



[1,3] Sigmatropic rearrangement of ketene silyl acetals derived from benzyl α -substituted propanoates

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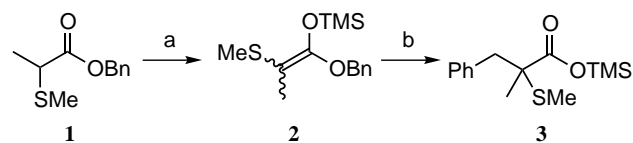
Abstract—A novel [1,3] sigmatropic rearrangement of ketene silyl acetals derived from benzyl α -substituted propanoates is developed. The reaction of ketene silyl acetal derived from optically active 1-phenylethyl 2-methylpropanoate mainly proceeds with the retention of chirality at the benzyl position to give the corresponding optically active silyl ester under thermodynamic conditions. © 2002 Elsevier Science Ltd. All rights reserved.

Recently, the synthetic utility of ketene silyl acetals (KSAs) for the preparation of various organic molecules has been widely recognized because KSAs react with electrophiles in the presence of Lewis acids. Mukaiyama et al. developed directed aldol reactions of silyl enolates including KSAs, which are quite versatile protocols for the regio- and stereoselective syntheses of β -hydroxy- or β -alkoxy-carbonyl compounds.^{1,2} Further, an effective C–C bond forming reaction via the [3,3] sigmatropic rearrangement of KSAs derived from allyl acetates or propanoates was developed by Ireland et al. in 1972.³ This method is also applicable for the synthesis of complicated organic molecules and the total syntheses of natural products were accomplished by employing the sigmatropic rearrangement as a key step.

To study the utilization of KSAs for the syntheses of optically active compounds,⁴ we planned to use 1-benzyloxy-1-trimethylsiloxy-2-methylthio-1-propene (**2**) as one of the nucleophiles derived from benzyl 2-methylthio-1-propanoate (**1**). The ¹H NMR of a crude mixture derived from **1**, LDA and chlorotrimethylsilane showed the formation of the corresponding KSA **2** (*E/Z* = 17/83) from **1** in high yield. However, it was proved that an undesirable rearranged compound, trimethylsilyl 2-methyl-2-methylthio-3-phenylpropanoate (**3**), was mainly obtained after distillation of the reaction mixture

(Scheme 1), i.e. there was no desired KSA **2** but a mixture of 58% silyl ester **3** and 16% benzyl ester **1**.

This formation of the silyl ester **3** via the benzyl migration of KSA **2** was unexpected since other derivatives such as 1-ethoxy-1-trimethylsiloxy-2-methylthio-1-propene and 1-benzyloxy-1-trimethylsiloxyethene were easily prepared from ethyl 2-methylthio-1-propanoate and benzyl acetate, respectively, according to the usual procedure followed by distillation. A similar rearrangement was reported by Arnold et al. in 1980, namely, when the reaction of benzyl 2-methylpropanoate (**4**) with LDA, chlorotrimethylsilane and HMPA was carried out in THF at 70°C, the rearranged product, trimethylsilyl 2,2-dimethyl-3-phenylpropanoate (**6**), was formed via the 1-benzyloxy-1-trimethylsiloxy-2-methyl-1-propene (**5**), and the corresponding carboxylic acid **7** was obtained in 30% yield after hydrolysis.⁵ As of today, there appears to be no other reports on the benzyl migration of KSA under thermodynamic conditions,⁶ and therefore, we would like to describe a unique and useful method for the synthesis of various β -aromatized- α,α -disubstituted carboxylic acid derivatives via the [1,3] sigmatropic rearrangement of KSAs derived from benzyl α -substituted propanoates. Fur-



Scheme 1. Attempted synthesis of KSA **2**. (a) LDA, TMSCl, -78°C to rt, quant.; (b) distillation, 58%.

Keywords: [1,3] sigmatropic rearrangement; ketene silyl acetals; benzyl vinyl ethers; benzyl transfer; retention of chirality.

