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STEREOSELECTIVE REACTIONS OF (+)-(R)-α(p-TOLYLSULFINYL)ACETOPHENONE WITH ALKYL GRIGNARD REAGENTS IN ETHYL ETHER

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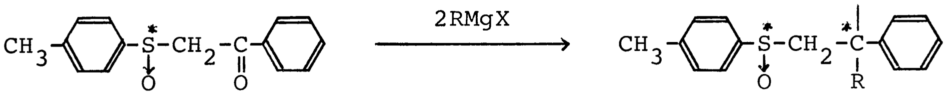
(+)-(R)-α(p-Tolylsulfinyl)acetophenone (I) reacts with alkyl Grignard reagents in ethyl ether to give the corresponding diastereomeric alcohols (II). The ratio of R_SS_C-II and R_SR_C-II obtained was about 7 : 3. The 1,3-asymmetric induction in this reaction is discussed.

Cram et al.[1)] proposed the 1,3-asymmetric induction in addition reactions of organometallics toward ketones having a chiral center at β-carbon position to the carbonyl group. During the course of the studies on the stereochemistry of chiral sulfinyl compounds,[2)] we have now found that the reaction of β-ketosulfoxides bearing the chiral sulfur atom with alkyl Grignard reagents also displays the feature of the same type of stereoselective reaction. Namely, when (+)-(R)-α-(p-tolylsulfinyl)acetophenone (I)[3)] was treated with an alkyl Grignard reagent in ethyl ether at 0°C, a mixture of the corresponding diastereomeric alcohols R_SS_C-II and R_SR_C-II was obtained in the ratio of about 7 : 3.[5)] This reaction required 2 equiv. of the Grignard reagent.[6)]



(+)-(R)-I

II
(Mixture of R_SR_C and R_SS_C)

IIa; $R=CH_3-$, IIb; $R=C_2H_5-$, IIc; $R=n-C_3H_7-$, IId; $R=C_6H_5CH_2-$

In a typical reaction, a stirred solution of (+)-(R)-I (0.50 mmol) in 20 ml of dry ethyl ether was cooled to 0°C and treated with an ethereal solution of ethylmagnesium bromide (1.25 mmol) under a nitrogen atmosphere. After completion of the addition, the mixture was stirred for 1 hr at 0°C, followed by hydrolysis.

The ethereal layer was concentrated to an oil. Thin-layer chromatography on silica gel using 1 : 1 ether - n-hexane as eluent afforded pure product, which was characterized as IIb on the basis of elemental analysis, NMR and IR evidences. The ratio of the diastereoisomers in IIb can readily be evaluated from the NMR spectra of the methylene protons by integration of the respective signals, since the difference in chemical shift between the diastereotropic methylene groups is large enough. The per cent ratio of the two isomers was 71 : 29. Though we have not isolated either of the pure diastereoisomer, desulfurization of IIb with Raney Nickel afforded levorotatory 2-phenyl-2-butanol (III) $[\alpha]_D$ -6.0°(acetone). Since the reported specific rotation of optically pure (S)-III is $[\alpha]_D$-17.7°(neat),[7] the absolute configuration of the major isomer in IIb should be R_SS_C.

Moreover, the same treatment was applied to the reactions of (+)-(R)-I with some other alkyl Grignard reagents yielding analogous results in the yield and the diastereomeric ratio of the corresponding carbinols. The results are summarized in Table 1. In all the cases, one finds that the predominant diastereoisomer produced

Table 1. Reaction of (+)-(R)-I with RMgX (in ethyl ether, at 0°C, 1 hr.)

RMgX	II obtained (Yield %)		Ratio of diastereoisomer(%) R_SS_C : R_SR_C
CH_3MgI	IIa	(90)	70 : 30
CH_3CH_2MgBr	IIb	(91)	72 : 28
CH_3CH_2MgI	IIb′	(91)	71 : 29
$CH_3CH_2CH_2MgI$	IIc	(76)	74 : 26
$C_6H_5CH_2MgCl$	IId	(88)	72 : 28

IIa; $[\alpha]_D^{26}$ +97.8°(c;0.09,acetone), Anal. Calcd. for $C_{16}H_{18}O_2S$: C, 70.04; H, 6.61%, Found: C, 70.62; H, 6.64%, NMR(100 MHz,$CDCl_3$): R_SS_C; δ 1.98(s,3H,CH_3-), 2.39(s,3H,$\underline{CH}_3C_6H_4$-), 3.08(q,2H,-CH_2-), R_SR_C; δ 1.62(s,3H,CH_3-), 2.39(s,3H,$\underline{CH}_3C_6H_4$-), 3.21(q,2H,-CH_2-)

