THERMAL REARRANGEMENT OF *CIS-N*-ALKYL-3-PHENYLAZIRIDIN-2-YL-PHENYL KETONE TOSYLHYDRAZONES IN DIMETHOXYETHANE. PREPARATION OF 5-ALKYLAMINO-2-PYRAZOLINE DERIVATIVES

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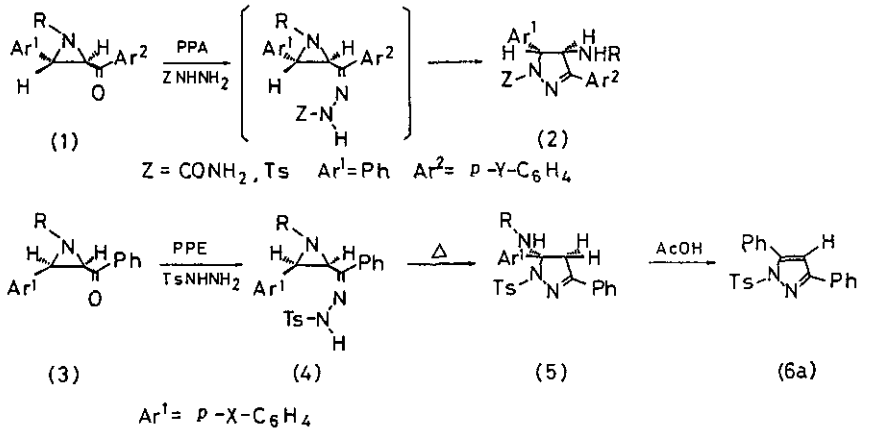
Abstract—Thermal rearrangement of *cis*-aziridinyl ketone tosylhydrazones (**4**) in refluxing dimethoxyethane produced 5-alkylamino-3,5-diphenyl-1-tosyl-2-pyrazolines (**5**) in good to excellent yields. The reaction of *cis*-1-isopropyl-3-phenyl-aziridin-2-yl phenyl ketone tosylhydrazone (**4a**) in refluxing chloroform in the presence of acetic acid yielded 3,5-diphenyl-1-tosyl-pyrazole (**6a**). Under the similar conditions, 5-isopropylamino-3,5-diphenyl-1-tosyl-2-pyrazoline (**5a**) was rearranged into **6a**. The rearrangement from **4** to **5** was assumed to be initiated with ionic cleavage of the bond between ring nitrogen and C2 carbon.

Previously, we reported that 1-carbamoyl- and 1-tosyl derivatives of 4,5-*trans*-4-alkylamino-2-pyrazoline (**2**) were derived from *trans*-aziridinyl ketone (**1**) in high yield (Scheme 1).[1] Subsequently, we showed that the tosylhydrazones (**4**)[2] and semicarbazones[3] were prepared from *cis*-aziridinyl ketone (**3**) in high yield with the use of polyphosphoric acid ethyl ester (PPE) as a catalyst, maintaining the aziridinyl ring intact, although **3** tended to be ring-open under the general conditions of obtaining hydrazones. In the present paper, we report that **4** is easily rearranged into 5-(alkylsubstituted amino)-2-pyrazolines (**5**) in good to excellent yields when **4** is heated in refluxing dimethoxyethane (DME). A few reports for preparation of 2-pyrazoline derivatives which have 5-amino[4] or 5-substituted amino[5,6,7,8] or 5-isothiocyanato[9] or 5-arylazo[10] substituents have been appeared. Cromwell *et al.*[11] and Southwick *et al.*[12] studied the condensa-

tion of 1 or 3 with phenylhydrazine in acetic acid, obtaining 2-pyrazoline derivatives (2) from 1 and pyrazol (6) from 3. However, the isolation of 2-pyrazoline derivatives, an intermediate product expected in the latter reaction, has not been reported. In order to investigate the reaction route from 4 to 5, the substrate (4a-d_1) with H2 methine hydrogen labeled with deuterium was prepared and refluxed in DME.



