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Stereoselective Synthesis of Ethyl (2*E*,4*E*)-Alkadienoates from Ethyl Sulfolane-2-carboxylate

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α,β,γ,δ-Unsaturated esters were conveniently synthesized from ethyl sulfolane-2-carboxylate through alkylation and oxidation followed by the retro Diels-Alder reaction of the resulting 3-sulfolene derivatives. The reaction proceeded with high *E,E*-selectivity.

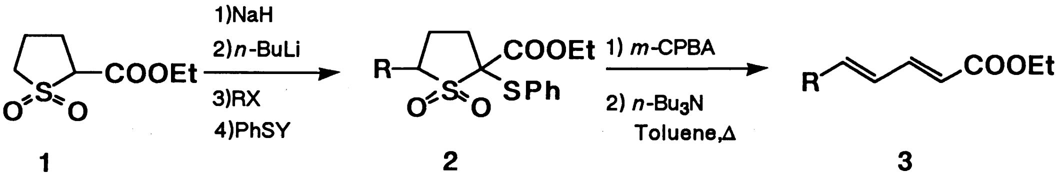
3-Sulfolene, the Diels-Alder adduct of butadiene and sulfur dioxide, has acidic protons at α-position and is converted into butadiene and sulfur dioxide on heating (the retro Diels-Alder reaction). Therefore, 3-sulfolene α-anion is considered to be a butadienyl anion equivalent, and functionalized dienes can be prepared by the reaction of the anion with electrophiles, followed by the retro Diels-Alder reaction. However, this methodology is not practical, because 3-sulfolene α-anion is very labile and easily undergoes ring opening reaction even at −78 °C.[1] Recently, the methods to improve this difficulty have been appeared in literatures, but the decomposition of 3-sulfolene α-anion still occurred to a considerable extent.[2] Furthermore, Bloch *et al.* reported the synthesis of α,β,γ,δ-unsaturated esters and amides with high *E,E*-selectivity by starting with a masked sulfolene, which was the Diels-Alder adduct between 3-sulfolene and cyclopentadiene.[3] This method is, however, limited because 1) multi-step manipulations are required for the synthesis of the starting material and 2) the retro Diels-Alder reaction proceeds under rather drastic conditions.

In this letter, we report a simple method for the synthesis of α,β,γ,δ-unsaturated esters using readily available ethyl sulfolane-2-carboxylate as a starting material.

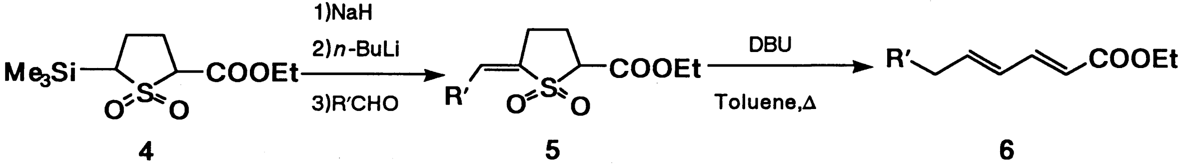
It is known that α-anion of sulfolane derivatives is easily handled without decomposition[4] and that 2-sulfolene derivative can isomerize into the corresponding 3-sulfolene derivative under basic conditions.[5] On the basis of the above facts, we designed two methods for the preparation of 3-sulfolene intermediate *via* 2-sulfolene derivative: A) α-Sulfenylation of ethyl sulfolane-2-carboxylate (**1**), followed by the oxidation to the corresponding sulfoxide and elimination of sulfenic acid, and B) the Peterson reaction of ethyl 5-trimethylsilylsulfolane-2-carboxylate (**4**), followed by a base-induced *exo-endo* isomerization of the resulting double bond.[4] To compare these methods, ethyl

