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Reaction of a Cyclic Oxosulfonium Ylide with Acetates of the Baylis-Hillman Adducts: Tandem Michael–Intramolecular Corey-Chaykovsky Reactions

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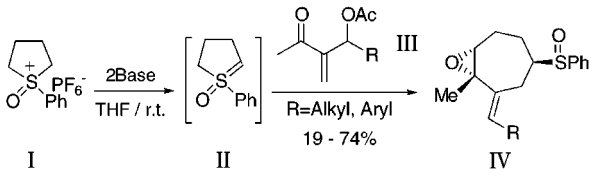
ABSTRACT



The reaction of the five-membered cyclic oxosulfonium ylide 2 with α-methylene-β-acetoxy ketones in the presence of two equimolar amounts of base afforded the cycloheptene oxide derivatives with stereoselectivity in 19–74% yield via a Michael-type addition of the ylide followed by elimination of the acetoxy group and an intramolecular Corey-Chaykovsky reaction.

The reaction of a five-membered cyclic phosphonium ylide with enones,[1] enoates,[2] and α,β-unsaturated thioesters[3] provides cycloheptene or hydroazulene derivatives by tandem Michael−intramolecular Wittig reactions. These tandem reactions proceed via a rigid phosphabicyclic or phosphatricyclic intermediate so that the products form with stereoselectivity.

In the present work, we attempted to develop novel tandem reactions employing a cyclic oxosulfonium ylide via the above tandem reactions of the cyclic phosphonium ylide.

The Corey-Chaykovsky reaction of oxosulfonium ylides has provided a useful method for the synthesis of cyclopropane derivatives[4−6] by Michael-type addition of the ylide to the activated carbon−carbon double bond. The reaction has also been used for the synthesis of epoxide[4a,7] and aziridine[4c,8]

(1) (a) Fujimoto, T.; Takeuchi, Y.; Kai, K.; Hotei, Y.; Ohta, K.; Yamamoto, I. *J. Chem. Soc., Chem. Commun.* **1992**, 1263. (b) Fujimoto, T.; Uchiyama, Y.; Kodama, Y.; Ohta, K.; Yamamoto, I.; Kakehi, A. *J. Org. Chem.* **1993**, *58*, 7322.

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(3) Manuscript submitted for publication.

(4) (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 867. (b) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 3782. (c) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

(5) (a) Clive, D. L. J.; Daigneault, S. *J. Chem. Soc., Chem. Commun.* **1989**, 332. (b) Okuma, K.; Ikari, K.; Ono, M.; Sato, Y.; Kuge, S.; Ohta, H.; Machiguchi, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2313. (c) Cativiela, C.; Díaz-de-Villegas, M. D.; Jiménez, A. I. *Tetrahedron* **1995**, *51*, 3025.

(6) For a review of the reaction of oxosulfonium ylides see: Gololobov, Y. G.; Nesmeyanov, A. N.; Lysenko, V. P.; Boldeskul, I. E. *Tetrahedron* **1987**, *43*, 2609.

(7) Childers, W. E.; Furth, P. S.; Shih, M.-J.; Robinson, C. H. *J. Org. Chem.* **1988**, *53*, 5947.

(8) García-Ruano, J. L.; Fernández, I.; Hamdouchi, C. *Tetrahedron Lett.* **1995**, *36*, 295.

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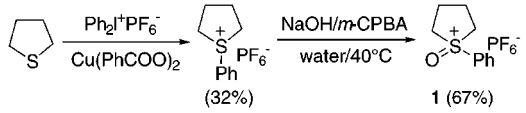
derivatives by nucleophilic addition of the ylide to carbonyl and imine functionalities. However, only limited examples of the reaction using cyclic oxosulfonium ylides have been thus far reported.[9]