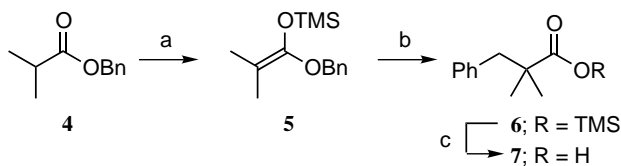
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thermore, two alternative reaction mechanisms will be discussed based on the experimental results and theoretical calculations.

First, the reaction conditions for the formation of KSA **5** were examined using **4**. It was then found that a better yield was obtained when LHMDS was used in place of LDA, since *N,N*-diisopropyl-2-methylpropanamide was produced as a by-product when using LDA. The ¹H NMR experiment showed that the benzyl migration of **5** quantitatively proceeded without solvent at 100°C for 0.5 h, and the treatment of the formed reaction mixture with 1 M hydrochloric acid gave **7** in 70% isolated yield (Scheme 2).

Next, the KSAs (**8–11**) that possess several silyl groups were synthesized and their reactivities were studied as shown in Table 1. While the reactions of the trimethylsilyl ether **5** and triethylsilyl ether **8** smoothly proceeded and the corresponding silyl esters were produced in good yields under mild conditions (at 80°C for 0.5 h), the rearrangement of trisopropylsilyl ether **10** and *t*-butyldiphenylsilyl ether **11** did not take place under severer conditions (at 100°C for 0.5 h). Furthermore, the isolated *t*-butyldimethylsilyl ether **9** also reacted at 80°C for 2 h in the absence of lithium salt and HMDS to give the corresponding silyl ester in 55% conversion yield. Generally, KSAs that have a trimethylsilyl group are not stable and handling these derivatives requires difficulty; therefore, triethylsilyl ethers are more suitable for further studies.

Since the complete conversion of **8** was observed at 100°C for 0.5 h, the generation of various triethylsilyl ethers **12–16** and successive rearrangement of these KSAs were then examined under the standard reaction



Scheme 2. [1,3] Sigmatropic rearrangement of KSA **5**. (a) LHMDS, TMSCl, -78°C to rt, quant.; (b) 100°C , 0.5 h; (c) 1 M HCl, 70% (two steps).

Table 1. Reaction conditions and conversion yields of the [1,3] sigmatropic rearrangement of several KSAs derived from **4**, LHMDS and RCl

Entry	R	KSA	Temperature ($^{\circ}\text{C}$)	Time (h)	Yield ^a
1	TMS	5	80	0.5	96
2	TES	8	80	0.5	84
3 ^b	TBS	9	80	2	55
4	TMS	5	100	0.5	Quant.
5	TES	8	100	0.5	Quant.
6 ^b	TBS	9	100	0.5	53
7	TIPS	10	100	0.5	0
8	TBDPS	11	100	0.5	0

^a Conversion yield from **4**. Determined by ¹H NMR using internal standard.

^b Isolated **9** was used for the rearrangement. KSA **9** was prepared from **4**, LHMDS and TBSOTf.

conditions (Table 2). The reactions of KSAs **12**, **13** and **14** (*E/Z* = 60/40) as well as the reaction of KSA **8** gave the desired rearranged products in good to high yields (entries 1–4). Furthermore, the benzyl migration of KSAs **15** (*E/Z* = 17/83) and **16** (*E/Z* = 7/93), which possess alkylthio groups at the 2-position, proceeded quite smoothly to afford the corresponding β -aromatized- α -alkyl- α -alkylthio carboxylic acid derivatives in high yields (entries 5 and 6). It was observed that KSAs **2** and **15** slowly transformed into the corresponding silyl esters at room temperature whereas the rearrangement of **5** and **8** did not take place at the same temperature.

