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Highly Regioselective Pinacol Rearrangement of Sulfenylmethylated Glycols

Kazuaki KUDO, Kazuhiko SAIGO,* Yukihiko HASHIMOTO,
Katsuyuki SAITO, and Masaki HASEGAWA†
Department of Synthetic Chemistry, Faculty of Engineering,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

Pinacol rearrangement of glycols having a sulfenylmethyl group smoothly proceeded with high regioselectivity to give ketones which were derived by the elimination of the β hydroxyl group to the sulfur atom. This selectivity is due to the neighboring group participation of the sulfenyl group.

Pinacol rearrangement of tetrasubstituted glycols offers a unique way to make α-trisubstituted ketones including spiro systems.[1] However, with unsymmetrically tetraalkyl-substituted glycols, this rearrangement suffers disadvantage that mixtures of isomeric products were produced due to non-selective nature about the elimination of the hydroxyl groups.[2,3] In the course of our continuous investigation to explore selective reactions through an episulfonium ion intermediate,[4] we found regiocontrolled pinacol rearrangement of glycols having a sulfenylmethyl group.

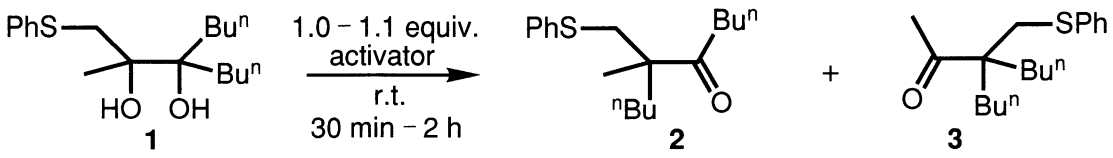


Table 1. The Reaction of **1** under Various Conditions

Run	Activator	Solvent	Yield/%	**2**:**3**
1	$BF_3{\cdot}OEt_2$	CH_2Cl_2	52	89:11
2	TfOH		38	93:7
3	$SbCl_5$		41	68:32
4	TMSOTf		68	94:6
5		CH_3CN	30	67:33
6		Et_2O	23	90:10
7		Toluene	53 (72)[a]	95:5 (97:3)[a]

a) The values in parentheses are those obtained at 0 °C.

† Present address: Department of Materials Science and Technology, Toin University of Yokohama, Kurogane-cho, Midori-ku, Yokohama 225.

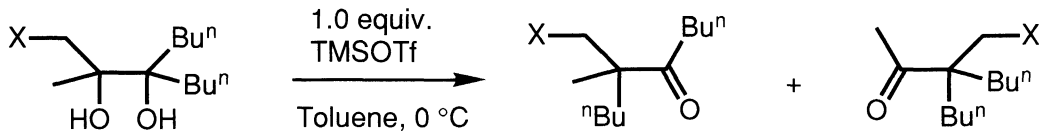
At first, the reaction of **1**[5] was carried out under various conditions (Table 1). Obtained ketones **2** and **3** were easily separated by chromatography. In every case, the major product was **2**, which was formed by the abstraction of the β hydroxyl group to the sulfenyl group. Among the activators examined, trimethylsilyl trifluoromethanesulfonate gave the best result in the yield and selectivity (Runs 1-4). Moreover, the solvent effect was apparent; with decreasing the polarity of the solvent, the selectivity was improved (Runs 4-7). This solvent effect may be explained by the terms that the coordination of the solvent toward the cationic center reduces the selectivity. The temperature somewhat affected both yield and selectivity (Run 7). However, the reaction in toluene was very slow below 0 °C; only low conversion was observed by tlc analysis even after 48 h when the reaction was performed at -23 °C.

Next, rearrangement of several substrates was carried out under the optimized conditions (Table 2). In general, very high selectivity was attained. Especially when a substrate has a ring structure, only one rearranged ketone was detected (Runs 3-5). It is noteworthy that substrates having the same carbon framework gave entirely different products depending on the position of the sulfenyl group (Runs 4,5).

Pinacol rearrangement is known to proceed through a concerted mechanism; the configuration at the carbon bearing the leaving hydroxyl group is inverted. In contrast, the pinacol rearrangement of the sulfenylmethylated glycols characteristically proceeded with complete retention of the configuration (Run 5). This result ensures an episulfonium-ion-like intermediate.

Representative procedure is as follows: to a stirred solution of glycol **1** (157.2 mg, 0.51 mmol) in 3 ml toluene was added TMSOTf (0.87 $mol \cdot l^{-1}$ solution in toluene, 0.58 ml, 0.50 mmol) at -78 °C. Then, the solution was allowed to warm up to 0 °C. After stirring for 1.5 h, saturated aqueous $NaHCO_3$ (5 ml) was added, and the reaction mixture was partitioned between dichloromethane and water layers. The organic layer was dried over sodium sulfate, and the solvent was removed under reduced pressure. Purification by preparative tlc gave ketones **2**[6] (102.8 mg, 69% yield) and **3**[7] (3.3 mg, 2% yield) as colorless oils.