8-phenyl-2,4-octadienoate was synthesized: Method A) Addition of 3-phenylpropyl bromide and benzenesulfenyl chloride to the dianion of 1 afforded sulfide 2 ($R=Ph(CH_2)_3$) in 95% yield. Oxidation to sulfoxide, followed by heating with tributylamine in toluene, gave ethyl 8-phenyl-2,4-octadienoate in 66% yield. Method B) Addition of 3-phenylpropanal to the dianion of 4 yielded olefin 5 ($R'=Ph(CH_2)_2$) in 49% yield. Heating with DBU in toluene gave ethyl 8-phenyl-2,4-octadienoate in 59% yield. In both cases, the resulting octadienoate was mainly *E,E*-isomer.$^{6)}$

[A]



[B]



Since method A gave higher yield, this reaction was investigated in detail. The yield of sulfide 2 was generally improved when the reaction of the dianion of 1 was carried out in tetrahydrofuran by using alkyl bromide/sulfenyl chloride or alkyl iodide/thiosulfonate as alkylating and sulfenylating agents, respectively. Alkyl iodide/sulfenyl chloride caused liberation of iodine and resulted in a lower yield. The oxidation of the resulting sulfide 2 was critical. Among the oxidants examined, such as *m*-chloroperbenzoic acid, hydrogen peroxide, sulfuryl chloride, nitric acid, sodium periodate, potassium periodate with 18-crown-6, and *N*-bromosuccinimide, only *m*-chloroperbenzoic acid and hydrogen peroxide gave the desired sulfoxide, and the others did not react at all. The results are summarized in Table 1.

Typical procedure is as follows: To a suspension of sodium hydride (1.1 mmol) in dry tetrahydrofuran (5 ml) was added $1^{7)}$ (1.0 mmol), and the resulting mixture was refluxed for 5 min and then cooled to 0 °C. Butyllithium (hexane solution, 1.0 mmol) was added to the solution, and the mixture was stirred for 15 min. After cooling the mixture to −20 °C, propyl iodide (1.0 mmol) and *S*-phenyl benzenethiosulfonate (1.1 mmol) (after 20 min) were added, successively. The reaction mixture was allowed to warm up to room temperature and stirred for 2 h. After quenching with saturated aqueous ammonium chloride, the mixture was extracted with ethyl acetate (3 × 5 ml). The extracts were combined and dried

Table 1. Synthesis of Ethyl Alkadienoates from Ethyl Sulfolane-2-carboxylate

Run	RX	PhSY	Oxidant	Yield/%		(*E*,*E*) /%[a]
				2	3	
1	$CH_3(CH_2)_2Br$	PhSCl		61		
2	$CH_3(CH_2)_2I$	PhSCl		49		
3		PhSSPh		11		
4		$PhSSO_2Ph$		89		
5			*m*-CPBA		59	97
6	$(CH_3)_2CHBr$	PhSCl		49		
7	$(CH_3)_2CHI$	$PhSSO_2Ph$		67		
8			H_2O_2		51	
9			*m*-CPBA		66	96
10	$PhCH_2Br$	PhSCl		72		
11		$PhSSO_2Ph$	*m*-CPBA	88	67	94
12	$CH_2=CHCH_2Br$	PhSCl	*m*-CPBA	80	61	96
13		$PhSSO_2Ph$		68		
14	$CH_3(CH_2)_4I$	$PhSSO_2Ph$	*m*-CPBA	83	62	96
15	$Ph(CH_2)_3Br$	PhSCl	*m*-CPBA	95	66	88
16	$THPO(CH_2)_5I$	$PhSSO_2Ph$	*m*-CPBA	87	38	95
17	$TsO(CH_2)_{10}OTs$	$PhSSO_2Ph$	*m*-CPBA	81	20[b]	89[c,d]

