C-H bond of the methyl group.

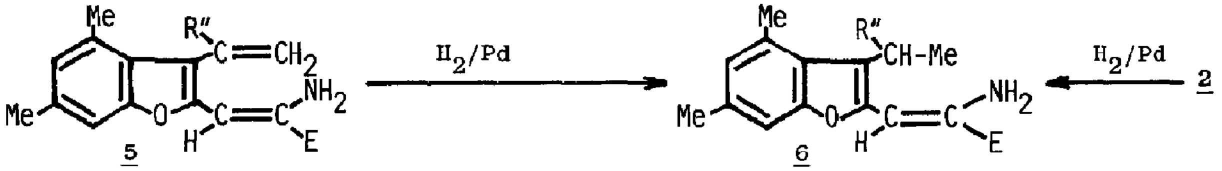
In this paper, we found that thermal reaction of azirines having an ethyl or an *i*-propyl group for blocking gave enemines at low temperatures, which cyclized into 6-membered ring compounds at higher temperatures. These results provided no only new type of thermal rearrangement of azirines, but also the mechanistic rationale, which is against the insertion mechanism.

The azirines 3a-e, examined in this paper, were prepared by photolysis (0°C in acetone-hexane, 100W high pressure mercury lamp) of the corresponding vinyl azides 2a-e, which were synthesized by base-catalyzed condensation of the benzofuran-2-carboxaldehyde 1a-e with ethyl azidoacetate.[6]



R, R', R", X, Y = H or Me
E = CO_2Et

The results of thermal rearrangement of these azirines in $CDCl_3$ at 35.5°C and in xylene under reflux for 12 hr are summarized in Table. The azirine 3a having a methyl group at 3-position of the benzofuran ring gave benzofuro[3,2-c]pyridine 4a even at 35.5°C in $CDCl_3$, as expected. On the other hand, the azirines 3b and 3c gave the enamines 5b and 5c, respectively, in quantitative yields at 35.5°C. These were the first examples in thermal reaction of azirines. The structures of 5b and 5c were unambiguously assigned by their spectral data,[7] micro analyses, and catalytic reduction into 6b and 6c, which were identical with the compounds formed by catalytic reduction of the corresponding vinyl azides 2b and 2c. Although thermal rearrangement of 3a and 3c in xylene under reflux gave the same products, 4a and 5c, as low temperature rearrangements, 3b gave 4b. This result implied that 5b was the intermediate of 4b. This consideration was proved to be correct by quantitative formation of 4b by heating 5b in xylene under reflux. The enamine 5c was stable in refluxing xylene, but gave dihydrobenzofuropyridine 7c, when a xylene solution of 5c was heated at 180°C for 20 hr in a sealed tube.



b) R'' = H, c) R'' = Me

Table. Thermal rearrangement of 2H-azirines 3a-e

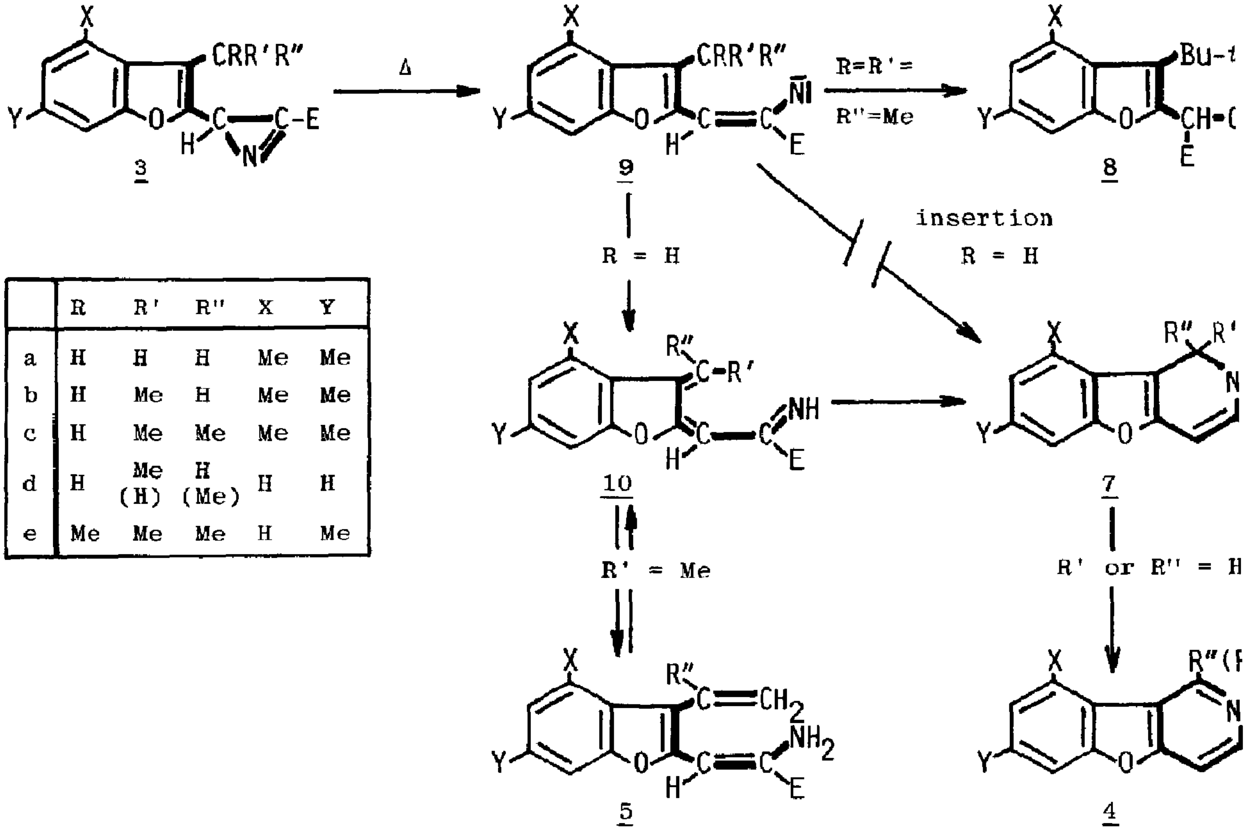
2H-Azirine	Half life (min.) in $CDCl_3$ at 35.5°C	Product(s) (%) in $CDCl_3$ at 35.5°C	Product(s) (%) in refluxing xylene[a]
3a	30	4a (quant.)	4a (quant.)
3b	15	5b (quant.)	4b (quant.)
3c	298	5c (quant.)	5c (quant.)
3d	173	4d (14) + 5d (86)	4d (quant.)
3e		3e (recovered)	8e (67)[b]

