CHEMISTRY LETTERS, pp. 1541-1544, 1988.

Diastereofacial Control in the Reaction of (R)-α-(*p*-Tolylsulfinyl)acetophenones with Several Organometallics

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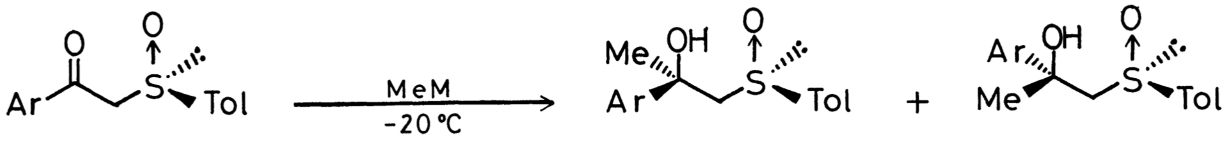
The diastereofacial controlled addition of organometallics to optically active β-ketosulfoxide was achieved to furnish both diastereomers of β-hydroxy sulfoxide depending on the selection of organometallic reagents. Trichloromethyltitanium added to (R)-α-(*p*-tolylsulfinyl)acetophenones to give (RsRc)-β-hydroxy sulfoxides, while (RsSc)-β-hydroxy sulfoxides were obtained by utilizing trimethylaluminum. The utility of the present reaction was demonstrated in the synthesis of both enantiomers of sydowic acid.

Optically active sulfoxide is one of the most useful compounds in asymmetric synthesis.1) Among the various reactions of chiral sulfoxides, β-ketosulfoxide is known to reduced by diisobutylaluminum hydride (DIBAL) to give β-hydroxy sulfoxide with very high diastereomeric excess, while in the presence of zinc chloride DIBAL reduction gave an opposite diastereomer of β-hydroxy sulfoxide stereoselectively.2) Diastereoselective alkylation of β-ketosulfoxide, however, is very difficult because β-ketosulfoxide has much acidic methylen protons and enolization is expected to occur in prior to alkylation when basic organometallic reagents are used. Only in the case of Grignard reagent3) and alkynyl aluminum reagent,1d) addition reaction to β-ketosulfoxide was reported to proceed. But stereoselective synthesis of both diastereomers of β-hydroxy sulfoxides by the alkylation reaction using organometallics has still remained open. On the other hand, we recently reported the diastereofacial control reaction of the alkylation to chiral α-ketoenamine and α-aminoketone containing (S)-2-(methoxymethyl)pyrrolidin-1-yl group as a chiral auxiliary with several organometallics utilizing the difference of coordination ability of the metal used.4) We wish to disclose here diastereoface differentiation reaction of β-ketosulfoxide with several organometallics.



1

RsRc - 2

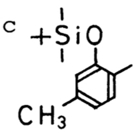
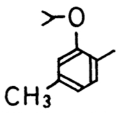
RsSc - 2

When (R)-α-(*p*-tolylsulfinyl)acetophenone (**1a**) was treated with methyllithium, the expected methylated product could not be obtained in any solvent systems owing to the enolization.[1d] Although methylmagnesium bromide did not give the addition product in THF, employing toluene or ether as a solvent at 0 °C afforded 1-(*p*-tolylsulfinyl)-2-phenyl-2-propanol (**2a**) in 36% or 34% yield with the diastereomeric ratio for (RsRc)-**2a** : (RsSc)-**2a** of 24 : 76 or 29 : 71, respectively.[3,5]

Organocerium reagent is often used in the alkylation of enolizable carbonyl compounds.[6] When methylating reagent prepared from methylmagnesium bromide and cerium trichloride in toluene was used at 0 °C for 2 h, (S)-tertiary alcohol (RsSc)-**2a** was obtained in good selectivity (Entry 3). Performing trimethylaluminum as a methylating reagent to sulfoxide **1a** in toluene gave (RsSc)-**2a** in a ratio of 26 : 74 (Entry 2). By the addition of zinc salt in the reaction of β-ketosulfoxide and aluminum reagents, the nucleophilic reaction is known to proceed in chelation-control.[1d,2] But in the reaction of **1a** with trimethylaluminum in DME, presence of zinc bromide failed in giving no addition product. In sharp contrast, methyltrichlorotitanium, which is also known to be the chelation-control reagent,[7] was used in the methylation reaction of sulfoxide **1a** in ether, reversal of selectivity was observed to afford (R)-β-hydroxy sulfoxide (RsRc)-**2a** selectively (Entry 1).