Scheme 1

RESULTS AND DISCUSSION

The rearrangement of 4a-h in refluxing dimethoxyethane produced 5a-h in good to excellent yields. The reaction was continued until the starting material disappeared on a thin-layer chromatogrphy (silica gel, hexane : ethyl acetate = 4:1). The yields, melting points, and elemental analysis data of 5a-h are shown in Table 1. The ^{1}H-NMR and IR spectral data of 5a-h are shown in Table 2. The IR spectra of 5a-h show sulfonyl group stretching vibration signals at 1346-1355 cm^{-1} and 1159-1170 cm^{-1}. An NH stretching vibration signal appeared at 3350-3381 cm^{-1}. The ^{1}H-NMR spectra of 5a-h show signals of CH_2 and NH that were not intramolecularly hydrogen-bonded. In the case of 5c, AB coupling patterns of two kinds of methylene-type hydrogen appeared. The ^{13}C-NMR data of 5a-h are listed in Table 3. The spectra show methylene carbon C4 signals at δ=46.3-47.8 ppm and new signals resulting from quarternary aliphatic carbon C5 and C=N carbon at δ=90.2-91.6 ppm and 150.0-150.5 ppm, respectively. The rearrangement of 4a and 5a yielded 3,5-diphenyl-1-tosylpyrazole(6a)[13] under the refluxing conditions of chloroform in the presence of acetic acid. Based on the results of the transformation from 5a to 6a and comparison of the spectral data of 5 with those

of 2, 5 was classified as a 5-alkylamino-2-pyrazoline derivative. X-Ray crystallographic analysis of 5g lends further credence to the structure proposed in Figure 1.

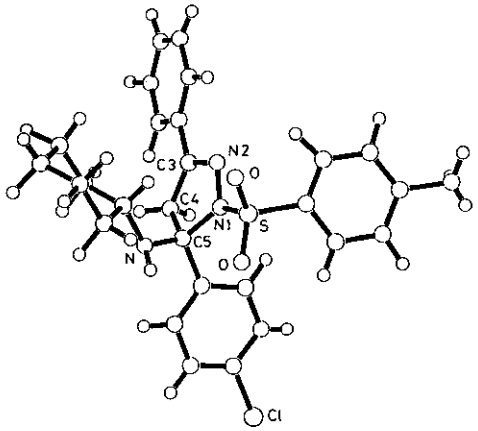
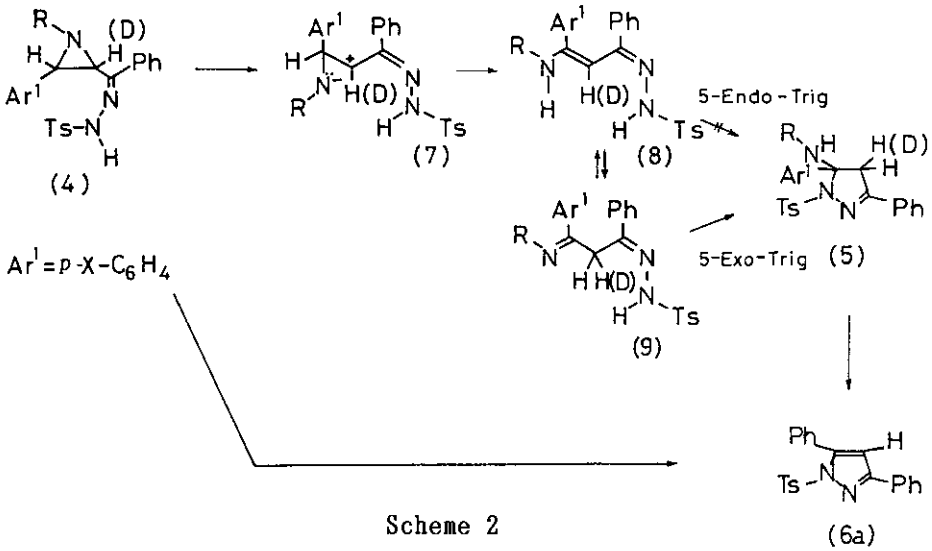


