ANOMALOUS BAMFORD-STEVENS REACTION OF *cis*-*N*-ALKYL-3-PHENYL-AZIRIDIN-2-YL PHENYL KETONES. PREPARATION OF 1,6-DIHYDRO-1,2,3-TRIAZINE DERIVATIVES

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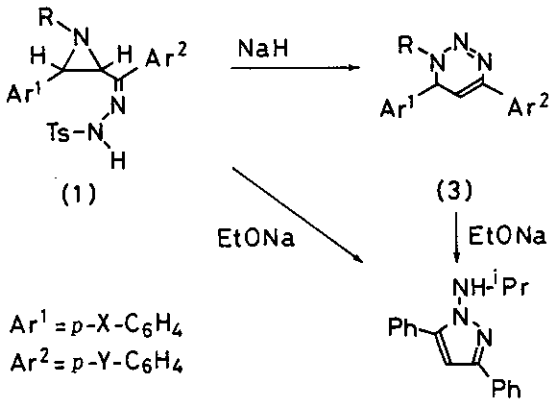
Abstract---The Bamford-Stevens reaction of *cis*-aziridinyl ketone tosylhydrazones (1a-k) yielded 1,6-dihydro-1,2,3-triazine derivatives (3a-k) without eliminating the nitrogen molecule. The reaction was induced using a slight excess of sodium hydride (2) or sodium ethoxide. When a large amount of sodium ethoxide was used, 1-isopropylamino-3,5-diphenylpyrazole (4a) was formed from the corresponding substrate (1a).

Substantial research on the Bamford-Stevens reaction has shown that the manner of the reaction depends on the structure of the substrate,[1] such as whether a strain exists in the molecule and whether the carbon adjacent to the carbon bonded to the hydrazono group has branches. Previously, we have reported the thermal and the photochemical decomposition of tosylhydrazones of six-membered cyclic ketones containing sulfur atoms.[2] In contrast with the reaction of cyclohexanone derivatives, azine derivatives were the main products in both the thermal decomposition in the presence of sodium methoxide in ethylene glycol and the photolytic decomposition in the presence of sodium hydride in diglyme. Although a large number of investigations[1] on the Bamford-Stevens reaction of cyclopropyl and oxiranyl ketones have been performed, that of aziridinyl ketones has not yet been investigated. In a previous paper,[3] we have reported the preparation of *cis*-aziridinyl ketone tosylhydrszones (1). In the present paper, we report their Bamford-Stevens reaction. The reaction of 1 with sodium hydride

(2) in dimethoxyethane resulted in a good yield of 1,6-dihydro-1,2,3-triazine derivatives (3) (Scheme 1). The products were formed without the elimination of the nitrogen molecule, in contrast with the products formed from cyclopropyl or oxiranyl ketone tosylhydrazones. Ohsawa *et al.*[4] reported that 3 was formed by the reduction of 1,2,3-triazine oxide with sodium borohydride. However, relatively little is known about the preparation and properties of 3.

