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NOVEL ASYMMETRIC ALKYLATION OF CYCLIC β-KETO ESTERS WITH OPTICALLY ACTIVE SULFONIUM SALTS

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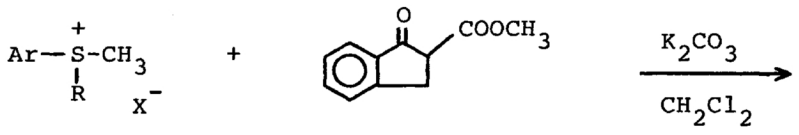
A new asymmetric alkylation of cyclic β-keto esters with optically active sulfonium salts, which are easily prepared by optical resolution methods, has been investigated. Relative reactivities for alkyl substituents are found to be quite different from those for S_N2 alkylation. Stereochemical reaction course via S-O sulfurane intermediate for this new reaction is proposed.

S-Adenosylmethionine is an important biological alkylating agent. In recent years, extensive studies have been published on the alkylation reactions of oxygen nucleophiles such as carboxylate and phenolate ions with various alkylsulfonium salts.[1,2] However, to date there has been no report on the uses of optically active alkylsulfonium salts as a new chiral alkylating agent to carbon nucleophiles (e.g. enolate ions of cyclic β-keto esters). It seems of interest to exploit a new asymmetric alkylation of cyclic β-keto esters with optically active sulfonium salts, which are readily prepared by optical resolution methods. We now report this new asymmetric alkylation and propose the stereochemical reaction course via S-O sulfurane intermediate for the reaction between enolate ions of cyclic β-keto esters and optically active alkylsulfonium ions.

A mixture of racemic sulfonium salt (1) (1 mmol), cyclic β-keto ester (2) (1 mmol), and potassium carbonate (1.3 mmol) was stirred in dichloromethane (10 ml) at room temperature for 2 d. After filtration of insoluble materials, alkylated products of 2 were purified by preparative TLC and medium pressure column chromatography. The results are summarized in Table 1. Table 1 shows that C-alkylation is main reaction in all cases (entries 1-4). The ratios between the yields of C-methylated (3) and C-alkylated products (4) are close to one in entry 1 (3 : 4= 26: 32 ; R= C_2H_5) and entry 2 (3 : 4= 34 : 27 ; R= i-C_3H_7). They are quite different from what are expected for ordinary S_N2 reactions on carbon. For instance, the relative reactivities of phenylmethylalkylsulfonium perchlorates with iodide anion in acetone at 50 °C are CH_3 1.0, C_2H_5 0.20, and i-C_3H_7 0.05, and apparently these reactions involve S_N2 attack on the sulfonium alkyl groups.[3] In entry 3, the reaction is exclusive benzylation of 2 with no accompanying methylation. In entry 4, selective C-methylation of 2 took place in good yield.



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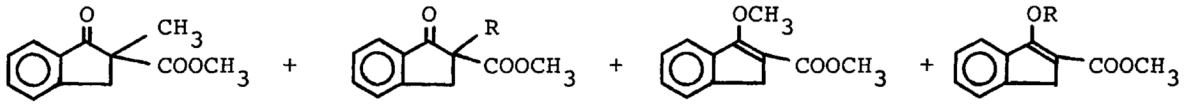


3 4 5 6

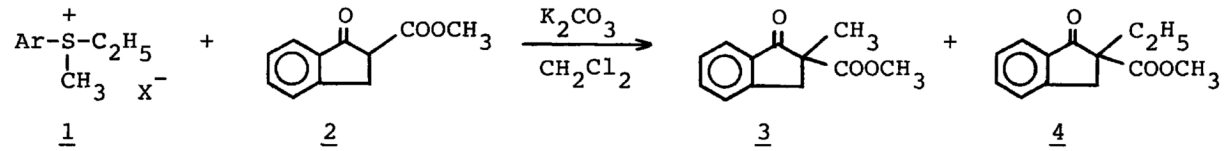
Table 1. Alkylation of 2 with Racemic Sulfonium Salts (1)[a)]

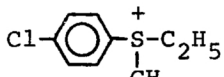
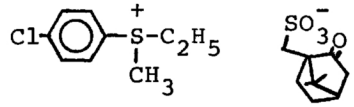
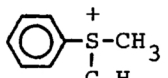
Entry	Salts (1)			Products and Yield/%				
	Ar	R	X^-	C-Alkylation	3	4	5	6
1	C_6H_5	C_2H_5	ClO_4^-	58	26	32	7	14
2	C_6H_5	i-C_3H_7	ClO_4^-	61	34	27	6	33
3	C_6H_5	$C_6H_5CH_2$	ClO_4^-	86	0	86	0	4
4	C_6H_5		BF_4^-	74	74	0	25	0

a) For the reaction procedure, see the text.

