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REACTION OF β-KETOSULFOXIDES WITH ALKYL GRIGNARD REAGENTS IN TETRAHYDROFURAN

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The reaction of (+)-(R)-α(p-tolylsulfinyl)acetophenone(**1**) with alkyl Grignard reagents in tetrahydrofuran is described. When **1** was treated with 2 equiv of ethylmagnesium iodide in tetrahydrofuran at 0°C, (-)-ethyl p-tolyl sulfoxide and α(ethylsulfinyl)acetophenone were obtained.

During the course of studies on asymmetric induction by chiral sulfinyl group, recently, we reported that (+)-(R)-α(p-tolylsulfinyl)acetophenone(**1**), $[\alpha]_D$ +264° (acetone), reacted with 2 equiv of an alkyl Grignard reagent in ethyl ether to yield a diastereomeric mixture of β-hydroxy sulfoxides R_SR_C- and R_SS_C-**2** (see Scheme 1).1) However, we have now found that a similar treatment of **1** with 2 equiv of an alkyl Grignard reagent in tetrahydrofuran(THF) affords not the β-hydroxy sulfoxide(**2**) but quite different products.

Namely, when **1** was treated with 2 equiv of ethylmagnesium iodide in THF2) at 0°C followed by hydrolysis, (-)-ethyl p-tolyl sulfoxide and α(ethylsulfinyl) acetophenone3) were produced. Similarly, when **1** was treated with 2 equiv of methylmagnesium iodide(prepared in ethyl ether) in THF, levorotatory methyl p-tolyl sulfoxide, $[\alpha]_D$ -143°(acetone), was obtained.4) Since the specific rotation of optically pure (+)-(R)-methyl p-tolyl sulfoxide is reported to be $[\alpha]_D$ +145.5°(acetone),5) the optically purity of the product should be 98%.

Moreover, we have found that treatment of **1** with benzylmagnesium chloride in THF causes a reduction of sulfoxide moiety to yield α(p-tolylsulfenyl)acetophenone.6)

These results are summarized in Table 1.

Table 1. Typical reactions of **1** with alkyl Grignard reagents in THF at 0°C

Grignard reagents (Mol. equiv)	Reaction time (Hour)	Products (Yield %)	Recovered **1** (%)
CH_3MgI[a] (2)	2	(-)-p-$CH_3C_6H_4S(O)CH_3$ (12)	88
CH_3MgI[a] (4)	2	(-)-p-$CH_3C_6H_4S(O)CH_3$ (17)	83
CH_3CH_2MgI[a] (4)	2	(-)-p-$CH_3C_6H_4S(O)CH_2CH_3$ (46)	38
CH_3CH_2MgBr[b] (2)	2	(-)-p-$CH_3C_6H_4S(O)CH_2CH_3$ (20) $CH_3CH_2S(O)CH_2COC_6H_5$ (38)	23
$C_6H_5CH_2MgCl$[a] (2)	2	p-$CH_3C_6H_4SCH_2COC_6H_5$ (50) (-)-p-$CH_3C_6H_4S(O)CH_2C_6H_5$ (15)	35
$C_6H_5CH_2MgCl$[b] (2)	2	p-$CH_3C_6H_4SCH_2COC_6H_5$ (65)	25

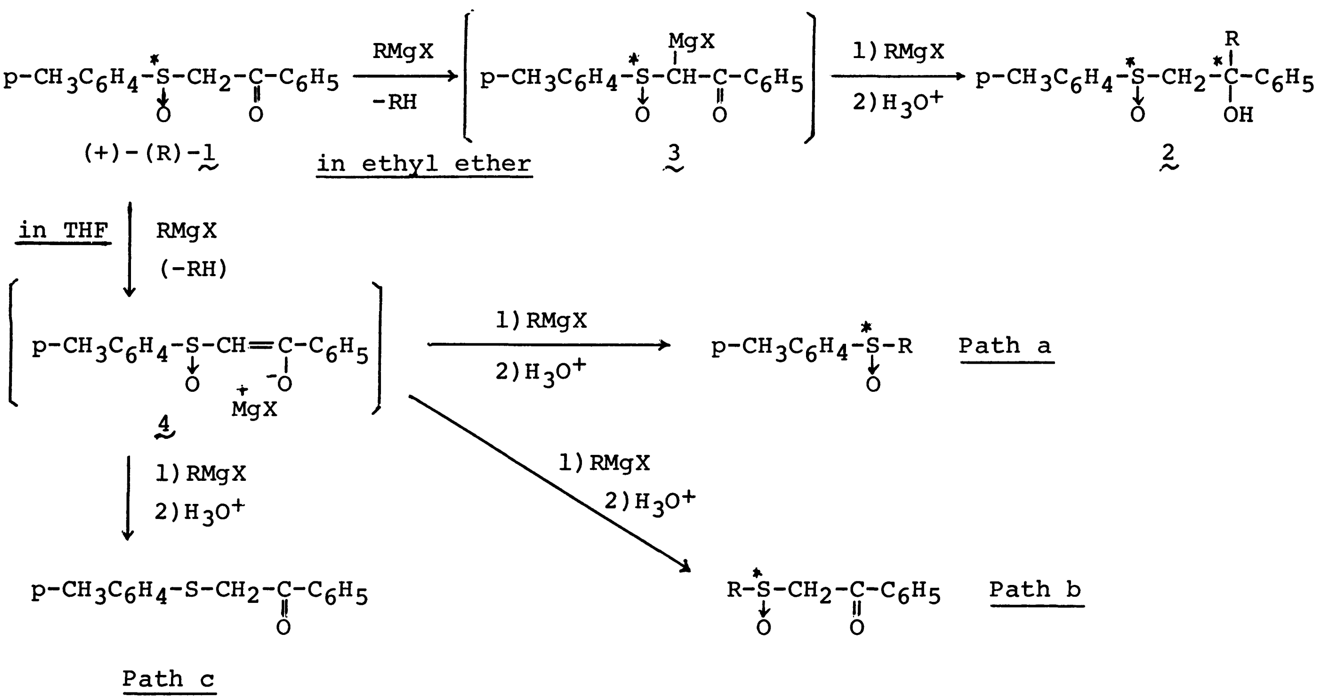
a) Prepared in ethyl ether.