Figure 1 X-Ray crystallographic structure of 5g



Scheme 2

The tentative reaction path from 4 to 5 was postulated based on the formation of suspected intermediates (7), (8), and (9) (Scheme 2). The rearrangement of 4 was speculated to begin with ionic cleavage of the bond between aziridinyl ring nitrogen and C2 carbon, following which the proton on the C3 carbon transferred to the formed aminyl anion thus expanding the resonance system. It can be presumed that imine-enamine tautomerism is between 8 and 9. According to the Baldwin rule,[14] the ring closure of 8 to 5 is difficult to proceed because of 5-

endo-trig type but the reaction of **9** to **5** proceeds easily for 5-exo-trig type. Then the deuterium content contained in **9a** must be reduced in the course of the tautomerism between **8** and **9**. Consequently the present study suggests that **9** cyclized according to the Baldwin rule, since approximately 54% of the deuterium at the C2 of substrate (**4a-d**$_1$) prepared from **3a-d**$_1$ was retained on the C4 carbon of 2-pyrazoline (**5a-d**$_1$) after the rearrangement.

EXPERIMENTAL

General The apparatus used in this study is described in a previous paper.[2] CHN analysis was performed at the Elemental Analysis Laboratory, Institute for Chemical Reaction Science, Tohoku University.

X-Ray crystal structure determination of compound **5g**

Crystals of compound **5g** were grown by slow evaporation of methanol solutions. A crystal of 0.30 mm × 0.2 mm × 0.3 mm was mounted on a glass fiber on Rigaku AFC7R diffractometer with graphite monochromated Cu-Kα radiation and the lattice parameter were obtained by a least-squares refinement of 25 accurately centered reflections in the range $55.84° < 2\theta < 56.95°$. The structure was solved by direct methods using the SAPI 91 suit of programs and conventional Fourier syntheses. The nonhydrogen atoms were refined isotropically and anisotropically, and hydrogen atoms isotropically.

Crystal data

$C_{28}H_{30}ClN_3O_2S$, M = 508.08, monoclinic, space group $P2_1/c$, a = 8.100(2) Å, b = 19.841(2) Å, c = 16.579(2) Å, β = 98.04(1)°, V = 2638.4(6) Å^3, Z = 4, D_c = 1.279 g·cm^{-3}, μ(CuKα) = 22.55 cm^{-1}, F_{000} = 1072.00

Data collection

The data were collected at a temperature of 20±1 ℃ using the ω-2θ scan technique to a maximum 2θ value of 120.2°. Scans of 1.73 + 0.30tanθ were made at a speed of 16.0°min^{-1}(in omega). number of data collected 4381, number of unique data 4060, number with $I \geq 3.00\sigma(I)$ 3176.

Structure refinement

$R = \Sigma \| F_o | - | F_c \| / \Sigma | F_o | = 0.059$

$R_w = (\Sigma w (| F_o | - | F_c |)^2 / \Sigma w F_o^2)^{1/2} = 0.049$

Preparation of *cis*-*N*-alkyl-3-phenylaziridin-2-yl phenyl ketone tosylhydrazones (**4**) All starting materials were prepared according to a method described previously.[2]

Thermal rearrangement of **4** in dimethoxyethane **4a** (0.100 g, 0.230 mmol) was dissolved in dimethoxyethane (10 mL). The solution was refluxed for 2 h. After disappearance of the starting material the reaction mixture was evaporated *in vacuo* and the residue was purified using preparative thin layer chromatography (silica gel ; eluate-hexane / ethyl-acetate = 5 / 1). 5-Isopropylamino-3,5-diphenyl-1-tosyl-2-pyrazoline (**5a**) was produced in a 67% (0.067 g) yield. **5b-d,g,h** were also prepared according to a similar procedure. In the case of **4e,f**, the residue (**5e,f**) was crystallized using a small amount of dichloromethane and ether in order to avoid decomposition on silica gel.