Chiral sulfonium salts 1a-c were prepared by optical resolution of racemic sulfonium d-camphorsulfonates. Their absolute configurations were determined by their circular dichroism spectra[4)] and new determination procedure (sulfonium salt (S) → oxosulfonium salt (R) → sulfoxide (R)).[5)] Under the alkylation conditions (1 (1 mmol), 2 (1 mmol), potassium carbonate (1.3 mmol) and dichloromethane (10 ml); at room temperature for 2 d), cyclic β-keto ester (2) was alkylated with arylethylmethylsulfonium salt (R-1a) to give C-methylated product R-(+)-3 (30% chemical yield; 4% ee) and C-ethylated product S-(-)-4 (44% chemical yield; 10% ee) (see Table 2, entry 1). On the other hand, the alkylation of 2 with sulfonium salt (S-1c) afforded S-(-)-3 (26% chemical yield; 2.3% ee) and R-(+)-4 (32% chemical yield; 4.1% ee) (see Table 2, entry 3). It is of great interest that the configurations of C-methylated product (3) and C-ethylated product (4) are opposite. The absolute configuration was estimated in comparison with known copounds[6)] and the enantiomeric excess (ee) was determined by ^1H NMR analysis in the presence of Eu(hfc)$_3$. In a similar manner, asymmetric reaction was conducted using chiral sulfonium salt (R-1b). These results are summarized in Table 2. The stereochemistries of methylated product (3) and ethylated product (4) depend on the stereochemistries of chiral sulfonium salts (1) used as asymmetric alkylating agent. No influences were observed for the absolute configurations of 3 and 4 in entries 1 and 2 when the counter anion was changed to d-camphorsulfonate (entry 2) from perchlorate (entry 1).

Table 2. Asymmetric Alkylation of 2 with Optically Active Sulfonium Salts(1)



Entry	Sulfonium salts (1) (confn)	$[\alpha]_D$/deg.	Isolated yield/%	$[\alpha]_D$/deg.[a] (c, $CHCl_3$)	ee/%[b] (confn)	CD spectra[c] [θ] (λ_{320nm})
1	 ClO_4^-		3 30.0	+1.45 (0.92)	4 (R)[d]	+61
			4 43.9	-7.11 (1.26)	10 (S)[d]	-154
	(R)-1a	-28.4 (c 1.2, CH_2Cl_2)				
2			3 25.9	+2.59 (0.94)	7.1 (R)[d]	+108
			4 33.3	-8.17 (1.17)	11 (S)[d]	-246
	(R)-1b	+7.52 (c 1.1, CH_3OH)				
3	 ClO_4^-		3 25.7	-0.83 (0.65)	2.3 (S)[d]	-34
			4 31.6	+3.03 (0.81)	4.1 (R)[d]	+64
	(S)-1c	+20.3 (c 1.85, acetone)				

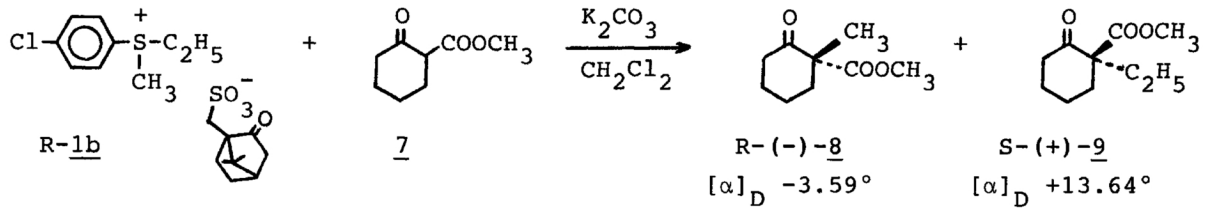
a) Optical rotations were taken in chloroform at 32 °C (entry 1) and 26 °C (entries 2 and 3).

b) These values for entry 2 were determined by the LIS-NMR technique ($Eu(hfc)_3$) and for entries 1 and 3, the values (ee of 3 and 4) were calculated in comparison with the optical rotations of entry 2.

c) CD spectra were taken in chloroform (entry 2) and methanol (entries 1 and 3).

d) Absolute configuration was estimated by correlating 3 and 4 with (-)-(2S)-2-methoxycarbonyl-2-(3-oxobutyl)indanone; Ref. 6.

