The Formation of Cyclopropane Derivatives Bearing 1,2-Dicarbonyl Groups through Tandem Michael–Favorskii-Type Reactions with (*E*)-β-Styrylselenonium Triflate

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A novel tandem Michael–Favorskii-type reaction is described. Treatment of active methylene carbanions, prepared by the reaction of NaH and active methylene compounds, with (*E*)-β-styrylselenonium triflate in DMF at 70 °C for 3 h gave cyclopropane derivatives bearing 1,2-dicarbonyl groups in moderate to good yields. On the other hand, the carbanions derived from malonates reacted with the selenonium salt to afford 1,1-dicarbonylcyclopropane compounds in good yields.

Introduction

The versatility of carbonylcyclopropane compounds has made them regarded as useful synthons in organic chemistry.[1] In particular, the efficient behavior of dicarbonylcyclopropanes as good Michael acceptors[2] and important precursors of bioactive derivatives may be cited.[3] Treatment of an α,β-unsaturated carbonyl compound with a chalcogenonium ylide derived from the corresponding chalcogenonium salt is known as a typical procedure for the preparation of cyclopropane derivatives bearing electron-withdrawing groups.[4] Although it is familiar that the betaine intermediate – the key compound for the cyclopropane ring formation – can be generated by the reaction of electron-deficient olefins with β-oxo-onium ylides,[5] betaine elaboration from an alkenylchalcogenonium salt and a nucleophile has hardly been reported.[6] On the other hand, Kuwajima reported a cyclopropane synthesis using vinyl selenones as the Michael acceptors and active methylene or active methylidyne carbanions, and prepared various types of carbonylcyclopropane compounds.[7]

Recently, we developed a new Michael-type reaction of alkynylselenonium salts as Michael acceptors with nucleophiles.[8] In particular, the tandem Michael addition–cyclization route between alkynylselenonium salts and active methylene carbanions afforded highly functionalized furan derivatives.[9] These interesting results prompted us to investigate a tandem reaction of an alkenylselenonium salt involving multiple carbon–carbon bond formation to afford a useful compound. We now report tandem Michael–Favorskii-type reactions of β-styrylselenonium salts with 1,1-dicarbonyl compounds, through which 1,2-dicarbonylcyclopropane derivatives are formed.

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Results and Discussion

We first examined the reaction of (*E*)-β-styrylselenonium triflate (**1**)[10] with an active methylene carbanion generated from benzoylacetone and a base (Table 1). The use of sodium hydride as a base gave 1-(2-benzoyl-3-phenylcyclopropyl)ethanone (**2a**) with a trace amount of its diastereoisomer **3a** after 24 h at room temperature (Entry 1). The yields of the desired compounds were improved under reflux for 3 h, to afford **2a** and **3a** in 66% and 8% yields, respectively (Entry 2). However, the use of a different base, potassium *tert*-butoxide or DBU, did not improve the yield obtained with sodium hydride (Entries 3 and 4) under the conditions of Entry 2. When DMF was used at 70 °C for 3 h, the cyclopropane derivatives were obtained in 81% yield (Entry 5). The stereochemistry of compounds **2a** and **3a** was determined by comparison with known compounds;[11] in particular, NOE measurements of **2a**[12] showed the relative configuration of the cyclopropane ring to be (1*R**,2*S**,3*R**).

Secondly, to broaden the scope of this transformation, a variety of active methylene compounds were allowed to react with alkenylselenonium salt **1** under these reaction conditions (Table 2). A series of cyclopropanes **2**, with *anti* relationships between the phenyl group and the other functional groups, were prepared as the main products in moderate to good yields from active methylene compounds possessing at least one ketone group by application of this new methodology (Entries 1–5). The ^{1}H and ^{13}C NMR spectra

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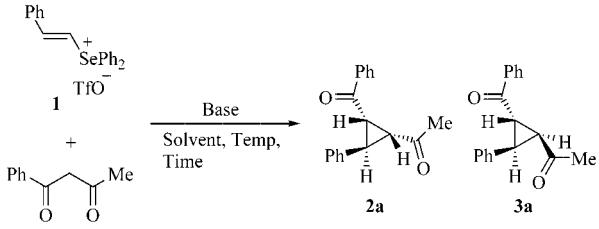
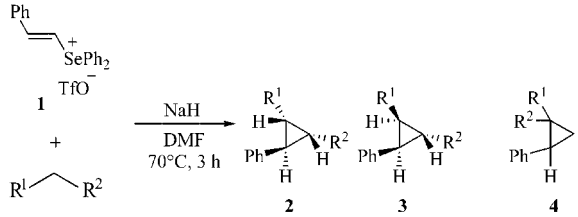
Table 1. Cyclopropane formation from alkenylselenonium salt **1** and benzoylacetone.