Thermal rearrangement of **4a** to **6a** in chloroform /acetic acid **4a** (0.100 g, 0.230 mmol) was dissolved in a mixture of chloroform (10 mL) and acetic acid (0.10 g). The mixture was refluxed for 17 h, quenched with 20 % aqueous ammonium chloride, washed three times with water, dried with anhydrous sodium sulfate, and evaporated *in vacuo*. The residue was dissolved in ether and the solution was filtered, and evaporated *in vacuo*. The residue was crystallized using a small amount of methanol. 3,5-Diphenyl-1-tosyl-pyrazole (**6a**) was produced in a 75% (0.064 g) yield. mp 119.5-121℃(118-119℃)[13]

Thermal rearrangement of **5a** to **6a** in chloroform /acetic acid **4a** (0.100 g, 0.230 mmol) was dissolved in dimethoxyethane (10 mL). The mixture was refluxed for 1 h and evaporated *in vacuo*. After the residue was identified as **5a** using ^{1}H-NMR spectroscopy, a mixture of chloroform (10 mL) and acetic acid (0.10 g) was added to the residue. The mixture was refluxed for 10 h and subjected to the procedure described above. **6a** was produced in a 58% (0.050 g) yield.

Preparation of *cis*-1-isopropyl-3-phenyl[2-$^2H_1$]aziridin-2-yl phenyl ketone tosylhydrazone (**4a-d$_1$**) labeled with deuterium A substrate (**4a-d$_1$**) was prepared using [2,2,2-$^2H_3$]acetophenone as the starting material according to a method described previously. The percentage of deuterated product : [α-$^2H_1$]chalcone (*ca.*100%), [2-$^2H_1$]-2,3-dibromo-1,3-diphenyl-1-propanone (*ca.*95%), *cis*-1-isopropyl-3-phenyl[2-$^2H_1$]aziridin-2-yl phenyl ketone (**3a-d$_1$**) (55%), and **4a-d$_1$** (35%). ^{1}H-NMR($CDCl_3$, δ): 1.25(3H,d,*J*=6.2 Hz,$(C\underline{H}_3)_2CH$), 1.44(3H,d,*J*=6.2 Hz,$(C\underline{H}_3)_2CH$), 1.91(1H,septet,*J*=6.2 Hz,$(CH_3)_2C\underline{H}$), 2.40(3H,s,tolyl CH_3), 3.00(1H,s,C(3)$\underline{H}$-C(2)D), 6.8-7.9(14H,m,Ph), 12.4(1H,s,NH); ^{13}C-NMR($CDCL_3$,δ): 21.4(q), 21.8(q), 47.85($\underline{C}$(3)H-C(2)D),{cf. **4a** 47.94($\underline{C}$(3))}, 62.2(d), 125.7(d), 126.4(d), 127.2(d), 127.6(d), 127.9(d),129.0(d), 129.4(d), 134.5(s), 135.6(s), 136.3(s), 143.2(s), 143.3(C=N).

Thermal rearrangemnt of **4a-d_1** in dimethoxyethane 5-Isopropylamino-3,5-diphenyl-1-tosyl-[4-$^2H_1$]-2-pyrazoline (**5a-d_1**) was prepared using **4a-d_1** as the substrate according to the procedure described above. The deuterated yield was (19%). ^{1}H-NMR($CDCL_3$, δ): 1.18(3H, d, *J*=6.2 Hz, $(C\underline{H}_3)_2CH$), 1.33(3H, d, *J*=6.2 Hz, $(C\underline{H}_3)_2CH$), 2.37(3H, s, tolyl CH_3), 2.82(1H, br, NH), 3.16-3.35(1H, m, $(CH_3)_2C\underline{H}$), 3.29 (C(4)$\underline{H}$D), 6.9-8.0(14H, m, Ph); ^{13}C-NMR($CDCL_3$, δ): 21.4(q), 24.5(q), 26.1(q), 47.344 (t, *J*=23Hz, $\underline{C}$(4)HD){cf. **5a** 47.553($\underline{C}$(4)H_2)}, 44.1(d), 125.3(d), 126.2(d), 127.3(d), 127.7(d), 128.1(d), 128.6(d), 128.9(d), 129.8(d), 91.5(s, C(5)), 131.4(s), 137.5 (s), 142.9(s), 144.0(s), 150.2(C=N).

