HETEROCYCLES. Vol.9, No.9, 1978

UNUSUAL FORMATION OF OXAZOLES BY BASE- OR ACID-CATALYZED RING OPENING OF 2-ACYL-2H-AZIRINES

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Formation of 2-acyl-2H-azirines was confirmed in thermolyses of β-acylvinyl azides to establish the generality of azirine formation from vinyl azides. Unusual C-C bond fission of 3-unsubstituted 2-acyl-2H-azirine to give oxazole was found to be a base catalyzed reaction. On the other hand, 3-substituted analogues were found to undergo acid-catalyzed reaction to give oxazoles.

Maiorana reported that thermolysis of β-azidomethacrylophenone 1a gave 4-methyl-5-phenylisoxazole 4a besides 2-benzoylpropionitrile 3a,[1] whereas Nesmeyanov and his co-workers reported that 4-methy-5-phenyloxazole 5a was the main cyclic product which was formed via 2-benzoyl-2-methyl-2H-azirine 2a.[2] These reports brought us two interesting questions. One is whether 2H-azirine does surely intervene in this reaction, since 2H-azirines have not yet been detected in decomposition of β-acylvinyl azides,[3] although formation of 2H-azirine can be thought as the general reaction of vinyl azides.[4,5] The other is how oxazole is formed. Thermal reaction of 2-acyl-2H-azirines was reported to give isoxazoles[6] by C-N bond fission.[7] However, some 2-

acyl-2H-azirines were postulated as the intermediates in thermal transposition reaction of isoxazoles into oxazoles,[8,9] which must be formed by C-C bond fission of 2H-azirines. Recently, Schmid et al. confirmed that an 2-acyl-2H-azirine gave an oxazole on heating.[10] In this paper, we wish to make clear whether 2-acyl-2H-azirines are formed from β-acylvinyl azides and how oxazoles are formed from these azirines.

The azide **1a** (mp 69-70°C)[11] was thermolyzed by heating in toluene (0.020 M) under reflux for 8 hr. Separation of the resulting yellow oil by chromatography on silica gel gave **3a**, **4a**, and **5a**, which were identified by comparison with authentic compounds. Examination of the nmr spectrum of the crude product showed that **3a**, **4a**, and **5a** were formed in 37, 23, and 40% yields, respectively. Product distributions were remarkably influenced by the concentration of **1a** as shown in Table 1.

Table 1. Dependence of the product distributions on the concentration in thermolyses of **1a** in toluene under reflux for 8 hr.

Conc. of **1a** (M)	**3a** (%)	**4a** (%)	**5a** (%)
0.50	29	1	70
0.10	31	6	63
0.020	37	23	40
0.0040	42	42	16

When thermolysis of **1a** in chlorobenzene (0.30 M) at 95°C was monitored at interval of time by nmr spectroscopy, formation of a labile compound which changed into both **4a** and **5a** was detected as shown in Figure. This compound was easily assigned as 2-benzoyl-2-methyl-2H-azirine **2a** by comparing its nmr signals at δ 1.44 (3H, d J 1.5 Hz) and 9.75 (1H, q J 1.5 Hz) with those of 2-methyl-2-phenyl-2H-azirine[12] [δ 1.50 (3H, d J 1.5 Hz), 7.2-7.4 (5H, m), and

9.80 (1H, q J 1.5 Hz)]. This result clearly shows that the primary products in thermolysis of 1a are 2a and 3a, and that 2a is unstable enough to change mainly into 4a and 5a under the present conditions, as shown in Scheme 1. An interesting point is that the curve for the formation of 5a in Figure could not be explained by assuming a consecutive two-step reaction from 1a via 2a, since the slope of the curve for the formation of 5a is not largest at the time when 2a becomes maximum in concentration.[13] This situation indicates that 5a is formed by catalysis of some product in the reaction mixture.

