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Substituent Effect of the Benzene Ring on Thermal Rearrangement of the Substituted Benzyl Group from *exo*-S to N(3) in (*rac*)2-Substituted Benzylthio-4-methoxycarbonyl-Δ^2-1,3-thiazolines[1)]

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The substituent effect of the benzene ring in the catalytic thermal rearrangement of the substituted benzyl group from *exo*-S to N(3) in compounds **1a**—**o** was investigated. The reactivity order of the rearrangement with various substituents was as follows: (high) *p*-OMe$\gg$*p*-Me$>$H, *p*-F, *p*-Cl, *p*-Br$\gg$*p*-CN, *p*-NO_2, *p*-CO_2Me (low). A crossover experiment employing compounds **1k** and **2d** (Exp. 2 in Chart 3) or compounds **1d** and **2k** (Exp. 3 in Chart 3) furnished interesting and informative results. Detailed comparison of these results with those of the ordinary experiments (Exp. 1 and Exp. 4 in Chart 3) provided support for a reaction mechanism involving benzylic cation formation of substituted benzyl bromides as the key step in the catalytic thermal rearrangement.

Keywords——catalytic thermal rearrangement; substituent effect; crossover experiment; (*rac*)2-substituted benzylthio-4-methoxycarbonyl-Δ^2-1,3-thiazoline

Recently, we have synthesized many kinds of N(3)-substituted 1,3-thiazolidines **3a**—**o** with the aim of developing new inhibitors of aldose reductase, which is believed to be related to several chronic complications of diabetes.[2)] For the efficient synthesis of compounds **3a**—**o**, we utilized the catalytic thermal rearrangement of the RCH_2 the group on the *exo*-S atom to the N(3) atom in compounds **1a**—**o** (see Chart 1).[2)] Based on the preliminary experimental results, this rearrangement reaction seemed to be ionic and controlled by the stability of the cation formed at the methylene carbon of RCH_2Br **2a**—**o** employed as a catalyst.[2)] In the work described here, we investigated the rearrangement reaction in detail using various *exo*-S substituted benzyl derivatives **1a**—**m**.

exo-S Substituted benzyl derivatives **1a**—**m** were heated at 120 °C under N_2 in the presence of the corresponding substituted benzyl bromide **2** (0.1 mol eq with respect to **1**)[3)] for 1, 3, and/or 5 h. All experimental results were evaluated by quantitative analysis utilizing high performance liquid chromatography (HPLC) (see Table I).

The rearrangement rate in the cases of electron-donating groups (*e.g.*, –OMe, –Me) on the aromatic ring of substituted benzyl bromides was generally higher than that in the cases of electron-withdrawing groups such as –F, –Cl, –Br, –CO_2Me, –CN, and –NO_2. The rearrangement in the case of the *p*-OMe group proceeded very smoothly: heating **1d** with 0.1 mol eq of **2d** for 1 h gave compound **3d** in 98% yield. Similar reactions in the cases of *o*- and *p*-CO_2Me, *p*-CN, and *p*-NO_2 groups gave the corresponding migrated products **3i** (14%), **3k** (13%), **3l** (17%), and **3m** (15%), respectively, in very low yields. In these cases, large amounts of the

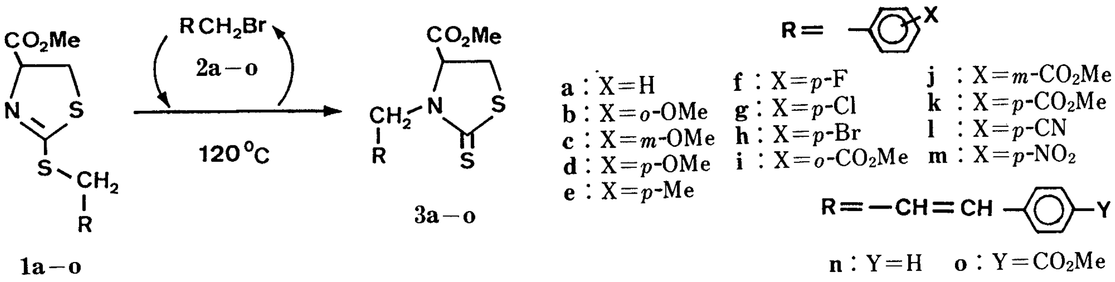

Chart 1

Table I. Rearrangement of the Substituted Benzyl Group from the *exo*-S Atom to the N(3) Atom in (*rac*)2-Substituted Benzylthio-4-methoxycarbonyl-Δ^2-1,3-thiazolines (**1a**—**m**)