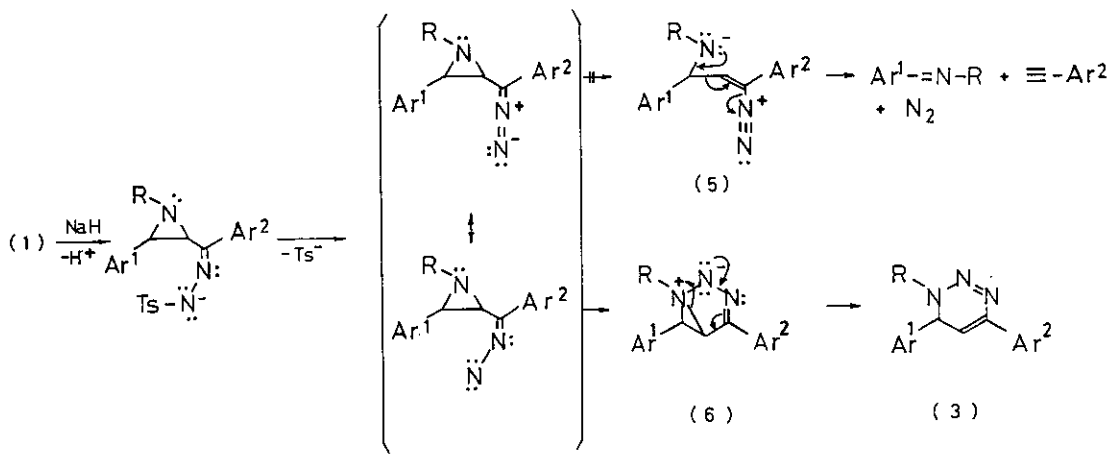


Scheme 1

RESULTS AND DISCUSSION

The reaction of 1a-k with 2 in dimethoxyethane resulted in good yields of 3a-k. The yields, melting points, and elemental analysis data of 3a-k are shown in Table 1 and the ^{1}H-nmr data are summarized in Table 2. The spectra showed AB pattern signals due to the coupling of the methine proton on C6 at δ= 4.99-5.44 ppm and the vinyl proton on C5 at δ= 5.52-5.84 ppm. The ^{13}C-nmr data of 3a-k are listed in Table 3. The spectra showed signals corresponding to methine carbon C6 at δ= 52.7-56.7 ppm, to vinyl carbon C5 at δ= 102.3-106.8 ppm, and to vinyl carbon C4 at δ= 140.9-147.9 ppm. The ^{13}C-nmr chemical shifts of C6 and C4 of 3a-k were similar to those of C6 and C4 of 1,2,5,6-tetrahydro-1,2,3-triazine derivatives, respectively.[3] The C6 carbon of 3 was derived from the C3 carbon of 1, and the ^{13}C-nmr chemical shift of the former shifted to a lower field than that of the latter. Comparing the chemical shift of the ring carbon adjacent to the nitrogen of *N*-methylaziridine with those of other cyclic amines, that of the four-membered or higher ring cyclic amines shift to a lower field than those of the aziridine carbon.[5] The chemical shift of the C2 carbon of *N*-methyl-1,2,5,6-tetrahydropyridine, corresponding to the C6 carbon of 3, occurs at δ=54.2 ppm.[5] These results indicate that 3 was formed by ring expansion. The C4-carbon of 3 shifted to a higher field, and that of the C5-carbon to a lower field with an

increase in the electron-withdrawing effect of the substituent at C4 of 3. This tendency was similar to the previously described substituent effect of styrene.[6,7] The rearrangement of 3a yielded 1-isopropylamino-3,5-diphenylpyrazole (4a) (61%) under refluxing with ethyl alcohol for five hours in the presence of an excess of sodium ethoxide. Moreover, the reaction of 1a with a large excess of sodium ethoxide yielded the same product as that of 4a (27%) under similar conditions. When the amount of sodium ethoxide was 1.2-fold molar, the reaction produced 3a (49%). We were able to isolate the intermediate product 3 from 1 to 4 using a 1-equivalent of sodium hydride. Based on the results of the transformation from 3a to 4a and a comparison of the spectral data of 3 with that of 1,2,5,6-tetrahydro-1,2,3-triazine derivatives, 3 was classified as a 1,6-dihydro-1,2,3-triazines derivative. After the deprotonation and elimination of the *p*-tolylsulfinate anion from 1, this reaction can be assumed to be the formation of 5 by an aziridinyl ring opening, or to be the formation of an aziridinium intermediate (6). The products expected from the former, such as acetylene derivatives and nitrogen, were not observed. Poon *et al.*[8] demonstrated that the reaction of *N*-substituted 1,2,4-triazoline-3,5-dione and *trans*-cyclooctene proceeded through an aziridinium intermediate using nmr spectroscopy. Hammer *et al.*[9] showed that the nucleophilic displacement of 3-chloro-1-ethylpiperidine occurred through the formation of a bicyclic aziridinium ion intermediate. Consequently, assuming an intermediate(6), the formation of 3 was elucidated (Scheme 2).



Scheme 2

Table 1 Physical properties of compounds (3)

Compd	R	X	Y	Yield/%	mp/℃	Found (Calcd)(%) C	H	N
3a	*i*-Pr	H	H	89	134-136	77.73	7.02	15.22
						(77.95	6.90	15.15)
3b	*c*-C_6H_{11}	H	H	92	136-139	78.79	7.27	12.87
						(79.46	7.30	13.24)
3c	$PhCH_2$	H	H	91	167-170	81.00	5.60	13.00
						(81.20	5.89	12.91)
3d	*t*-Bu	H	H	65	121-124	77.72	7.28	14.23
						(78.32	7.26	14.42)
3e	*c*-C_6H_{11}	H	MeO	95	120-123	75.96	7.36	11.63
						(76.05	7.25	12.09)
3f	*c*-C_6H_{11}	H	Me	82	118-121	79.73	7.47	12.55
						(79.72	7.60	12.68)
3g	*c*-C_6H_{11}	H	Cl	90	145-148	71.52	6.36	11.82
						(71.68	6.30	11.94)
3h	*c*-C_6H_{11}	H	NO_2	83	120-123	69.43	6.16	15.37
						(69.59	6.12	15.46)
3i	*c*-C_6H_{11}	MeO	H	90	>120(dec)	76.11	7.32	12.32
						(76.05	7.25	12.09)
3j	*c*-C_6H_{11}	Me	H	90	134-136	79.59	7.59	12.43
						(79.72	7.60	12.68)
3k	*c*-C_6H_{11}	NO_2	H	93	115-118	69.62	5.98	15.24
						(69.59	6.12	15.46)