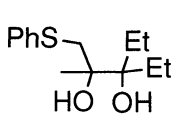
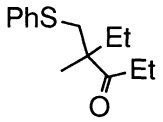
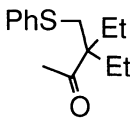
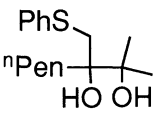
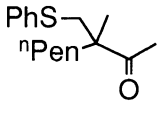
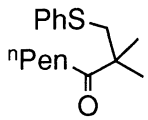
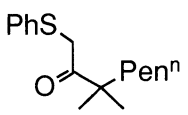
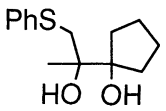
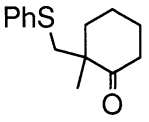
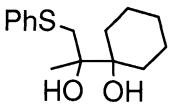
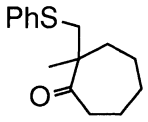
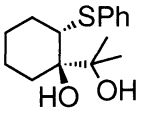
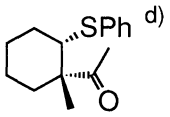
A control experiment was carried out for 3-butyl-2-methyl-2,3-heptanediol (Scheme 1). The result indicates that the sulfenyl group is not only effective for high selectivity but also for preventing side reactions. In addition, when the sulfenyl group was absent, obtained isomeric ketones were chromatographically inseparable.



X = H	34%	66	:	34
X = PhS	72%	97	:	3

Scheme 1.

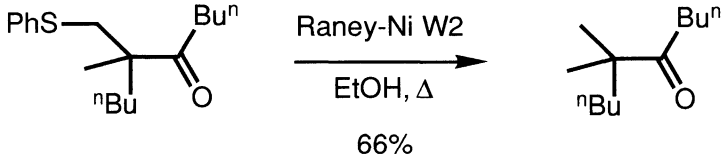
Table 2. Pinacol Rearrangement of Various Glycols Having a Sulfenylmethyl Group[a)]

Run	Substrate	Product	Yield/%
1		 :  97 : 3	62
2		 :  :  90 : 5 : 5	65[b)]
3			40
4			37[c)]
5		 **4**	71

a) The reaction was performed in toluene in the presence of 1.1 equiv. TMSOTf at 0 °C. b) TBSOTf was used as an activator. c) At room temperature. d) Relative stereochemistry was determined by X-ray crystallographic analysis of the corresponding sulfone.[8)]

Generally, unsymmetrically tetrasubstituted glycols are synthesized by inefficient reductive coupling of different ketones, which make it difficult to apply pinacol rearrangement for such type of glycols. In contrast, our starting materials were easily prepared through three steps; (1) the Barbier reaction of alkenyl halides and ketones,[9)] (2) epoxydation of the allylic alcohols, and (3) ring opening of the epoxides by a thiolate anion.

Moreover, it was revealed that the rearranged β-sulfenylketone could be easily desulfenylated by usual procedure (Scheme 2).



Scheme 2.

In conclusion, our method provides an equivalent to hydroxyl group differentiating pinacol rearrangement.

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References

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2) H. Christol, A. P. Crapcho, and F. Pietrasant, *Bull. Soc. Chim. Fr.*, **11**, 4059 (1969); B. P. Mundy and R. Srinivasa, *Tetrahedron Lett.*, **1979**, 2671.

3) Although Nybergh reported regioselective pinacol rearrangement of 3-ethyl-2-methyl-2,3-pentanediol (Et migration / Me migration = 20 / 1), this reaction is substrate specific; B. Nybergh, *Ber. Dtsch. Chem. Ges.*, **55**, 1960 (1922).

4) K. Saigo, K. Kudo, Y. Hashimoto, H. Kimoto, and M. Hasegawa, *Chem. Lett.*, **1990**, 941; K. Kudo, K. Saigo, Y. Hashimoto, H. Houchigai, and M. Hasegawa, *Tetrahedron Lett.*, **32**, 4311 (1991).

5) Readily obtained by two-step reaction [(1) ethyl piruvate and $PhSCH_2Li$ (2) >3 equiv. n-BuLi].

6) The spectral data for **2**: ^{1}H-NMR (60 MHz, CCl_4); δ = 0.88 (t, 3H, J = 5 Hz), 0.91 (t, 3H, J = 6 Hz), 1.21 (s, 3H), 1.20 - 1.70 (m, 10H), 2.38 (t, 2H, J = 8 Hz), 3.10 (s, 2H), and 7.20 - 7.40 (m, 5H); IR (neat) 1704 cm^{-1} (C=O); MS (70 eV); *m/z* (rel intensity) 292 (M^+; 22), 207 (17), 183 (89), 123 (67), 110 (14), 85 (100), and 57 (50); Found: C, 73.70; H, 9.56%. Calcd for $C_{10}H_{28}OS$: C 73.92, H 9.65%.

7) ^{1}H-NMR data for **3** (400 MHz, $CDCl_3$); δ = 0.84 (t, 6H, J = 7.3 Hz), 1.22 - 1.78 (m, 12H), 2.12 (s, 3H), 3.18 (s, 2H), and 7.17 - 7.38 (m, 5H).

8) Ketone **4** was treated with OXONE® to give sulfone,[10] mp 108 °C (EtOH), which was used for single crystal X-ray structural analysis (the crystal data: $C_{15}H_{20}O_3S$, MW = 280.4, space group $P2_1/a$, a = 11.798 Å, b = 11.312 Å, c = 11.340 Å, β = 108.38°, V = 1436.4 $Å^3$, Z = 4, D_{calc} = 1.29 $g \cdot cm^{-1}$, R = 0.061, number of independent reflections = 1978).

9) The ultrasound-assisted Barbier reaction using lithium dispersion was reported as an efficient method; J.-L. Luche and J.-C. Damiano, *J. Am. Chem. Soc.*, **102**, 7926 (1980).

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