Table 1 Physical properties of compound (5)

Compd.	R	X	Yield %	mp/℃	Found (Calcd)(%) C	H	N
5a	i-Pr	H	67	121[a]	69.00	6.31	9.43
					(69.26	6.28	9.69)
5b	c-C_6H_{11}	H	89	170[a]	71.27	6.66	8.85
					(71.01	6.60	8.87)
5c	$PhCH_2$	H	86	170[a]	72.26	5.70	8.75
					(72.32	5.65	8.72)
5d	t-Bu	H	58	131[a]	69.53	7.17	9.33
					(69.77	6.53	9.39)
5e	c-C_6H_{11}	MeO	91	148[a]	69.20	6.66	8.15
					(69.16	6.60	8.34)
5f	c-C_6H_{11}	CH_3	96	138[a]	71.26	6.83	8.46
					(71.43	6.82	8.62)
5g	c-C_6H_{11}	Cl	95	153[a]	66.01	5.99	8.41
					(66.19	5.95	8.27)
5h	c-C_6H_{11}	NO_2	90	165[a]	64.70	6.26	10.50
					(64.85	5.83	10.80)

a: decomposed

Table 2 Spectroscopic data of compound (5)

Compd.	IR (KBr) ν /cm^{-1}	^{1}H-NMR ($CDCl_3$, TMS) δ/ppm, *J* /Hz
5a	3380(νNH)	1.18(3H, d, *J*=6.2, i-propyl CH_3), 1.33(3H, d, *J*=6.2, i-propyl
	1355(νSO_2)	CH_3), 2.37(3H, s, tolyl CH_3), 2.82(1H, br, NH), 3.16-3.35(1H, m,
	1170(νSO_2)	i-propyl CH), 3.29(1H, d, *J*=18.0, CH_2), 3.69(1H, d, *J*=18.0, CH_2),
		6.9-8.0(14H, m, Ph)