Table 2 Spectroscopic data of compounds (3)

Compd	^{1}H-Nmr ($CDCl_3$, TMS) δ, *J* /Hz
3a	1.30(3H, d, *J*=6.0, CH_3), 1.34(3H, d, *J*=6.0, CH_3), 3.70(1H, septet, *J*=6.0, i-propyl CH), 5.21(1H, d, *J*=5.4, CHPh), 5.64(1H, d, *J*=5.4, CH=C), 7.1-7.9(10H, m, Ph)
3b	0.7-2.4(10H, m, CH_2), 2.9-3.6(1H, m, c-hexylCH), 5.18(1H, d, *J*=5.4, CHPh), 5.62(1H, d, *J*=5.4, CH=C), 7.1-8.1(10H, m, Ph)
3c	4.31(1H, d, *J*=14.4, HCHPh), 4.99(1H, d, *J*=4.8, CH-C=), 5.15(1H, d, *J*=14.4, HCHPh), 5.63(1H, d, *J*=4.8, CH=C), 7.2-8.0(15H, m, Ph)
3d	1.40(9H, s, $C(CH_3)_3$), 5.44(1H, d, *J*=6.0, CHPh), 5.75(1H, d, *J*=6.0, CH=C), 7.2-8.1(10H, m, Ph)
3e	0.8-2.4(10H, m, CH_2), 2.8-3.5(1H, m, c-hexylCH), 3.80(3H, s, OCH_3), 5.17(1H, d, *J*=5.4, CHPh), 5.50(1H, d, *J*=5.4, CH=C), 6.7-7.9(9H, m, Ph)
3f	0.8-2.3(10H, m, CH_2), 2.35(3H, s, CH_3), 2.9-3.5(1H, m, c-hexylCH), 5.15(1H, d, *J*=5.0, CHPh), 5.55(1H, d, *J*=5.0, CH=C), 7.0-7.8(9H, m, Ph)

3g 0.9-2.4(10H,m,CH_2), 2.9-3.7(1H,m,c-hexylCH), 5.23(1H,d,*J*=5.4, CHPh), 5.65(1H,d,*J*=5.4,CH=C), 7.1-8.0(9H,m,Ph)

3h 0.8-2.5(10H,m,CH_2), 3.0-3.6(1H,m,c-hexylCH), 5.30(1H,d,*J*=5.4, CHPh), 5.84(1H,d,*J*=5.4,CH=C), 7.2-8.4(9H,m,Ph)

3i 0.9-2.2(10H,m,CH_2), 2.9-3.5(1H,m,c-hexylCH), 3.81(3H,s,OCH_3), 5.17(1H,d,*J*=4.8,CHPh), 5.52(1H,d,*J*=4.8,CH=C), 6.8-7.8(9H,m,Ph)

3j 0.9-2.6(10H,m,CH_2), 2.34(3H,s,CH_3), 3.0-3.5(1H,m,c-hexylCH), 5.14(1H,d,*J*=5.1,CHPh), 5.59(1H,d,*J*=5.1,CH=C), 7.1-8.1(9H,m,Ph)

3k 0.8-2.4(10H,m,CH_2), 2.9-3.6(1H,m,c-hexylCH), 5.34(1H,d,*J*=5.4, CHPh), 5.62(1H,d,*J*=5.4,CH=C), 6.7-7.9(9H,m,Ph)

Table 3 ^{13}C—Nmr Spectroscopic data of compounds (3)

	^{13}C-Nmr ($CDCl_3$), δ									
						aromatic				
Compd	CH_3	CH_2	C(6)H	N-CH	CH			C(4')	-CH=	=C-N
3a	21.4		55.0	56.5	125.3	127.1	128.1	135.7	104.0	143.4
					128.4	128.9		136.8		
3b		25.3 25.7	56.6	63.3	125.5	127.1	128.2	135.9	104.0	143.8
		31.9 32.0			128.5	129.0		137.1		
3c		57.4	54.9		125.6	127.7	128.1	135.0	104.9	141.6
					128.3	128.4	128.5	135.7		
					128.8	129.1		137.0		
3d	29.6	61.8(4')	52.7		125.5	126.2	128.2	135.8	104.3	145.3
					129.0			136.9		
3e	55.3	25.4 25.7	56.7	63.2	113.7	126.9	127.2	132.7	102.3	144.0
		31.9 32.1			128.5	129.0		136.6		
								156.5		
3f	21.1	25.3 25.6	56.5	63.1	125.4	127.1	128.4	133.1	103.2	143.9
		31.8 32.0			128.6	128.9		136.9		
								137.9		
3g		25.3 25.7	56.6	63.4	126.9	127.1	128.4	134.2	104.1	143.6
		31.9 32.1			128.6	129.1		134.4		
								136.1		
3h		25.3 25.7	56.5	63.6	123.6	126.3	127.1	135.6	106.8	142.1
		31.9 32.1			128.9	129.2		143.1		
								151.5		
3i	55.3	25.4 25.7	56.7	63.2	113.7	126.9	127.2	128.6	102.3	144.0
		31.9 32.1			128.5	129.0		136.6		
								159.9		
3j	21.1	25.3 25.7	56.3	63.1	125.5	127.1	128.2	135.9	104.1	140.9
		31.9 32.0			129.6			136.9		
								138.4		
3k		25.1 25.6	55.7	64.0	124.4	125.6	127.6	135.3	102.6	147.9