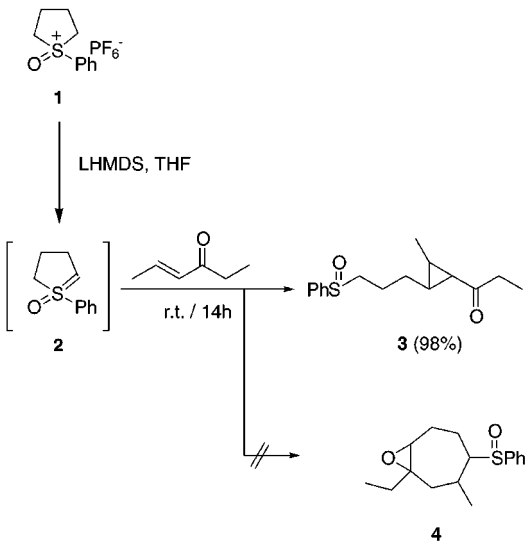
Cyclic oxosulfonium salt **1** was prepared by arylation[10] of tetramethylene sulfide using diphenyliodonium salt followed by oxidation of the resulting *S*-phenyl sulfonium salt using *m*-CPBA[11] (Scheme 1). At first, the reaction of

Scheme 1



oxosulfonium ylide **2**, generated from **1** using LHMDS as a base, with 4-hexen-3-one was examined. If the regeneration of the ylide after Michael-type addition followed by an intramolecular Corey-Chaykovsky reaction proceeds in a manner similar to a cyclic phosphonium ylide, the cycloheptene oxide derivative **4** would be obtained. However, cyclopropane derivative **3**[12] was formed in 98% yield via the addition of the ylide and the elimination of the oxosulfonium group (Scheme 2). These results indicated that the

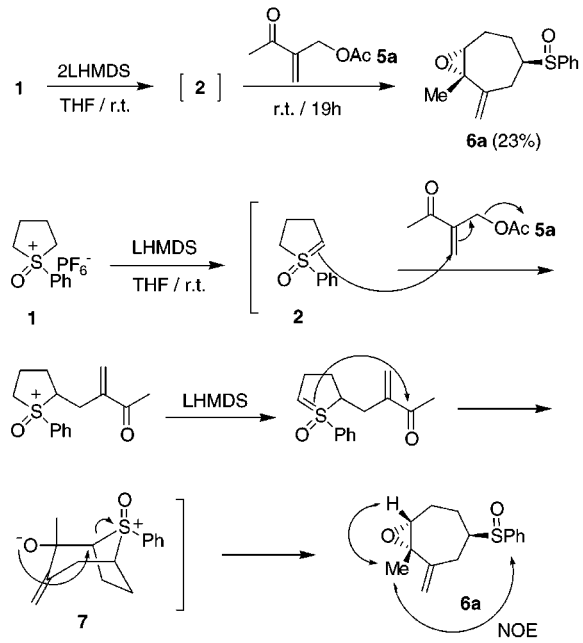
Scheme 2



intramolecular nucleophilic substitution of the enolate anion would be preferred to the regeneration of the ylide for the reaction of cyclic oxosulfonium ylide with enone.

Therefore, we considered that substrates suitable for the desired tandem reactions would be those in which no enolate anion generated after an initial Michael addition remains.[13] The reaction of the oxosulfonium ylide **2** with 4-acetoxy-3-methylene-2-butanone (**5a**), which was prepared from the corresponding Baylis-Hillman adduct,[14] was then attempted in the presence of two equimolar amounts of LHMDS. Consequently, the cycloheptene oxide derivative **6a** was obtained in 23% yield with stereoselectivity (Scheme 3). This

Scheme 3



reaction would proceed via a Michael-type addition of the ylide **2** followed by elimination of the acetoxy group and an intramolecular Corey-Chaykovsky reaction of the regenerated ylide. Although the intramolecular Michael-type addition of the regenerated ylide is also possible, the compound stemming from the reaction was not isolated. The structure and stereochemistry of cycloheptene oxide derivative **6a** was determined by ^{1}H NMR, ^{13}C NMR, and NOESY spectra. Especially in the NOESY spectrum, the correlation between the proton in the oxirane ring and Me and between Me and the aromatic protons of the phenyl sulfinyl group was observed. Accordingly, it was clarified that **6a** has a trans relationship between the phenyl sulfinyl group and the oxirane ring, as shown in Scheme 3. Moreover, no peaks

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(10) (a) Crivello, J. V.; Lam, J. H. W.*J. Org. Chem.* **1978**, *43*, 3055. (b) 1-Phenylthiolanium salt was synthesized from ω-bromoalkyl sulfide with silver perchlorate[10c] or from the reaction of ω-phenylthio alcohol with trimethylsilyl iodide.[10d] (c) Yano, Y.; Ishihara, M.; Tagaki, W. *Int. J. Sulfur Chem. A* **1972**, *2*, 169. (d) Ceré, V.; Pollicino, S.; Fava, A. *Tetrahedron* **1996**, *52*, 5989.