exo-S Derivative **1** X=		Yield (%)[a] of **3** and (Recovery (%)[a] of **1**)			Substituent constant (σ^+) of solvolysis of cumyl chloride derivatives **4**[4]
		1 h[b]	3 h[b]	5 h[b]	
p-OMe	**1d**	98 (0)			−0.778
o-OMe	**1b**	79 (7)			
p-Me	**1e**	45 (50)	74 (18)		−0.331
p-F	**1f**	39 (56)	73 (14)		−0.073
H	**1a**	42 (54)	66 (25)	78 (21)	0
m-OMe	**1c**	41 (55)	87 (7)		0.047
p-Cl	**1g**	39 (56)	69 (27)		0.114
p-Br	**1h**	33 (62)	67 (29)		0.150
m-CO_2Me	**1j**	20 (77)	49 (46)	74 (6)	0.368
p-CO_2Me	**1k**	13 (86)	31 (67)	67 (25)	0.489
o-CO_2Me	**1i**	14 (81)	27 (72)	51 (10)	
p-CN	**1l**	17 (77)	37 (53)	62 (17)	0.659
p-NO_2	**1m**	15 (80)	38 (55)	66 (18)	0.790

a) Determined by HPLC analysis. *b*) Reaction time.

corresponding starting compounds **1i** (81%), **1k** (86%), **1l** (77%), and **1m** (80%) were recovered. *p*-Halo derivatives **1f**—**h** under similar conditions (for 1 h) were converted to the N(3)-derivatives **3f**—**h** in 33—39% yields. Comparison of the rearrangement rates provided the following sequence: *p*-OMe$\gg$*p*-Me$>$H, *p*-F, *p*-Cl, *p*-Br$\gg$*p*-CN, *p*-NO_2, *p*-CO_2Me (see Table I). Interestingly, the rearrangement rate among the compounds **1b**—**d** having an –OMe group as a typical electron-donating group clearly increased in the following order: *p*-$>$*o*-$\gg$*m*-position on the benzyl moiety. Conversely, the rate among the compounds **1i**—**k** having a –CO_2Me group as a typical electron-withdrawing group clearly decreased in the following order: *p*-$\leqq$*o*-$<$*m*-position on the benzyl moiety. Therefore, the mesomeric effect of aromatic substituents on the benzylic position should be a key factor for this thermal rearrangement in the presence of catalytic amounts of suitable benzyl bromides.

The substituent effects in this rearrangement are in accord with the substituent constants (σ^+) obtained from solvolysis of cumyl chlorides **4** in 90% aqueous acetone by Brown and Okamoto (Chart 2).[4] On the basis of our experimental results and the reported data,[4] we are confident that the stability of the benzylic carbocation of substituted-benzyl bromides **2** should regulate this catalytic thermal rearrangement.

Subsequently, we carefully carried out two kinds of crossover experiments (Exps. 2 and 3 in Chart 3) employing a pair of compounds **1k** and **2d** and another pair of compounds **1d** and **2k** in order to clarify the reaction mechanism. Compounds **1d** and **2d** were chosen as the

