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Studies on the Stereochemistry in the Alkylation of Enolate Ion of Cyclic β-Keto Ester with Sulfonium Salts Containing Optically Active Alkyl Groups

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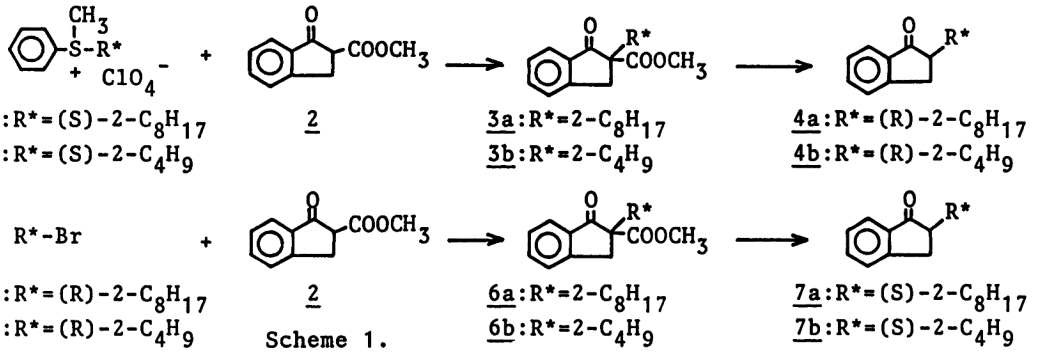
Alkylation of cyclic β-keto ester with racemic sulfonium salts containing optically active alkyl groups such as (S)-2-octyl and (S)-2-butyl was found to afford C-alkylated products with inversion of configuration at asymmetric alkyl carbon atom. Stereochemical reaction course via formation of S-O sulfurane intermediate and successive stereoselective intramolecular alkyl migration to enolate is described.

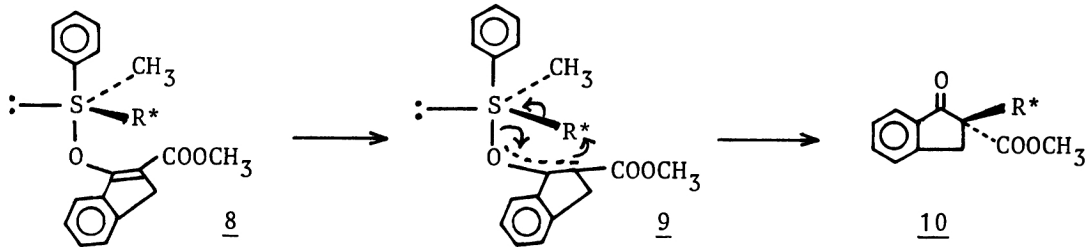
Much attention has been focused on the enantioselective reactions in organic synthesis.[1] We have recently described asymmetric alkylation of enolate anion with optically active sulfonium salts as a new alkylating reagent and proposed stereochemical reaction course via S-O sulfurane intermediate for this new reaction. In that study,[2] question whether the steric configuration of the entering alkyl group was retained or inversed, was left unanswered. We will describe the result of the investigation on the reaction between enolate ion of cyclic β-keto ester 2 and racemic sulfonium ions containing optically active alkyl groups such as (S)-2-octyl (1a) and (S)-2-butyl (1b) in this paper. Phenylmethyl-(S)-2-octylsulfonium perchlorate (1a) ($[\alpha]_D$ -4.52° (c 2.71, EtOH)) was prepared by methylation (CH_3I, $AgClO_4$, CH_3CN) of phenyl (S)-2-octyl sulfide ($[\alpha]_D$ +1.72° (c 4.97, $CHCl_3$)) which was obtained from (R)-2-octyl bromide (5a) ($[\alpha]_D$ -34.12° (c 8.74, EtOH)) and sodium benzenethiolate in ethanol. Under the alkylation conditions (1a (3.4 mmol), 2 (3.9 mmol), potassium carbonate (5.9 mmol), and dichloromethane (15 ml); at room temperature for 2 days), 2-methoxycarbonyl-1-indanone 2 was alkylated with sulfonium salt 1a to give C-octylated product 3a (8.3% yield) as a mixture of diastereoisomers together with O-octylated (50.7%), C-methylated (35.7%), and O-methylated product (5.3%). 3a was transformed into 2-octyl-1-indanone 4a ($[\alpha]_D$ -20.35° (c 1.6, $CHCl_3$)) by demethoxycarbonylation (LiI, DMF-H_2O (9 : 1); reflux for 3 days) to remove asymmetry induced at quarternary carbon atom of 3a. Authentic 2-octyl-1-indanone 7a ($[\alpha]_D$ +20.68° (c 2.08, $CHCl_3$)) was obtained by alkylation (K_2CO_3, 18-crown-6, MeOH; reflux for 2 days) of 2 with (R)-2-octyl bromide (5a) ($[\alpha]_D$ -34.12° (c 8.74, EtOH)) and successive demethoxycarbonylation of diastereoisomers 6a as shown in Scheme 1. Since the configuration at 2-octyl carbon atom should be inversed during this S_N2 alkylation process from 5a to 6a, the configuration at 2-octyl carbon atom of 7a was established as (S). Based on the optical rotation and configuration of