(11) (a) Mori, M.; Takeuchi, H.; Minato, H.; Kobayashi, M.; Yoshida, M.; Matsuyama, H.; Kamigata, N. *Phosphorus, Sulfur Silicon Relat. Elem.* **1990**, *47*, 157. (b) Takeuchi, H.; Minato, H.; Kobayashi, M.; Yoshida, M.; Matsuyama, H.; Kamigata, N. *Phosphorus, Sulfur Silicon Relat. Elem.* **1990**, *47*, 165.

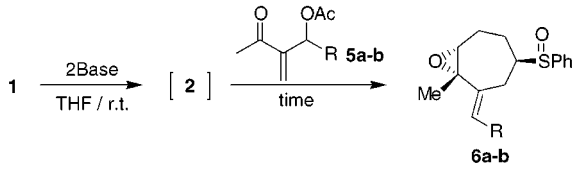
(12) Although the ^{13}C NMR spectrum indicated that the product **3** was a single stereoisomer, the stereochemistry was not determined.

(13) Smith, A. B., III; Wexler, B. A.; Slade, J. S. *Tetrahedron Lett.* **1980**, *21*, 3237.

(14) (a) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653. (b) Fort, Y.; Berthe, M. C. *Tetrahedron* **1992**, *48*, 6371. (c) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001.

ascribed to other possible stereoisomers were observed in the ^{1}H and ^{13}C NMR spectra. Therefore, the reaction was considered to proceed via the rigid thiabicyclic intermediate **7,** which is similar to that proposed in the reaction of the cyclic phosphonium ylide. The effect of bases on this reaction was examined for the sake of the enhancement of the yield (Table 1). Surprisingly, the same reactions using NaH or

Table 1. Reaction of α-Methylene-*β*-acetoxy Ketone with **2**



6a-b

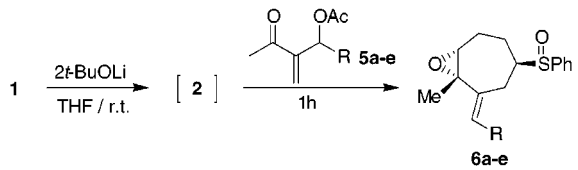
entry	base	R	time(h)	product	yield[a] (%)
1	LHMDS	H	19	**6a**	23
2	NaH	H	19	**6a**	-
3	*t*-BuOK	H	24	**6a**	-
4	LHMDS	Me	0.5	**6b**	35
5	*n*-BuLi	Me	0.5	**6b**	18
6	*t*-BuLi	Me	0.5	**6b**	37
7	*t*-BuOLi	Me	1	**6b**	56

[a] Isolated yield.

t-BuOK did not afford the cycloheptene oxide derivative **6a**. In addition, the reactions under various reaction conditions, the amount of base, the order of addition of reactants, and solvents, did not bring about an improvement in the yield for the reaction with 4-acetoxy-3-methylene-2-butanone (**5a**). However, the reaction of 4-acetoxy-3-methylene-8-pentanone (**5b)** using *t*-BuOLi as a base for 1 h at room temperature provided the corresponding cycloheptene oxide derivative **6b** in 56% yield.

To elucidate the versatility of this reaction, the reaction of the ylide **2** with some α-methylene-*β*-acetoxy ketones **5c**−**e** was examined under the same reaction conditions. Consequently, cycloheptene oxide derivatives **6c**−**e** were obtained in 66−74% yield (Table 2). Although the existence of the further two isomers relevant to the geometry of exo-methylene was possible in **6b**−**e**, any peaks ascribed to other possible isomers were not observed in the ^{1}H and ^{13}C NMR spectra. To clarify the geometry of the exo-trisubstituted olefin, the NOESY spectrum of compound **6c**[15] was analyzed.