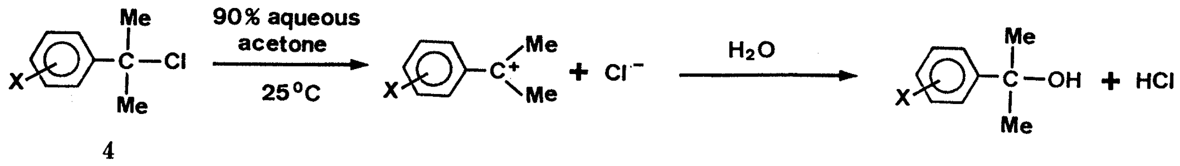

Chart 2

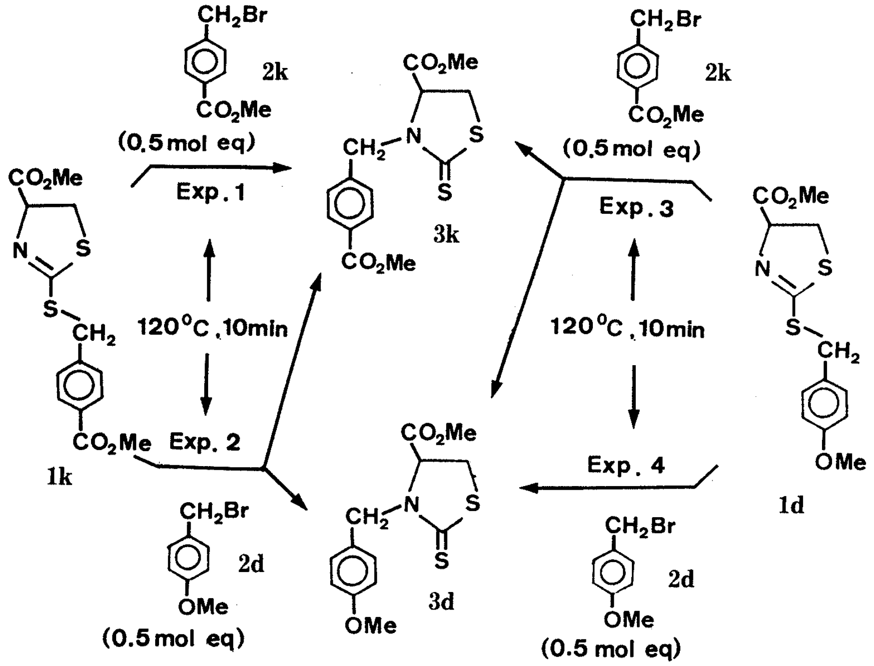

Chart 3

Table II. Thermal Rearrangement of *p*-Methoxybenzyl and *p*-Methoxycarbonylbenzyl Groups in *exo*-S Derivatives **1d** and **1k**

Experiment[a]	Yield (%)[b] or recovery (%)[b]			
	3d	**3k**	**1d**	**1k**
Exp. 1	0	11	0	83
Exp. 2	41	13	2	39
Exp. 3	29	11	50	6
Exp. 4	93	0	4	0

a) Correspond to Chart 3. *b*) Average value of the four-times-repeated experiments (HPLC analysis).

substances showing the highest reactivity in the rearrangement reaction. On the other hand, compounds **1k** and **2k** were chosen as the substances showing low reactivity. For comparison of these crossover experiments with the usual ones, the thermal rearrangement experiments using the ordinary system (**1k** and **2k** in Exp. 1 and **1d** and **2d** in Exp. 4) were also carefully done (Chart 1).

Thus, all experiments were carried out in the following general manner. A mixture of *exo*-S derivative (1 mmol) and the substituted benzyl bromide (0.5 mmol) was heated at 120 °C for 10 min[5] under N_2 and then the reaction mixture was quantitatively analyzed by HPLC. Yields of **3d** and **3k** and recoveries of **1d** and **1k** are shown in Table II.

In advance of considering the results of the crossover experiments, we confirmed the following important matters. Firstly, it was confirmed that compounds **1d** and **1k** were not converted to the corresponding N(3)-derivatives **3d** and **2k** under heating at 120 °C for 10 min without the corresponding catalyst **2d** or **2k** [recovery (97%) of **1d**]. Secondly, in order to check the possibility of the reverse rearrangement of the N(3)-substituted benzyl group to the *exo*-S atom, compound **3d** was heated at 120 °C for 10 min in the presence of the bromide **2d** or **2k**. Compound **3k** was also similarly treated with the bromide **2d** or **2k**. However, these four kinds of reactions resulted only in recovery of the starting N(3)-derivative **3d** or **3k** in 91—98% yield. Accordingly, we can discuss the net data shown in Table II.

We expected that suitable comparison of the difference (ΔY) between the yields of the N(3)-derivative might show which of the substituted benzyl bromide or the *exo*-S derivative more strongly affects the thermal catalytic rearrangement. Now, ΔY^{DB} is the difference between the chemical yield of the N(3)-derivatives obtained from two kinds of reactions employing different substituted benzyl bromides and the same *exo*-S derivative (Exps. 1 and 2 or Exps. 3 and 4 in Chart 2). ΔY^{DS} is the difference between the chemical yields of the N(3)-derivatives obtained from two kinds of reactions employing different *exo*-S derivatives and the same substituted benzyl bromide (Exps. 1 and 3 or Exps. 2 and 4 in Chart 2).