Entry	Base	Solvent	Temp.	Time	Products 2a	3a
1	NaH	THF	r.t.	24 h	30%	1%
2	NaH	THF	reflux	3 h	66%	8%
3	*t*BuOK	THF	reflux	3 h	55%	– [a]
4	DBU	THF	reflux	3 h	48%	– [a]
5	NaH	DMF	70°C	3 h	69%	12%
6	NaH	CH_3CN	70°C	3 h	31%	15%

[a] Inseparable mixtures.

Table 2. Cyclopropane formation from alkenylselenonium salt **1** with various active methylene compounds.



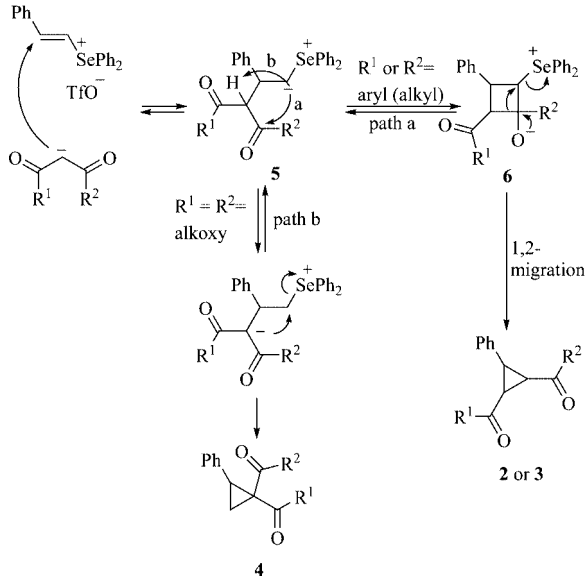
Entry	R^1	R^2	Products (% yield)		
1	MeC(O)	MeC(O)	**2b** (63)	**3b** (19)	
2	PhC(O)	PhC(O)	**2c** (58) [a]	**3c** (13)	
3	PhC(O)	CN	**2d** (56)	**3d** (13)	
4	MeC(O)	BnOC(O)	**2e** (44)		
5	PhC(O)	EtOC(O)	**2f** (38)		
6	EtOC(O)	EtOC(O)			**4a** (62)
7	BnOC(O)	BnOC(O)			**4b** (97)

[a] The yield was obtained after 20 h at 70 °C.

of products **2b** and **2c**[13] demonstrated highly symmetrical skeletons. The relative configurations of minor products were determined by the coupling constants in their ^{1}H NMR spectra. On the other hand, the reaction with diethyl malonate, which has no ketone group, afforded a good yield of diethyl 2-phenylcyclopropane-1,1-dicarboxylate (**4a**),[14] bearing 1,1-dicarbonyl groups (Entry 6). Treatment with dibenzyl malonate also afforded the corresponding 1,1-dicarbonylcyclopropane compound **4b** in excellent yield (Entry 7).

On the basis of these results, we propose a plausible mechanism for the reactions of the alkenylselenonium salt with active methylene carbanions (Scheme 1). Selenonium ylides **5** are formed from the Michael addition of the carbanion to the alkenylselenonium salt. When the active methylene compound possesses one or more ketone group(s), the ylide carbanion attacks the more active carbonyl group intramolecularly to form a cyclobutane ring, which is followed by the 1,2-migration of the *endo* carbon–carbon bond with the elimination of diphenyl selenide to form a cyclopropane derivative bearing 1,2-dicarbonyl groups (path a). This ring contraction reaction is similar to the semibenzylic pathway for the Favorskii rearrangement.[15] On the other hand, since the carbonyl groups derived from malonates in ylide **5** are less reactive toward the ylide carbanion, deprotonation of an active methyne proton occurs preferentially, to form another carbanion, followed by intramolecular nucleophilic substitution to give a cyclopropane derivative bearing 1,1-dicarbonyl groups (path b).