Table 2. Reaction of α-Methylene-*β*-acetoxy Ketone with **2**

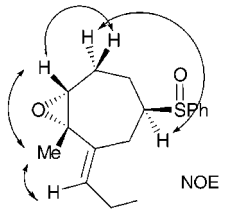


6a-e

entry	R	ketone	product	yield[a] (%)
1	H	**5a**	**6a**	19
2	Me	**5b**	**6b**	56
3	Et	**5c**	**6c**	66
4	*i*-Pr	**5d**	**6d**	74
5	Ph	**5e**	**6e**	67

[a] Isolated yield.

The correlation between the vinylic proton and the methyl group bonded to the oxirane ring was observed, but no correlation between methylene protons in the ethyl group and the methyl group was found. Therefore, the resulting product was determined to be the cycloheptene oxide derivative which has the geometry as shown in Figure 1.



6c

Figure 1.

It has been reported that the S_N2' addition of a hydride ion or a carbanion to acetates of the Baylis-Hillman adducts from acrylate produces an *E*-trisubstituted olefin[16] because of steric interaction in the transition state for elimination of the acetoxy group. Therefore, the *E*-trisubstituted enone intermediate was considered to be generated by the initial S_N2' addition of the cyclic oxosulfonium ylide into α-methylene-*β*-acetoxy ketone via the same transition state.

(15) **Typical Procedure for the Reaction of the Cyclic Oxosulfonium Ylide 2 Using 5c.** To a solution of five-membered oxosulfonium salt (0.10 g, 0.31 mmol) in dry THF (2 mL) was added dropwise a solution of lithium *tert*-butoxide (2.05 equiv) (in 1 M THF solution, 0.63 mL, 0.63 mmol), and the mixture was stirred at room temperature for 10 min. A solution of **5c** (0.05 g, 0.31 mmol) in dry THF (2 mL) was then added dropwise to the mixture, and the resulting solution was stirred for 1 h. The mixture was quenched with water and extracted with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using AcOEt as an eluent to give **6c** (0.0589 g, 66% yield) as a white solid: mp 92−94 °C; ^{1}H NMR (500.13 MHz, acetone-d_6) δ 0.78 (t, J = 7.5 Hz, 3H), 1.21−1.28 (m, 1H), 1.29 (s, 3H), 1.55−1.62 (m, 2H), 1.66−1.74 (m, 1H), 2.05−2.12 (m, 2H), 2.30−2.34 (m, 1H), 2.36−2.39 (m, 1H), 2.50−2.55 (m, 1H), 2.84−2.87 (m, 1H), 5.46 (t, J = 7.4 Hz, 1H), 7.57−7.70 (m, 5H); ^{13}C NMR (125.76 MHz, acetone-d_6) δ 14.13, 20.73, 22.71, 24.97, 25.98, 29.08, 60.97, 62.69, 65.38, 125.35, 129.83, 131.53, 132.23, 136.33, 144.33; IR (KBr) 1090 (oxirane), 1030 (S=O), 860 (C=C) cm^{-1}; HRMS (70 eV) calcd for $C_{17}H_{22}O_2S$ (M^+) m/z 290.1340, found (M^+) 290.1334.

(16) (a) Hoffmann, H. M. R.; Rabe, J. *J. Org. Chem.* **1985**, *50*, 3849. (b) Basavaiah, D.; Sarma, P. K. S. *J. Chem. Soc., Chem. Commun.* **1992**, 955. (c) Basavaiah, D.; Sarma, P. K. S.; Bhavani, A. K. D. *J. Chem. Soc., Chem. Commun.* **1994**, 1091. (d) Beltaîef, I.; Amri, H. *Synth. Commun.* **1994**, *24*, 2003. (e) Basavaiah, D.; Krishnamacharyulu, M.; Hyma, R. S.; Sarma, P. K. S.; Kumaragurubaran, N. *J. Org. Chem.* **1999**, *64*, 1197.

Consequently, the (*E*)-*exo*-methylene cycloheptene oxide derivative would be obtained by the subsequent intramolecular reaction.

In conclusion, we have developed novel tandem reactions of cyclic oxosulfonium ylide with acetates of the Baylis-Hillman adducts for the stereoselective synthesis of cycloheptene oxide derivatives. Further studies on the reaction mechanism and application of this method to the synthesis of other complex molecules are currently underway.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **3** and **6a**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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