From the yield (41%) of **3d** in Exp. 2 and the yield (11%) of **3k** in Exp. 1, we obtain $\Delta Y^{\mathrm{DB}}=41-11/2$[6]$=35.5$ (%) (see Table II). Similarly, from the yield (93%) of **3d** in Exp. 4 and the yield (11%) of **3k** in Exp. 3, we obtain $\Delta Y^{\mathrm{DB}}=93/2$[6]$-11=35.5$ (%). On the other hand, from the yield (11%) of **3k** in Exp. 1 and the yield (11%) of **3k** in Exp. 3, we have $\Delta Y^{\mathrm{DS}}=11-11/2$[6]$=5.5$ (%). From the yield (93%) of **3d** in Exp. 4 and the yield (41%) of **3d** in Exp. 2, $\Delta Y^{\mathrm{DS}}=93/2$[6]$-41=5.5$ (%). Based on these results, ΔY^{DB} (35.5%)$\gg\Delta Y^{\mathrm{DS}}$ (5.5%) and it is clear that the substituted benzyl bromide catalyst **2** contributes to this thermal rearrangement *ca.* 6.5 times more than the *exo*-S derivative. On the basis of all the experimental results mentioned above, we propose the reaction mechanism shown in Chart 4. The first step (formation of the carbocation on the benzylic position) would be slower than the other two steps.

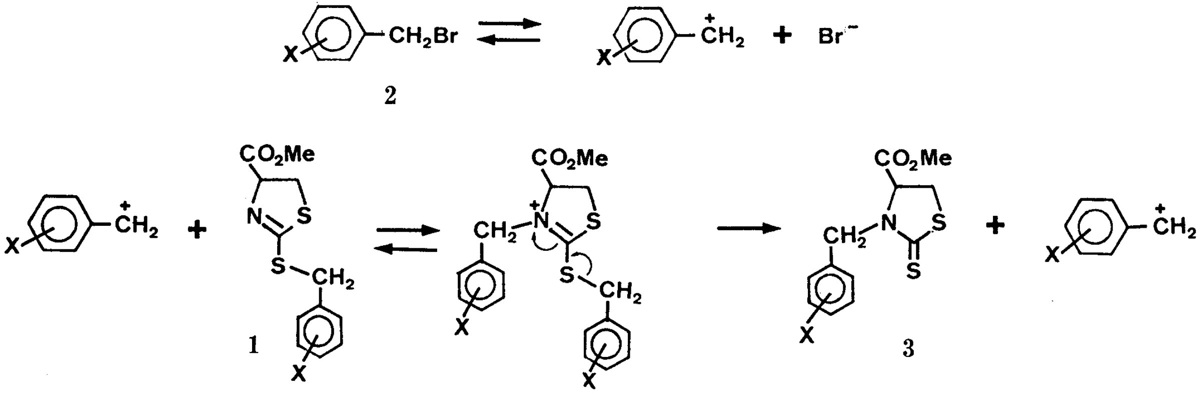

Chart 4

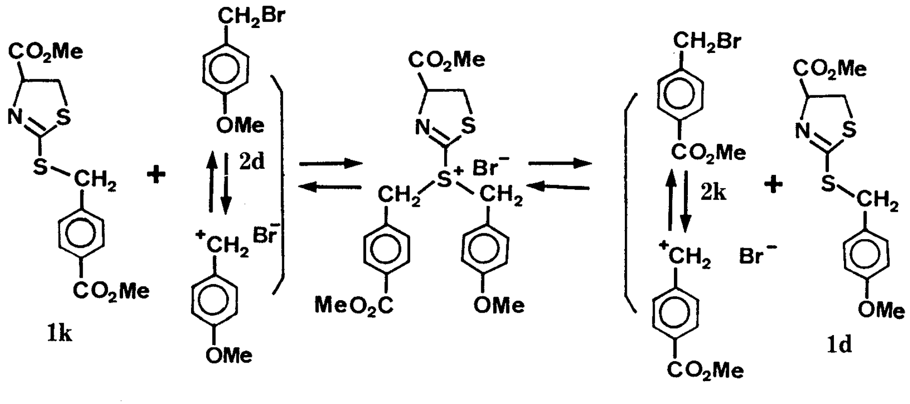

Chart 5

Formation of **1d** (2%) in Exp. 2 and of **1k** (6%) in Exp. 3 can be explained in terms of a very small contribution of a reaction path depicted in Chart 5. However, these very minor reactions do not substantially affect the experimental results shown in Chart 3.

Experimental

All standard compounds, **1a**—**m** and **3a**—**m**, were synthesized by our own method and their structures were confirmed by comparison of their spectroscopic data (infrared (IR), proton and carbon-13 nuclear magnetic resonance (^{1}H- and ^{13}C-NMR)) with those of authentic samples. All substituted benzyl bromides **2a**—**m** were commercially available. For the HPLC, a Shimadzu LC-3A instrument equipped with an SPD 2A detector was employed.

General Procedure for Investigation of Substituent Effect on the Benzene Ring——A mixture of *exo*-S substituted benzyl derivative **1** (1 mmol) with the corresponding substituted benzyl bromide **2** (0.1 mmol) was heated at 120 °C in a well stirred oil bath under N_2 for a suitable period (1, 3, and 5 h). Then, the reaction mixture was quantitatively analyzed by HPLC under the following conditions.