Table 2. Synthesis of various β -phenyl- α,α -disubstituted carboxylic acid derivatives via the [1,3] sigmatropic rearrangement of the KSAs

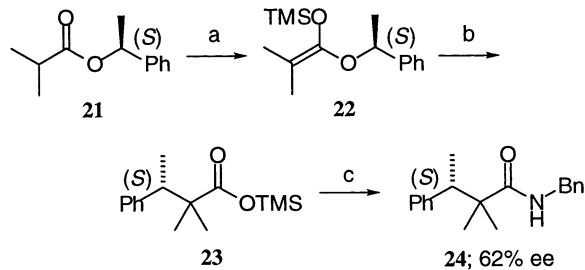
Entry	Benzyl Ester	KSA	Silyl Ester	Yield ^a
1				quant.
2				quant.
3				89
4				62
5				83
6				93

^a Conversion yield from the corresponding ester. Determined by ¹H NMR using internal standard.

It was noted that the alkylthio groups in the produced β -aromatized- α -alkylthio carboxylic acid derivatives could be removed by desulfurization, and further, the phenyl group in the formed compounds could be converted to a carboxyl group by oxidative cleavage using RuCl_3 and NaIO_4 .⁷ Therefore, various substituted succinic acid derivatives could be obtained from the corresponding benzyl esters by way of a two-carbon elongation at the α -position using the above mentioned rearrangement.

Among some possible reaction pathways during the benzyl migration of the KSAs, it is plausible that a concerted rearrangement or a benzyl cation transfer to the enolate anion after dissociation under thermal conditions occurred. In order to study the reaction mechanism, the effect of the 4-substituted aromatic rings in the benzyl groups of the KSAs was examined as shown in Table 3. Though the reactivities of KSAs **17**, **19** and **20** that possess methyl, chloro and trifluoromethyl groups at the 4-position appear similar at 80°C, a high conversion was attained at the same temperature by the reaction of KSA **18** with a methoxy group. The methoxy group at the 4-position might stabilize the corresponding benzyl cation which was formed after the dissociation of KSA according to the latter mechanism.

Next, a similar rearrangement of 1-phenylethyl 2-methylpropanoate was carried out via forming the corresponding KSA as shown in Scheme 3. An optically active β -aromatized butanoic acid derivative might be obtained if an optically active 1-phenylethyl carboxylate was employed as the starting material. Actually, the reaction of KSA **22** derived from (*S*)-1-phenylethyl 2-methylpropanoate (**21**, >98% ee) proceeded at 100°C to afford the trimethylsilyl 3-phenyl-2,2-dimethylbutanoate (**23**). The major stereochemistry at the C3 position of **23** was proved to be *S*, and the ee of the carboxamide **24** prepared from the silyl ester was determined to be 62% by HPLC analysis. It is noteworthy that the chiral transfer reaction from the carbinol carbon in the alcohol part of the carboxylic ester to the β -carbon of the corresponding silyl ester took place with the retention of configuration.⁸ The dissociated benzyl cation transfer of **22** might give the racemized



Scheme 3. (a) LHMDS, TMSCl , -78°C to rt, quant.; (b) 100°C , 0.5 h; (c) 1. 1 M HCl ; 2. BnNH_2 , DPC,⁹ DMAP, 25% (three steps).

compound in principle, therefore, it is assumed that ca. 40% of the racemic **23** was produced via a dissociated mechanism and ca. 60% of (*S*)-**23** was formed via a concerted [1,3] sigmatropic rearrangement mechanism if the latter process stereospecifically proceeded.

Several concerted transition states were found to give the rearranged products from the benzyl vinyl ether and **5** using the calculation at the B3LYP/6-31G**//B3LYP/6-31G* level.¹⁰ The existence of only one imaginary frequency for each structure and the analysis of these vibration sequences showed that these are certainly the transition states that give the corresponding aldehyde and silyl ester **6**. The lowest energy structure among these conformations was selected and depicted in Fig. 1. The benzyl transfer from oxygen to C2 simultaneously occurs with cleavage of the benzyl carbon–oxygen bond via the 4-membered transition state. Furthermore, it was calculated that the activation energies for the rearrangements of the benzyl vinyl ether and **5** were ca. 61 and ca. 54 kcal/mol, respectively.