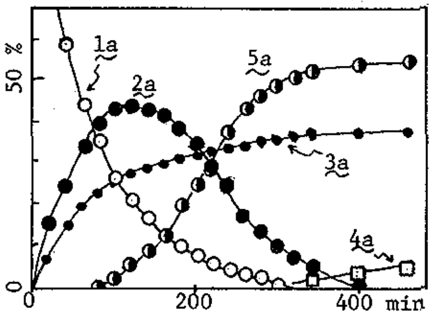
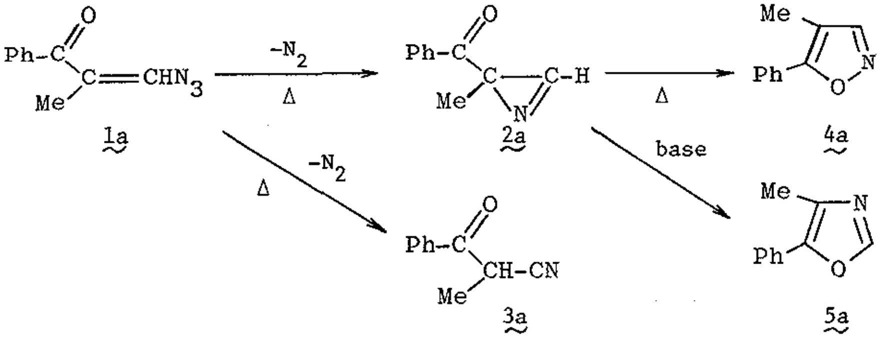


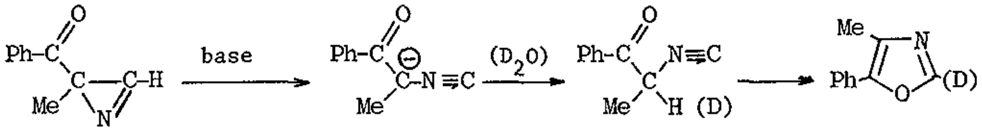
Figure. Thermolysis of 1a in chlorobenzene (0.30 M) at 95°C

Scheme 1.



In an attempt to obtain detailed insight into the oxazole formation, thermolysis of 1a in chlorobenzene at 95°C was quenched at the maximum concentration of 2a (110 min after heating) by cooling the reaction mixture to room *temperature*. The nmr spectrum of this reaction mixture did not changed at 35.5°C appreciably even for 6 hr, but addition of 20 mole% of pyridine caused smooth disappearance of the signals of **2a** with a half life of 40 min, and appearance of transient signals at δ 1.46 (3H, d J 6Hz) and 4.60 (1H, q J 6 Hz). Addition of diazabicyclo[2.2.2]octane, which is more stronger base than pyridine, showed the stronger effect and the signals of **2a** disappeared completely in 2 min. As the transient signals decreased the signals of **5a** increased. The ir spectrum also showed transient bands at 1690 and 2160 cm^{-1}, which finally disappeared and the absorption band of **5a** intensified. On the basis of these spectral properties,[14] this transient compound was assigned as the β-ketoisonitrile **6a**. Facile cyclization of β-ketoisonitrile into an oxazole was reported by Hagedorn et al.[15] Therefore, oxazole formation from **2a** would be written as shown in Scheme 2, in which base-catalyzed formation of

Scheme 2.

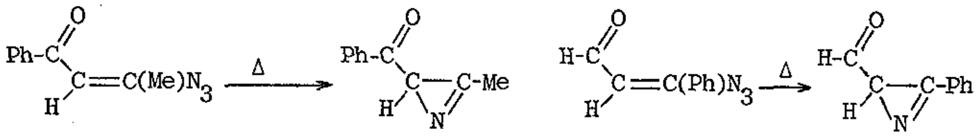


2a **6a** **5a**

6a from **2a** is the key step. Monitoring of thermolysis of **1a** in the presence of D_2O (5 mole eq.) showed no H-D exchange of C_3-H of **2a**, but **5a** formed had D at its 2-position. This result may be accomodated with a concerted abstraction of C_3-H synchronous with C_2-C_3 bond fission, giving an anion which is assisted by the carbonyl group to stabilize the negative charge. Large s character (58.5%) of the exocyclic orbital of C_3, which is obtained by ^{13}C-H coupling constant (242.5 Hz) by proton coupled ^{13}C-nmr spectrum of 3-phenyl-2H-azirine,[16] would also be the reason for easy hydrogen abstraction. Althogh an 3-unsubstituted 2-acyl-2H-azirine has been recently shown to form an oxazole thermally,[14] our results clearly show that base is necessary for this transformation.