The stereoselectivity of the formation of cyclopropane compounds **2** and **3** is explained as follows (Figure 1). Since these reactions were examined above room temperature and



Scheme 1. Plausible mechanism for cyclopropane formation.

were in equilibrium between the starting materials and cyclobutane intermediate **6**, the reactions proceeded via the thermodynamically stable configurations of **5** and **6**, each with a predominant *trans* configuration between a phenyl group and a carbonyl substituent. Conformer **5A**, which is sterically preferred over the other **5B**, cyclizes to form cyclobutane **6A**. The subsequent 1,2-migration of the *endo* carbon–carbon bond of **6A** occurs from the backside to the selenonio group. Consequently, compound **2** is obtained as a main product. Cyclopropane formation by tandem

Michael addition and Favorskii rearrangement has been reported in the reaction of vinyl selenones with active methylene or methylidyne compounds.[7] The reactions of alkenyl selenones with α-monosubstituted β-dicarbonyl compounds proceeded through a similar addition–rearrangement pathway to give 1,2-dicarbonylcyclopropanes,[7b,7c] but α-unsubstituted β-dicarbonyl compounds did not undergo Favorskii rearrangement to afford 1,1-dicarbonylcyclopropanes.[7c,7d] It is very interesting that α-unsubstituted β-dicarbonyl compounds have reacted with alkenylselenonium salt **1** to form 1,2-dicarbonylcyclopropanes, differently from the case of selenones.

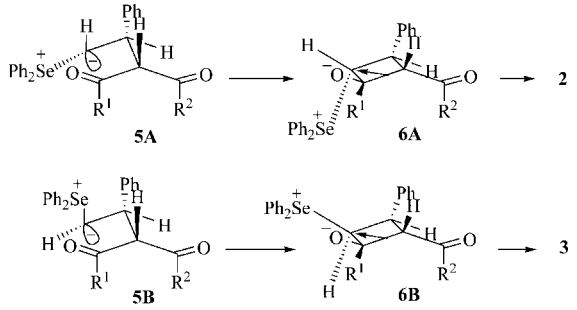
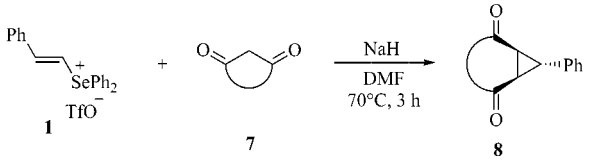


Figure 1. 1,2-Migration from the backside of the selenonio group.

Next, we tried to construct a fused bicyclic ring system through reactions with cyclic β-diketones (Table 3). The reaction of 1,3-indandione with alkenyl selenonium salt **1** was carried out under the same conditions as in Table 2 to afford a 2,3-dihydro[1,4]naphthoquinone derivative **8a**, fused to a cyclopropane ring, in moderate yield through the ring expansion process (Entry 1). On the other hand, the reactions with 1,3-cyclohexanedione derivatives did not give good results, and the condensed-ring compounds, obtained in low yields, each possessed a seven-membered ring (Entries 2 and 3). This would be attributable to the difficulties inherent in transformation to the flexible seven-membered ring. The ^{1}H and ^{13}C NMR spectra of the products indicated that products had highly symmetrical skeletons.

Table 3. Cyclopropane formation from alkenylselenonium salt **1** with cyclic β-diketones.



Entry	7	Products (% yield)
1	**7a**	**8a** (48)
2	**7b**	**8b** (16)
3	**7c**	**8c** (12)

Conclusion

In conclusion, we have found the first example of a tandem Michael–Favorskii-type process in reactions of alkenyl-substituted onium salts with active methylene carbanions bearing at least one ketone group to produce α,β-dicarbonylcyclopropane derivatives. On the other hand, cyclopropanes bearing α,α-bis(oxycarbonyl) groups were obtained in good yields from the reactions with malonates. It is noteworthy that the formation of the cyclopropane skeleton depends on the properties of the functional groups in active methylene compounds. In addition, it is valuable that diphenyl selenide, which was recovered in these reactions, could be reused as one of the starting materials for the preparation of the β-styrylselenonium salt. Further applications of this strategy are currently underway in our laboratory.

Experimental Section

General Procedure for Reactions of Alkenylselenonium Salt 1 with Active Methylene Compounds: In a typical experiment, an active methylene compound (0.20 mmol) was dissolved in anhydrous DMF (3 mL), and sodium hydride (60%, 8 mg, 0.20 mmol) was added to the solution at room temperature. After the mixture had been stirred at the same temperature for 1 h, alkenylselenonium salt **1** (146 mg, 0.30 mmol) was added. The whole was stirred at 70 °C for 3 h, then worked up with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried with $MgSO_4$, filtered, and concentrated. The crude product was separated by preparative TLC (silica gel, hexane/ethyl acetate mixture) to give cyclopropane derivatives **2**–**4** or **8**. For spectroscopic data for all compounds, see Supporting Information.

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