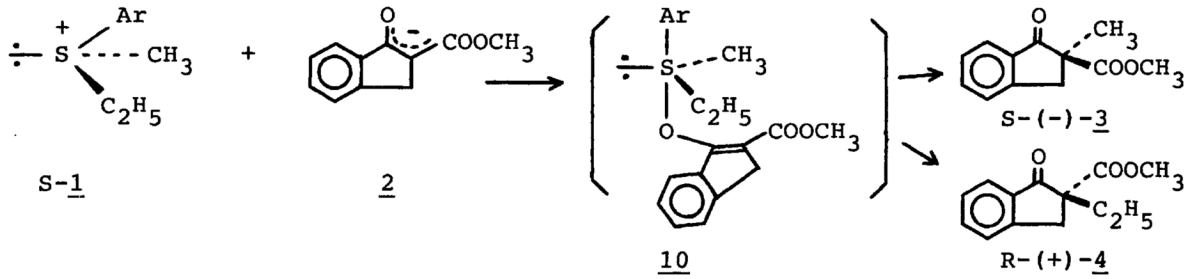
Asymmetric alkylation of cyclic β-keto ester 7 with sulfonium salt (R-1b) gave C-methylated product R-(-)-8 (21.3% chemical yield; 3.3% ee)[7] and C-ethylated product S-(+)-9 (12.1% chemical yield; 16.3% ee).[8] The configurations of 8 and 9 are found to be opposite.



R-(-)-8 $[\alpha]_D$ -3.59° (c 0.65, C_2H_5OH) (3.3% ee)

S-(+)-9 $[\alpha]_D$ +13.64° (c 0.41, C_2H_5OH) (16.3% ee)

To explain the phenomenon why the stereochemistries of 3 and 4 (or 8 and 9) are opposite, we propose the stereochemical reaction course via S-O sulfurane intermediate (10) for this new asymmetric alkylation of β-keto ester 2 with chiral sulfonium salt 1. First, enolate ion of cyclic β-keto ester 2 attacks on the cationic sulfur atom of S-1 to form S-O sulfurane intermediate (10). In the transition state, methyl group may exist in the bottom face (re face) of enolate π-face (S-O-C=C) of 10 and C-methylation may take place preferentially from the bottom face (re face) to give S-(-)-3. And C-ethylation takes place preferentially from the top face (si face) of 10 to yield R-(+)-4.



Continuing studies are in progress in our laboratory.

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References

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2) Recently, alkylation of enolate ion of 2-methoxycarbonylcyclopentanone with racemic alkylsulfonium salts was reported (NaH/THF-reflux conditions); B. J. McBride, M. E. Garst, and M. Hopkins, J. Org. Chem., 49, 1924 (1984).
3) H. Matsuyama, H. Minato, and M. Kobayashi, Bull. Chem. Soc. Jpn., 48, 3287 (1975).
4) Andersen et al. established that (+)-ethylmethyl-p-tolylsulfonium tetrafluoroborate had the absolute configuration of (S); K. K. Andersen, R. L. Caret, and D. L. Ladd, J. Org. Chem., 41, 3096 (1976).
5) M. Kobayashi, K. Kamiyama, H. Minato, Y. Oishi, Y. Takada, and Y. Hattori, J. Chem. Soc., Chem. Commun., 1971, 1577; The absolute configuration of sulfonium salt 1c (S-(+), $[\alpha]_D$ +20.3° (acetone))was determined by oxidation with peracids under basic conditions with retention. Then the oxosulfonium perchlorate (R-(+), $[\alpha]_D$ +14.5° (acetone)) was demethylated by reaction with sodium iodide in acetone to give R-(+)-ethyl phenyl sulfoxide (R-(+), $[\alpha]_D$ +185.6° (acetone)). Since the configuration at sulfur remained unchanged during this S_N2 process, the configuration of 1c was established. Similarly, the configuration of sulfonium salt 1a (R-(-), $[\alpha]_D$ -28.4° (CH_2Cl_2)) was determined.
6) H. Hermann and H. Wynberg, J. Org. Chem., 44, 2238 (1979).
7) The asymmetric synthesis of R-(-)-8 ($[\alpha]_D$ -108° (C_2H_5OH); ≥99% ee) was reported by Tomioka et al.; K. Tomioka, K. Ando, Y. Takemasa, and K. Koga, J. Am. Chem. Soc., 106, 2718 (1984).
8) CD spectra were taken in ethanol; R-(-)-8 (CD (C_2H_5OH) $[\theta]_{293}$ -91.9); S-(+)-9 (CD (C_2H_5OH) $[\theta]_{293}$ +560); The value (ee) was determined by use of chiral shift reagent, tris[3-(heptafluoropropyl)(hydroxymethylene)-d-camphorato]-europium (III) ($Eu(hfc)_3$).

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