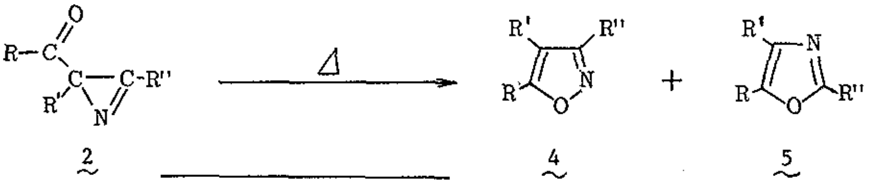
On the basis of above consideration, the results shown in Table 1 can be explained as follows. The formation of 5a is dependent on the concentration of the solution, since this transformation is catalyzed by bases such as 4a and 5a. On the other hand, the rate of isoxazole formation, which is considered as an unimolecular first-order thermal reaction of 2a is independent of the concentration. At high concentration, even a small amount of basis product is enough to catalyze the transformation of 2a into 5a. But formation of 5a is suppressed at lower concentration resulting in the predominant formation of 4a. Increased yield of 3a at lower concentration would imply that some amounts of 3a are also formed by thermal reaction of 2a.

Detection of 2H-azirine 2a in thermolysis of 1a led us to examine thermolyses of other β-acylvinyl azides. Heating the benzene solution of β-azidocrotonophenone 1b[17] under reflux for 2 hr followed by chromatography on silica gel afforded colorless crystalline compound of mp 40-41°C in 80% yield. This compound was identified as 2-benzoyl-3-methyl-2H-azirine 2b by comparison with the authentic sample prepared by the reported photochemical ring contraction of 3-methyl-5-phenylisoxazole.[18] Thermal decomposition of a mixture of E- and Z-β-azidocinnamaldehyde 1c[19] in benzene at 50°C followed by sublimation (35°C/0.05 mmHg) also gave 2-formyl-3-phenyl-2H-azirine 2c, mp 45.5-47°C,[20] in 57% yield.



1b 2b 1c 2c

These two azirines 2b and 2c were stable under the conditions of thermolyses, but on heating the chlorobenzene solutions of these azirines at higher temperatures in sealed tubes, there were obtained isoxazoles with small amount of oxazoles. Thermal reaction of 2-acyl-2H-azirines, including **2b** and **2c**, under various conditions were performed and the results obtained by nmr



	b	c	d	e
R	Ph	H	Ph	Ph
R'	H	H	Me	Me
R''	Me	Ph	Me	Ph

Table 2. Thermal reactions of **2b-e**.

Run	2H-Azirine	Compd Added. (mole %)	Temp. (°C)	Time (hr)	Product Ratio **4** (%)	**5** (%)
1	**2b**	none	170	17	91	9
2	**2b**	pyridine (10)	170	17	96	4
3	**2b**	$PhCO_2H$ (10)	170	17	55	45
4	**2c**	none	180	18	96	4
5	**2c**	$PhCO_2H$ (10)	180	18	69	31
6	**2c**	$BF_3 \cdot OEt_2$ (10)	150	5	0	100
7	**2d**	none	120	80	94	6
8	**2d**	$PhCO_2H$ (8)	120	80	69	31
9	**2e**	none	120	270[a]	79	21
10	**2e**	$PhCO_2H$ (8)	120	140	15	85
11	**2e**	$PhCO_2H$ (21)	120	38	8	92
12	**2e**	$BF_3 \cdot OEt_2$	120	2	0	100
13	**2e**	none	180	30	86	14

a) 73% conversion

and glc analyses are shown in Table 2.[21] From the Table we see that addition of pyridine to the reaction of 2b gives almost no effect on the yield of 5b. This result is in marked contrast with that in thermal reaction of 2a. However this fact is quite reasonable, because 2b has no hydrogen at 3-position. On the contrary, it was found that the yield of 5b increased in the presence of benzoic acid. Addition of benzoic acid raised the yields of oxazoles in thermal reactions of other azirines also. Controle experiments under the same conditions as in Table 2 confirmed no interconversion between isoxazoles and oxazoles, showing that the products were directly formed from azirines.