31.9 32.2	128.3 128.7	137.7	
		150.3	

EXPERIMENTAL

General. The apparatus is described in a previous paper.[9] CHN analysis was performed at the Elemental Analysis Laboratory, Institute for Chemical Reaction Science, Tohoku University.

Preparation of *cis*-*N*-alkyl-3-(4-substituted phenyl)aziridin-2-yl phenyl ketone tosylhydrazones and *cis*-*N*-alkyl-3-phenylaziridin-2-yl 4-substituted phenyl ketone tosylhydrazones (1).

All materials were prepared according to the method described previously.[3]

Decomposition of 1 using sodium hydride (2) in dimethoxyethane Sodium hydride (2) (0.0545 g, 55 %, 1.25 mmol) in a 50 ml flask was washed three times with hexane. Dry dimethoxyethane (20 ml) was added, and the washed 2 was dissolved. A substrate 1a (0.500 g, 1.15 mmol) was added to the solution and allowed to sit for 5 h at room temperature until the evolution of hydrogen ceased. The solution was refluxed for 15 min. A white precipitate of sodium *p*-tolylsulfinate was formed. The precipitate was filtered off, and the filtrate was neutralized with aqueous 20 % ammonium chloride. The reaction mixture was evaporated *in vacuo*, and the residue was dissolved in dichloromethane. The solution was washed with water, and dried over anhydrous sodium sulfate. The dichloromethane was evaporated *in vacuo*. The residue was purified by recrystallization using a small amount of dichloromethane and ether. The yield of 1-isopropyl-4,6-diphenyl-1,6-dihydro-1,2,3-triazine (3a) was 0.284 g (89 %). 3b-k were also produced by a similar procedure.

Rearrangement of 3a to 4a using sodium ethoxide 3a (0.100 g, 0.361 mmol) was added to ethyl alcohol solution (4 ml) of sodium (0.045 g, 1.96 mgatm). The mixture was refluxed for 5 h, quenched with aqueous 20 % ammonium chloride, and evaporated *in vacuo*. The residue was dissolved in ether. The solution was filtered, washed three times with water, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed with silica gel (hexane :AcOEt=5:1). 1-Isopropylamino-3,5-diphenylpyrazole (4a) was prepared in a 61 % (60.8 mg) yield. mp 63.5-65℃; ir: 3230cm^{-1}; ^{1}H-nmr($CDCl_3$, δ): 0.95(6H,d, J=6 Hz, $CH(C\underline{H}_3)_2$),3.5-4.1(1H,septet, J=6 Hz, $C\underline{H}(CH_3)_2$),5.01(1H,br,NH),6.64(1H,s,CH=C),7.2-8.1(10H,m,Ph); ^{13}C-nmr:20.3(q),52.2(d),100.6(d),125.4(d),127.6(d),127.9(d),128.1

(d),128.5(d),128.6(d),130.0(s),133.3(s),143.2(s),148.0(s); Anal.Calcd for $C_{18}H_{19}N_3$: C,77.95;H,6.90;N,15.15. Found: C,78.08;H,6.98;N,15.07.

Rearrangement of 1a to 4a using a large excess of sodium ethoxide

1a (0.500 g, 1.15 mmol) was added to ethyl alcohol solution (20 ml) of sodium (0.16 g, 7.0 mgatm). The mixture was refluxed for 7 h and processed as described above. 4a was prepared in a 27 % (86.4 mg) yield.

Rearrangement of 1a to 3a using a small excess of sodium ethoxide

1a (0.300 g, 0.692 mmol) was added to ethyl alcohol solution (20 ml) of sodium (0.019 g, 0.83 mmol). The mixture was refluxed for 3 h and processed as described above. 3a was prepared in a 49 % (94 mg) yield.

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