Analytical Conditions of HPLC: Column, μ-Porasil 4 mm i.d. × 25 cm (Waters); solvent system, CH_2Cl_2–EtOH (1000 : 1). Ultraviolet (UV) absorption frequencies (nm) of the detector, flow rates, and retention times of compounds **1** and **3** are summarized in Table III. Chemical yields (%) of **3** and recoveries (%) of **2** were determined on the basis of

Table III. Conditions for HPLC Analysis of Compounds **1** and **3** and Their Retention Times

Detector UV (nm)	Flow rate (ml/min)	Retention time (min) **1**		**3**	
251	1.0	**1d**	7.62	**3d**	4.21
245	1.0	**1b**	6.36	**3b**	3.99
247	1.0	**1e**	6.40	**3e**	3.75
245	0.8	**1f**	6.97	**3f**	4.68
245	1.0	**1a**	5.86	**3a**	3.71
241	1.5	**1c**	4.81	**3c**	2.74
251	0.8	**1g**	6.42	**3g**	4.56
245	1.5	**1h**	3.65	**3h**	2.48
244	1.5	**1j**	6.78	**3j**	3.53
245	1.5	**1k**	7.23	**3k**	3.54
244	1.5	**1i**	6.20	**3i**	3.21
250	1.5	**1l**	4.95	**3l**	3.07
250	1.5	**1m**	3.87	**3m**	2.61

Table IV. Chemical Yields of **3d** and **3k** or Recoveries of **1d** and **1k** in the Four-Times-Repeated Experiments in Chart 2

Exps. 1—4 in Chart 2	Compound 3 or 1	Yield (%) or recovery (%) 1st	2nd	3rd	4th	Average
Exp. 1	**3k**	11	11	11	11	11
	1k	84	79	84	85	83
Exp. 2	**3d**	39	41	42	40	41
	3k	13	15	13	12	13
	1d	2	4	1	2	2
	1k	40	37	37	40	39
Exp. 3	**3d**	26	28	32	31	29
	3k	13	9	11	12	11
	1d	47	54	52	48	50
	1k	6	7	3	7	6
Exp. 4	**3d**	95	93	89	95	93
	1d	2	6	2	4	4

the calibration curve obtained from HPLC analysis of the corresponding authentic compounds (see Table I).

General Procedure for Crossover Experiments and Related Experiments——(1) A mixture of the *exo*-S derivative **1d** (1 mmol) or **1k** (1 mmol) with the required substituted benzyl bromide **2d** (0.5 mmol) or **2k** (0.5 mmol) was heated at 120 °C for 10 min under N_2. Then, the reaction mixture was quantitatively analyzed by the HPLC method. The experiment (Exps. 1—4 in Chart 2) and HPLC analysis were carried out four times. Thse results and the average values of chemical yields and recoveries are shown in Table IV. (2) A mixture of the N(3)-derivative **3d** (1 mmol) or **3k** (1 mmol) with the required substituted benzyl bromide **2d** (0.5 mmol) or **2k** (0.5 mmol) was heated at 120 °C for 10 min under N_2. Then, the mixture was similarly checked by HPLC analysis.

Analytical Conditions of HPLC: Column, λ-Porasil 4 mm i.d. × 25 cm (Waters); solvent system, CH_2Cl_2–EtOH (1000 : 1); detector, UV 245 nm; flow rate, 2.0 ml/min; retention times, **3d** = 1.92 min, **3k** = 2.20 min, **1d** = 3.59 min, and **1k** = 4.10 min. The average values of the chemical yields and the recoveries obtained from Table IV are listed in Table II.

References and Notes

1) This paper forms Part II of the series "New Aldose Reductase Inhibitors." For Part I of this series, see ref. 2.
2) Y. Nagao, K. Inoue, M. Yamaki, S. Takagi, and E. Fujita, *Chem. Pharm. Bull.*, **36**, 495 (1988).
3) A. D. Clark and P. Sykes, *J. Chem. Soc.*, (*C*), **1971**, 103.
4) H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **80**, 4979 (1958).
5) We adopted reaction conditions (temp., 120 °C, time 10 min) based on the preliminary results with compounds **1d** and **2d** which showed the highest reactivity in the rearrangement reaction.
6) The chemical yield of **3d** or **3k** obtained from the ordinary reaction employing *exo*-S derivative and bromide which have the same substituted benzyl group should be a half of the original value based on the contribution of the double reaction of the same released substituted benzyl cation.