IIb; $[\alpha]_D^{26}$ +110.9°(c;0.340,acetone), Anal. Calcd for $C_{17}H_{20}O_2S$: C, 70.80; H, 6.99%, Found: C, 70.82; H, 7.03%, NMR(100 MHz,$CDCl_3$): R_SS_C; δ 0.82(t,3H,$\underline{CH}_3CH_2$-), 2.30(q,2H,$CH_3\underline{CH}_2$-), 2.35(q,3H,CH_3-), 3.15(q, 2H,-CH_2-), R_SR_C: δ 0.78(t,3H,$\underline{CH}_3CH_2$-), 1.86(q,2H,$CH_3\underline{CH}_2$-), 2.35(s, 3H,CH_3-), 3.21(q,2H,-CH_2-)

IIc; $[\alpha]_D^{25}$ +115.8°(c;0.640,acetone), Anal. Calcd. for $C_{18}H_{22}O_2S$: C, 71.49; H, 7.33%, Found: C, 71.52; H, 7.38%, NMR(100 MHz,$CDCl_3$): R_SS_C; δ 0.87(t,3H,$\underline{CH}_3CH_2CH_2$-), 1.45(t,2H,$CH_3\underline{CH}_2CH_2$-), 2.23(t,2H,$CH_3CH_2\underline{CH}_2$-), 2.36(s,3H,CH_3-), 3.14(s,2H,-CH_2-), R_SR_C; δ 0.86(t,3H,$\underline{CH}_3CH_2CH_2$-), 1.08(m,2H,$CH_3\underline{CH}_2CH_2$-), 1.78(t,2H,$CH_3CH_2\underline{CH}_2$-), 2.36(s,3H,CH_3-), 3.24 (q,2H,-CH_2-)

IId; $[\alpha]_D^{28}$ +122.6°(c;0.310,acetone), Anal. Calcd. for $C_{22}H_{22}O_2S$: C, 75.39; H, 6.33%, Found: C, 75.50; H, 6.38%, NMR(100 MHz,$CDCl_3$): R_SS_C; δ 2.36(s,3H,CH_3-), 3.26(s,2H,$C_6H_5\underline{CH}_2$-), 3.46(q,2H,-CH_2-), R_SR_C; δ 2.36(s,3H,CH_3-), 3.10(s,2H,$C_6H_5\underline{CH}_2$-), 3.23(s,2H,-CH_2-)

is R_SS_C-II, while the diastereomeric ratio is almost uninfluenced by changes in the alkyl moiety and the halogen species of Grignard reagents.

A model prediction which was devised by Cram et al.1) appears most reasonable in this case as well. And the stereochemical course in this 1,3-asymmetric induction attributed to the chirality of the β-sulfinyl group may be rationalized by supporting a rigid six-membered cyclic transition.8) The sulfoxide is considered to be basic and the oxygen atom of sulfoxides is known to have the donor abilities toward the acceptors such as iodine and phenol.9) Therefore, this cyclic transition is much plausible. Meanwhile, the open-chain and polar models1) do not correlate the stereochemical results.

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3) (+)-(R)-I (new compound) was obtained in 90% yield by the reaction of ethyl benzoate with p-tolylsulfinylcarbanion (V)4) prepared from (+)-(R)-methyl p-tolyl sulfoxide, mp 74°C, $[\alpha]_D^{20}$ +147°(acetone), and n-butyl lithium and diethylamine. (+)-(R)-I; $[\alpha]_D^{26}$ +264.2°(acetone), mp 74°C, Anal. Calcd. for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46%, Found: C, 69.61; H, 5.46%, NMR(60 MHz,$CDCl_3$): δ 2.41(s,3H, CH_3-), 4.43(q,2H,-CH_2-)

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5) Under the extreme condition, such as at a higher temperature and using an excess of Grignard reagent, a side reaction occurred with the formations of the corresponding (-)-(S)-alkyl p-tolyl sulfoxide and racemic α-alkyl-α-methylbenzyl alcohol, while II obtained was inert toward the Grignard reagent under these reaction conditions; our unpublished results.

6) When (+)-(R)-I was treated with 1 equiv. of the Grignard reagents at 0°C, a white precipitate appeared and (+)-(R)-I was recovered quantitatively from the reaction mixture by hydrolysis. Furthermore, when the hydrolysis was carried out with D_2O-D_2SO_4, the methylene hydrogens of recovered (+)-(R)-I were found to be deuterated (degree of deuteration; 45-50%).

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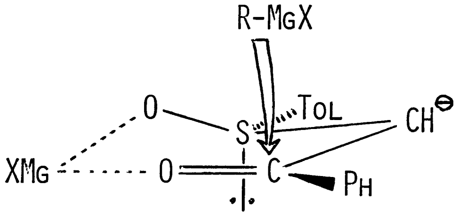

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