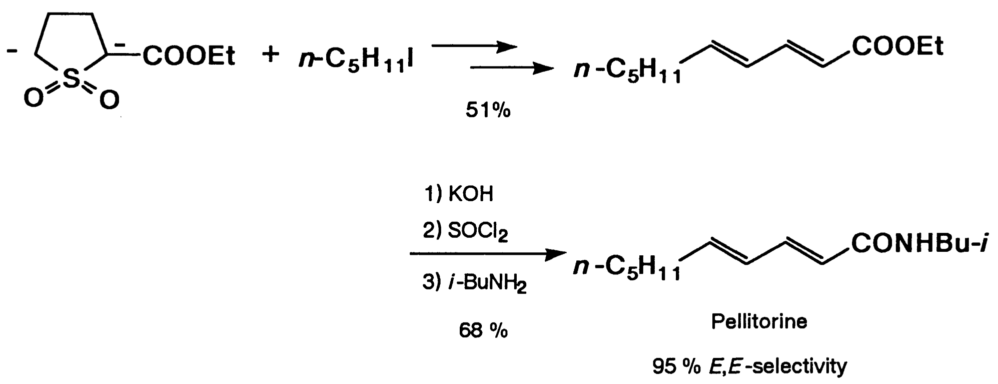
a) Determined by GC. b) Diethyl 2,4,16,18-eicosatetraenedioate.
c) 2*E*,4*E*,16*E*,18*E*-isomer. d) Determined by HPLC.

over sodium sulfate. After removal of the solvent, purification by silica gel column chromatography gave **2** (R=*n*-Pr) in 89% yield. To a solution of **2** (0.8 mmol) in dichloromethane (5 ml) was added *m*-chloroperbenzoic acid (0.9 mmol) in dichloromethane (5 ml) at −78 °C, and the reaction mixture was allowed to warm up to −20 °C then stirred for 2 h. After quenching with 10% aqueous sodium hydrogensulfite, the mixture was extracted with chloroform (2 × 5 ml). The extracts combined were dried over sodium sulfate and concentrated under reduced pressure. To this crude mixture were added tributylamine (0.9 mmol) and toluene (5 ml), and the mixture was heated at reflux temperature for 2 h. Hydrochloric acid (1 $mol \cdot l^{-1}$, 3 ml) was added, and the organic materials were extracted with ethyl acetate (3 × 5 ml). The extracts combined were dried over sodium sulfate and concentrated. Separation by preparative TLC gave **3** (R=*n*-Pr) in 59% yield with 97% *E*,*E*-selectivity.[6]

Generally, the α-anion of 3-sulfolene is so labile that the condensate can not be obtained by the reaction with less reactive secondary alkyl halide.[2b] But, by our method, the reaction product with such halide was also obtained (Table 1, Runs 6 and 7).

The *E,E*-selectivity in the alkadienoate formation may be explained as follows: The base-induced isomerization of ethyl 2-sulfolene-2-carboxylates to ethyl 3-sulfolene-2-carboxylates proceeds under thermodynamic control, and 2,5-*cis*-isomers (presumably di-*quasi*-equatorial conformation) are mainly produced, then these isomers undergo the retro Diels-Alder reaction to give (*E,E*)-alkadienoates according to the orbital symmetry rule.

This reaction could be applied for the simple synthesis of natural products. For example, pellitorine, one of insecticidal compounds,[8] was obtained by simple operations as shown in the following scheme.



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3) R. Bloch and D. Hassan-Gonzales, Tetrahedron, 42, 4975 (1986).

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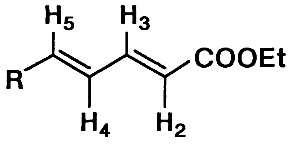
6) The geometry of alkadienoates was confirmed by 400 MHz ^{1}H-NMR spectra on the basis of the coupling constants; $J_{H2\text{-}H3}$ (15.3-15.6 Hz) and $J_{H4\text{-}H5}$ (15.3-15.7 Hz).



7) 1 was obtained by the reaction of sulfolane α-anion (generated from sulfolane and butyllithium) (1.0 equiv.) and ethyl chloroformate (0.5 equiv.) in tetrahydrofuran at −78 °C (89% yield).

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