Instead of phenyl group in sulfoxide **1a**, several aryl groups such as *p*-tolyl, (2-*t*-butyldimethylsilyloxy-4-methyl)phenyl and (2-isopropoxy-4-methyl)phenyl groups were introduced to the β-ketosulfoxide and methylations with titanium reagent and aluminum reagent were performed, and the resulting yields and diastereoselectivities of the reactions were listed in Table 1. In all cases, reverse

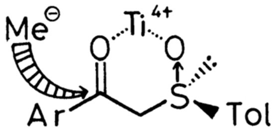
Table 1. Reaction of β-Ketosulfoxide **1** with Organometallic Reagents

Entry	Ar	MeM	Solvent	Time/h	Yield/%	RsRc : RsSc
1	a Ph	$MeTiCl_3$	Et_2O	13.5	79	82 : 18[a]
2		Me_3Al	toluene	26	66	26 : 74[a]
3		$MeMgBr-CeCl_3$	toluene	23	30	16 : 84[a]
4	b *p*-Tol	$MeTiCl_3$	Et_2O	22	60	80 : 20[a]
5		Me_3Al	toluene	49	50	16 : 84[a]
6	c 	$MeTiCl_3$	Et_2O	24	96	97 : 3[b]
7		Me_3Al	toluene	13.5	71	13 : 87[b]
8		$MeMgBr-CeCl_3$	toluene	24	36	34 : 66[b]
9	d 	$MeTiCl_3$	Et_2O	13	77	94 : 6[b]
10		Me_3Al	toluene	24	48	4 : 96[b]

a) Determined by ^1H NMR. b)Determined by HPLC (Finepak SIL).

diastereoselection between trichloromethyltitanium and trimethylaluminum was occurred. Especially, aryl ketones which were substituted by alkoxyl group at ortho position reacted in higher selective manner.

The different stereochemistry of methylation can be elucidated in terms of different conformations of the β-ketosulfoxide according to the nature of the alkylating reagents.[2] In the presence of titanium chloride, the β-ketosulfoxide adopts the chelated conformation 3 and subsequent nucleophilic addition is occurred from the less hindered lone pair side (*si* face) of the sulfoxide, while trimethylaluminum attacks from *re* face in the conformation 4 caused by dipolar interaction.



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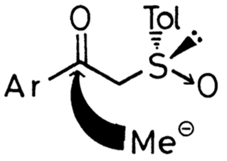