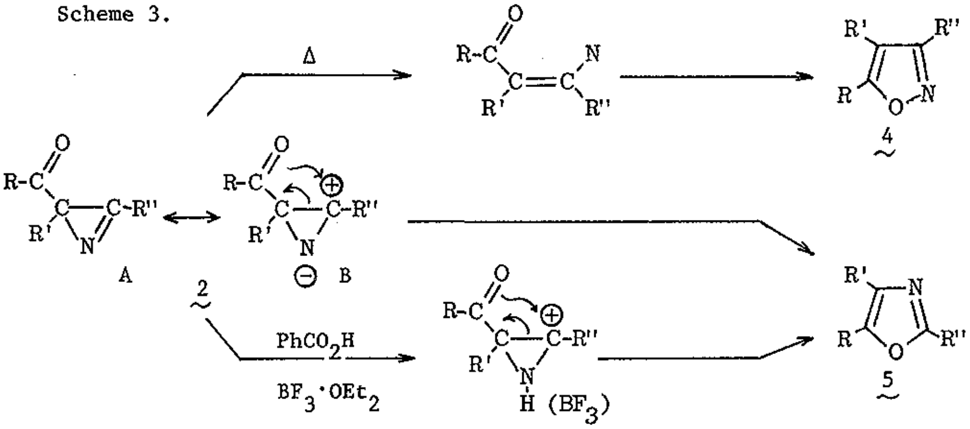
Table 3. Rate constants of thermal reaction of 2e and partial rate constants for the formation of 4e and 5e at 120°C.

Benzoic Acid Added (mole %)	Rate Constant for Consumption of 2e ($10^{-5}sec^{-1}$)	Partial Rate Constants ($10^{-5}sec^{-1}$)	
		4e	5e
0	0.16	0.13	0.03
8	1.03	0.16	0.86
21	2.95	0.24	2.71

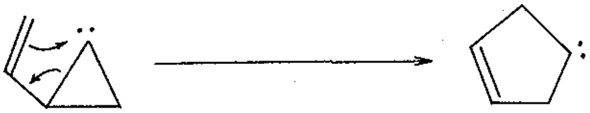
The reactions of 2e both in the absence and the presence of benzoic acid were followed by nmr spectroscopy. The rate constants for the consumption of 2e and the partial rate constants for formation of 4e and 5e are shown in Table 3. The data in Table 3 show that formation of 5e is profoundly accelerated by the benzoic acid while formation of 4e is accelerated only a little. Oxazole formation was also attained by $BF_3 \cdot OEt_2$ in the reactions of 2c and 2e, and in these cases reactions were selective.

On the basis of these results, thermal reaction of 3-substituted-2-acyl-2H-azirines would be depicted as Scheme 3. Isoxazoles may be formed by the

Scheme 3.



usually observed C-N bond fission producing vinyl nitrene intermediates followed by recyclization. The oxazole formation would be explained by attack of the carbonyl oxygen to the imino carbon, which has partial positive charge owing to some contribution of the canonical form B.[16] Dependence of the product distributions on temperatures (120 and 180°C) in the thermal reaction of 2e implies that the entropy of activation for the formation of 5e is lower than that for the formation of 4e by 12.7 eu, which is also consistent with Scheme 3, because degree of freedom of the transition state for the formation of 5e is much restricted. Acceleration of oxazole formation by acids would be ascribed to the positive charge caused by addition of acid to nitrogen. A good chemical analogy is provided by the transformation of 2-vinylcyclopropylidene into 3-cyclopentenylidene, which was considered as the $\pi 2_s + \sigma 2_a$ electrocyclic



reaction where the attractive interaction of the vacant p-orbital with the vinylic π-bond plays the important role.[22]

In conclusion, we could make clear that 2H-azirines were also formed from β-acylvinyl azides, which is very important to establish the generality of azirine formation from vinyl aizdes. Unusual C-C bond fission of 2-unsubstituted 2-acyl-2H-azirine forming oxazole, which compete withe the usually observed C-N bond fission forming isoxazole, was revealed to be catalyzed by a base. On the other hand, the thermal reactions of 3-substituted ones giving oxazoles were found to be catalyzed by an acid.

ACKNOWLEDGEMENT We are grateful to the Asahi Glass Foundation for financial support to this work.

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Received, 20th May, 1978