The above structure for the concerted mechanism could clearly explain that the chiral transfer of **22** to **23** mainly proceeded with retention of the stereochemistry at the benzyl carbon. The 1,3-silyl migration of the silylmethyl ketones or allylsilanes to give the rearranged products was well known and their 4-membered transition states were proposed in theoretical studies.¹¹ On the other hand, our experimental investigation of the present reaction revealed that there is the actual possibility of a concerted process in the 1,3-carbon migration of the benzyl vinyl ethers.

Table 3. Synthesis of various β -aromatized- α,α -dimethyl carboxylic acid derivatives via the [1,3] sigmatropic rearrangement of the KSAs

Entry	R	KSA	Temperature ($^\circ\text{C}$)	Time (h)	Yield ^a
1	H	8	80	0.5	34
2	Me	17	80	0.5	47
3	OMe	18	80	0.5	83
4	Cl	19	80	0.5	31
5	CF_3	20	80	0.5	37
6	H	8	100	0.5	Quant.
7	Me	17	100	0.5	Quant.
8	OMe	18	100	0.5	Quant.
9	Cl	19	100	0.5	Quant.
10	CF_3	20	100	0.5	99

^a Conversion yield. Determined by ^1H NMR.

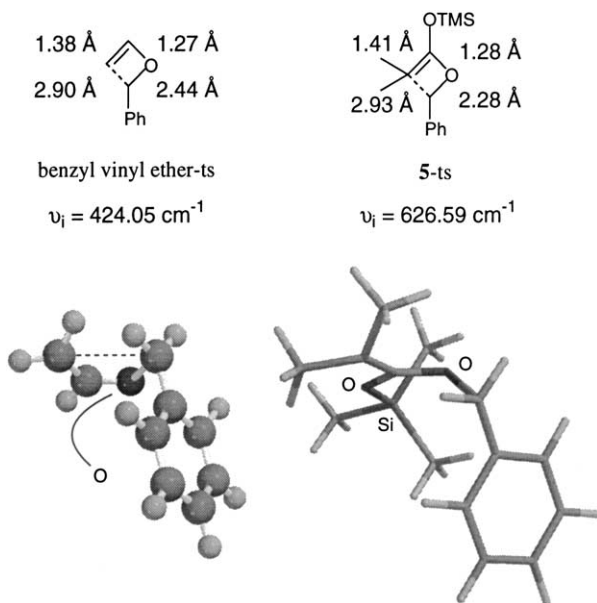


Figure 1. Transition states of [1,3] sigmatropic rearrangement of benzyl vinyl ether and KSA **5** estimated by molecular orbital calculations (B3LYP/6-31G**//B3LYP/6-31G*).

Thus, we developed the thermal [1,3] sigmatropic rearrangement of KSAs derived from benzyl α -substituted propanoates to give the corresponding silyl esters. The benzyl migration of KSAs is a practical methodology useful to produce β -aromatized- α,α -disubstituted carboxylic acid derivatives. It is proposed that the concerted 4-membered transition state principally participates in the reaction mechanism since chiral transfer mainly proceeds with retention under thermodynamic conditions. Other applications and further studies on the mechanism of the present reaction are now in progress.

A typical experimental procedure is described for the generation of **8** and its rearrangement: to a solution of hexamethyldisilazane (121.1 mg, 0.750 mmol) in THF (1.0 mL) at 0°C was added *n*-butyllithium in hexane (1.54 M, 0.480 mL, 0.750 mmol). The reaction mixture was stirred for 15 min at 0°C and then a solution of **4** (89.1 mg, 0.500 mmol) in THF (0.25 mL) was added at -78°C . After the mixture was stirred for 1 h at -78°C , chlorotriethylsilane (0.130 mL, 0.760 mmol) was added. The reaction mixture was stirred for 5 min at the same temperature and for 1 h at room temperature. After evaporation of the solvent, the crude product was filtered through a short pad of Celite to afford **8** (quant. determined by ^1H NMR) as a colorless oil. Heating **8** without solvent at 100°C for 0.5 h gave a rearranged compound, triethylsilyl 2,2-dimethyl-3-phenylpropanoate (quant. determined by ^1H NMR in benzene- d_6 using anisole as an internal standard), as a colorless oil.

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