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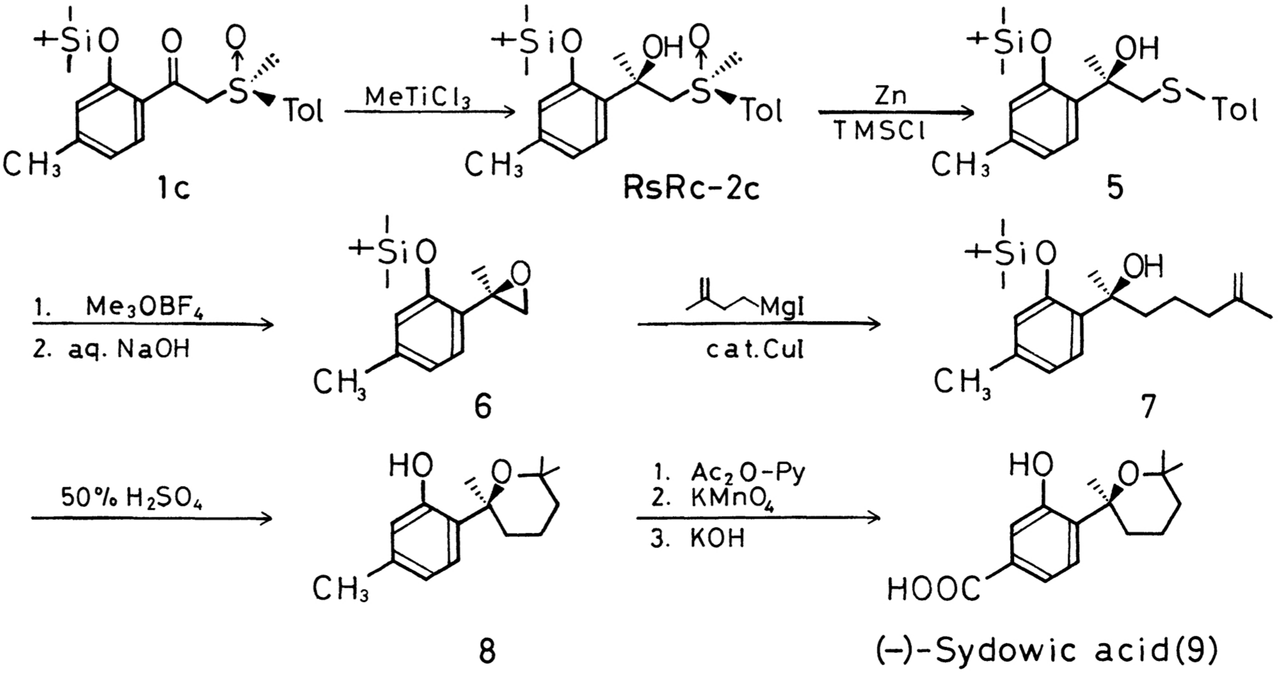
Sydowic acid 9, known as an antioxidant,[8] was isolated from *Aspergillus Sydowi*.[9] Racemic sydowic acid was already synthesized,[10] but synthesis in optically active form has not been accomplished so far. Now both enantiomers of sydowic acid were synthesized by the application of the present method. Diastereomeric pure methylated sulfoxide RsRc-2c ($[\alpha]_D^{23}$ +74.1° (c 0.98, MeOH)) was easily furnished after purification of the products by TLC on silica gel, which were obtained from (R)-(2-*t*-butyldimethylsilyloxy-4-methyl)phenyl (*p*-tolylsulfinyl)methyl ketone (1c) and trichloromethyltitanium. Next, sulfoxide RsRc-2c was reduced to sulfide 5 by the use of zinc and trimethylsilyl chloride[11] in 67% yield. The sulfide 5 was treated with trimethyloxonium fluoroborate followed by hydrolysis with aqueous sodium



hydroxide[12] to give epoxide **6** in 37% yield. Then homometallyl Grignard reagent was added to epoxide **6** in the presence of catalytic amount of copper(I) iodide to afford alcohol **7** in 52% yield. Ring closure of alcohol **7** to tetrahydropyran **8** was proceeded by the treatment with 50% sulfuric acid in 73% yield. Acetylation of hydroxy group of **8**, and oxidation of the acetate with potassium permanganate followed by hydrolysis of the crude acetate furnished (-)-sydowic acid **9** in 50% yield; $[\alpha]_D^{23}$ -6.1° (c 0.32, $CHCl_3$)(lit.[9a] $[\alpha]_D^{21}$ -6.4° (c 1.1, $CHCl_3$)). Similarly methylated β-hydroxy sulfoxide RsSc-**2c** ($[\alpha]_D^{23}$ +53.8° (c 0.93, MeOH)) obtained from **1c** and trimethylaluminum was purified by TLC, and (+)-sydowic acid ($[\alpha]_D^{23}$ +6.2° (c 0.36, $CHCl_3$)) was synthesized from RsSc-**2c** by the same route.

In conclusion, the diastereofacial control in the alkylation of β-ketosulfoxide was achieved depending on the selection of the organometallics used to give different diastereomers of β-hydroxy sulfoxide.

The present work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture.

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(Received June 30, 1988)