5b	3350(νNH)	0.9-2.1(10H,m,c-hexyl CH_2), 2.33(3H,s,tolyl CH_3), 2.1-2.4
	1350(νSO_2)	(1H,m,c-hexyl CHN), 2.83(1H,br,NH), 3.25(1H,d,*J*=18.7,CH_2),
	1167(νSO_2)	3.67(1H,d,*J*=18.7,CH_2), 6.9-8.0(14H,m,Ph)
5c	3350(νNH)	2.33(3H,s,tolyl CH_3), 3.18(1H,br,NH), 3.21(1H,d,*J*=18.3,CH_2)
	1350(νSO_2)	3.50(1H,d,*J*=18.3,CH_2), 3.73(1H,d,*J*=12.3,CH_2Ph), 3.87(1H,d,
	1160(νSO_2)	*J*=12.3,CH_2Ph), 7.0-8.0(19H,m,Ph)
5d	3381(νNH)	1.39(9H,s,t-Bu CH_3), 2.35(3H,s,tolyl CH_3), 2.30(1H,d,*J*=18.2
	1347(νSO_2)	CH_2), 2.48(1H,d,*J*=18.2,CH_2), 2.97(1H,br,NH), 7.0-7.9(14H,m,
	1161(νSO_2)	Ph)
5e	3355(νNH)	1.0-2.0(10H,m,c-hexyl CH_2), 2.37(3H,s,tolyl CH_3), 2.1-2.4
	1347(νSO_2)	(1H,m,c-hexyl CHN), 2.81(1H,br,NH), 3.26(1H,d,*J*=16.7,CH_2),
	1161(νSO_2)	3.66(1H,d,*J*=16.7,CH_2), 3.76(1H,s,CH_3O), 6.5-7.9(13H,m,Ph)
5f	3355(νNH)	1.0-2.0(10H,m,c-hexyl CH_2), 2.0-2.3(1H,m,c-hexyl CHN), 2.29
	1348(νSO_2)	2.37(3H×2,s,tolyl CH_3), 2.82(1H,br,NH), 3.26(1H,d,*J*=18.2,
	1160(νSO_2)	CH_2), 3.66(1H,d,*J*=18.2,CH_2), 6.8-7.9(13H,m,Ph)
5g	3351(νNH)	0.9-2.0(10H,m,c-hexyl CH_2), 2.0-2.3(1H,m,c-hexyl CHN), 2.39
	1348(νSO_2)	(3H,s,tolyl CH_3), 2.75(1H,br,NH), 3.21(1H,d,*J*=18.5,CH_2),
	1159(νSO_2)	3.69(1H,d,*J*=18.5,CH_2), 6.9-8.0(13H,m,Ph)
5h	3350(νNH)	1.0-2.0(10H,m,c-hexyl CH_2), 2.0-2.3(1H,m,c-hexyl CHN), 2.42
	1346(νSO_2)	(3H,s,tolyl CH_3), 2.78(1H,br,NH), 3.21(1H,d,*J*=18.5,CH_2),
	1159(νSO_2)	3.74(1H,d,*J*=18.5,CH_2), 7.1-8.4(13H,m,Ph)

Table 3 ^{13}C-NMR Spectroscopic data of compound (5)

	^{13}C-NMR ($CDCl_3$), δ/ppm									
Compd.	CH_3	CH_2		N-CH	CH			aromatic C(4°)	>C<	N=C
5a	21.4	47.6		44.1	125.3	126.2	127.3	131.4	91.5	150.2
	24.5				127.7	128.1	128.6	137.5		
	26.1				128.9	129.8		142.9		
								144.0		
5b	21.5	25.1	25.3	51.5	125.4	126.3	127.4	131.6	91.4	150.4
		25.8	34.4		127.8	128.1	128.6	137.6		
		36.8	47.8		128.9	129.9		142.9		
								144.0		
5c	21.5	47.0	47.7		125.6	126.3	127.2	131.2	91.6	150.0
					127.6	128.0	128.3	137.5		
					128.4	128.6	129.2	139.5		
					130.0			143.4		
								143.9		
5d	21.4	46.3		60.0(4°)	124.9	126.2	127.2	131.6	90.2	150.1
	31.9				127.6	128.0	128.6	137.7		
					128.7	129.2	129.5	142.7		
					129.8			145.7		

5e	21.4	25.1	25.7	51.5	113.2	126.2	126.4	131.5	91.4	150.5
	55.2	34.3	36.7		127.2	128.6	128.8	136.1		
		47.4			129.8			137.5		
								142.7		
								159.0		
5f	20.9	25.1	25.7	51.5	125.1	126.2	127.3	131.5	91.6	150.5
	21.4	34.3	36.8		128.5	128.6	128.7	137.4		
		47.6			129.8			137.5		
								141.0		
								142.8		
5g	21.4	24.9	25.2	51.6	126.2	126.8	127.2	131.3	90.9	150.4
		25.7	34.2		128.1	128.6	129.0	133.7		
		36.7	47.4		130.0			137.4		
								142.6		
								143.2		
5h	21.4	24.8	25.2	51.7	123.3	126.3	126.6	130.9	90.8	150.3
		26.6	34.3		127.1	128.7	129.2	137.3		
		36.6	47.5		130.2			143.7		
								147.3		
								151.1		

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