7a, the configuration at 2-octyl carbon atom of 4a could be determined as (R). In a similar manner, 2 was also alkylated with phenylmethyl-(S)-2-butylsulfonium perchlorate (1b) ($[\alpha]_D$ +3.29° (c 4.18, MeOH)) to afford 4b ($[\alpha]_D$ -15.78° (c 0.98, $CHCl_3$)) by demethoxycarbonylation of 3b (8.8% yield) which was obtained together with O-butylated (41.4%), C-methylated (41.8%), and O-methylated product (8%) of 2. The configuration at 2-butyl carbon atom of 4b was also determined as (R) in comparison with authentic (S)-7b ($[\alpha]_D$ +9.18° (c 0.92, $CHCl_3$)) which was prepared by alkylation of 2 with (R)-2-butyl bromide 5b ($[\alpha]_D$ -22.9° (c 4.91, EtOH)) and successive demethoxycarbonylation of 6b.



Scheme 1.

These results show that the optically active 2-alkyl groups of sulfonium salts (1a and 1b) were transferred to enolate ion of β-keto ester 2 with inversion of configuration at asymmetric carbon atom. However, it seems to be difficult to explain these alkylation reactions of β-keto ester 2 with sulfonium salts (1a and 1b) by simple S_N2 mechanism, because of the following reasons: (i) C-ethylated product was preferentially obtained to C-methylated product when 2 was reacted with ethylmethylphenylsulfonium salt; (ii) the configurations of C-methylated product ((S)-(-)) and C-ethylated product ((R)-(+)) are opposite when 2 was alkylated with (S)-ethylmethylphenylsulfonium salt; (iii) the solvent effects on C- vs. O-alkylation for 2 with sulfonium salts are quite different from those for S_N2 alkylation with alkyl halides. To explain the above all results, we propose the following stereochemical reaction course. Firstly, enolate ion of cyclic β-keto ester 2 attacks the cationic sulfur atom of 1a (or 1b) to form S-O sulfurane intermediate 8. Secondly, enolate π-face (S-O-C=C) attacks the alkyl group in the equatorial position of 8 from the rear side via quasi five-membered transition state 9 in an intramolecular fashion to permit C-alkylation product 10 with inversion of configuration at asymmetric carbon atom.



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References 1) K. Fuji, Yuki Gosei Kagaku Kyokai Shi, 44, 623 (1986).
2) M. Kobayashi, K. Umemura, N. Watanabe, and H. Matsuyama, Chem. Lett., 1985,1067.

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