b) Prepared in THF.

In view of these results, the formation of the products in THF, except α(p-tolylsulfenyl)acetophenone, can be attributed to the preferential attack of the Grignard reagent to the sulfur atom of **1** to cause a nucleophilic displacement with complete inversion of configuration at sulfur atom. The difference in the reaction products owing to the change of the solvent may be explained by considering the change of the character of the incipient intermediate.[2] We wish to propose from the evidences described above that the reaction intermediate in ethyl ether would be an ordinary Grignard reagent[7] such as **3** in which the C-Mg bond exhibits a covalent bond character rather than ionic, whereas the intermediate[2] in THF would be a conjugate anion such as **4** in which the negative charge is highly delocalized onto the oxygen atom of the carbonyl group. Therefore, in THF, the formation of the conjugate anion(**4**) militates against the addition of Grignard reagents toward the carbonyl carbon of **1**.

The following reaction scheme(Scheme 1) may be constructed for the reaction. The paths a, b, and c are considered to take place competitively.

Scheme 1.



References and Note

1) N. Kunieda, J. Nokami, and M. Kinoshita, Chem. Lett., 1974, 369.

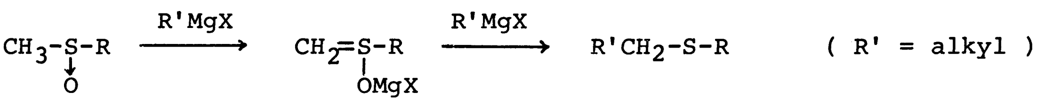
2) Treatment of 1 with 1 equiv of an alkyl Grignard reagent afforded an incipient reaction intermediate. When the intermediate was treated with H_2O-HCl, a quantitative recovery of 1 was obtained.

3) The absolute configuration of this compound has not been determined.

4) Johnson et al.8) and Durst et al.10) have found that treatment of optically active alkyl aryl sulfoxides with alkyllithium reagents yields the corresponding dialkyl sulfoxides in good optical yields.

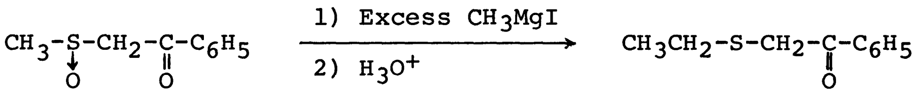
5) K. Mislow, M.M. Green, P. Laur, J.T. Melillo, T. Simmons, and A.L. Ternay, Jr., J. Am. Chem. Soc., 87, 1958 (1965).

6) Reduction of methyl substituted sulfoxides to sulfides with an alkyl Grignard reagent is known as shown below.9)



$$CH_3-\underset{\overset{\downarrow}{O}}{S}-R \xrightarrow{R'MgX} CH_2{=}\underset{\overset{|}{OMgX}}{S}-R \xrightarrow{R'MgX} R'CH_2-S-R \qquad (\ R' = \text{alkyl}\ )$$

A similar product was obtained by the reaction of α(methylsulfinyl) acetophenone(5) with methylmagnesium iodide in THF.



$$\mathrm{CH_3-\underset{\substack{\downarrow\\ O}}{S}-CH_2-\underset{\substack{\|\\ O}}{C}-C_6H_5} \xrightarrow[\text{2) } \mathrm{H_3O^+}]{\text{1) Excess } \mathrm{CH_3MgI}} \mathrm{CH_3CH_2-S-CH_2-\underset{\substack{\|\\ O}}{C}-C_6H_5}$$

5

7) N. Kunieda, J. Nokami, and M. Kinoshita, Tetrahedron Lett., 1974, 3997.

8) J.P. Lockard, C.W. Schroeck, and C.R. Johnson, Synthesis, 1973, 485.

9) R. Oda and K. Yamamoto. J. Org. Chem., 26, 4679 (1961); P. Manya, A. Sekera, and P. Rumpf, Tetrahedron, 26, 467 (1970).

10) T. Durst, M.J. LeBelle, R. Van den Elzen, and K.-C. Tin, Can. J. Chem., 52, 761 (1974).

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