a) 12 hr. b) In toluene under reflux for 10 hr.

In the case of 3d, which had an ethyl group as 3b but lacked two methyl groups on the benzofuran nucleus, thermal reaction at 35.5°C gave the enamine 5d and 4d. The enamine 5d, purified by recrystallization, was stable at 35.5°C. These results indicated that 4d obtained at low temperature was not formed via enamine 5d.

The azirine 3e bearing *t*-butyl group was intact at 35.5°C, but gave nitrile 8e by heating in toluene for 10 hr under reflux.

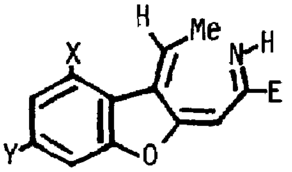
Although formation of 6-membered ring compounds from azirines might be considered to proceed by direct insertion reaction of vinyl nitrenes,[2-5] above results cannot be accomodated with insertion reaction but would be rationalized by the pathway as shown in Scheme, in which the imine (1-azahexatriene) 10 is the key



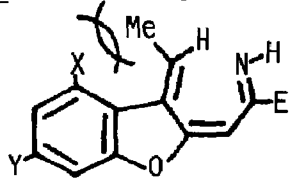
	R	R'	R"	X	Y
a	H	H	H	Me	Me
b	H	Me	H	Me	Me
c	H	Me	Me	Me	Me
d	H	Me (H)	H (Me)	H	H
e	Me	Me	Me	H	Me

intermediate. The vinyl nitrene intermediate 9 formed by C-N bond fission of azirine 3 gives 10 by [1,6] hydrogen shift, if the substituent at the 3-positio of the benzofuran has α-hydrogen. When R' in 10 is hydrogen, electrocyclic reac tion of 10 gives dihydropyridine 7 which can be easily oxidized into 4. But whe R' is a methyl group, [1,7] hydrogen shift from the methyl group to nitrogen tak place, because this methyl group is situated in favorable position for this antarafacial hydrogen shift.

In the reactions of 3-ethylbenzofuranyl derivatives, 3b and 3d, two stereoisomers of 10, E-10 and Z-10, are possible depending on the configuration of the terminal methyl group. In thermal reaction of 3b, steric repulsion between the



Z-10



E-10

methyl group at 4-position of the benzofuran ring and the terminal methyl group inhibits formation of E-10b, then forces preferential formation of Z-10b, which collapses into 5b. However, in the case of 3d, releasing of the steric repulsion allows formation of some fraction of E-10d, which by 6-electron cyclization gives 4d via 7d. Sluggish formation of 5c from 3c would be ascribed to the steric repulsion in the formation of 10c, in which R' and R" are methyl groups.

Recyclization of the enamines 5 into 6-membered ring compounds can also be considered to proceed via 10. This consideration was substantiated by deuterium scrambling experiment showing the equilibrium between the enamine 5 and the imine 10, as follows. When N-deuterated enamines 5b and 5d were heated in benzene under reflux for 4 hr, examination of the NMR spectra revealed that the terminal carbon of the vinyl group was deuterated. Therefore, we can consider that enamines and 6-membered ring compounds are kinetically and thermodynamically controlled product, respectively, and that the imines 10 are the common intermediates. Higher temperatures required for cyclization of enamines would reflect the disadvantage in disrotatory 6-electron cyclization of 10, where the methyl group (R') imposes steric hindrance.

From the results in this paper, we can make clear that formation of 6-membered ring compounds from azirines does not proceeds by insertion reaction but proceeds by consecutive hydrogen shift and electrocyclic reaction, in which the imines 10 are the key intermediates. Furthermore, we can demonstrate that 6-membered nitrogen containing heterocycles are easily obtained quantitatively, if the substituent at the cyclization position of vinyl nitrene to form 5-membered ring is substituted by an alkyl group having α-hydrogen.

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