Tetrahedron Letters No. 45, pp 4605 - 4608, 1972. Pergamon Press. Printed in Great Britain.

ASYMMETRIC SYNTHESIS USING α-SULFINYLCARBANIONS. I.
SYNTHESIS OF OPTICALLY ACTIVE ALCOHOLS

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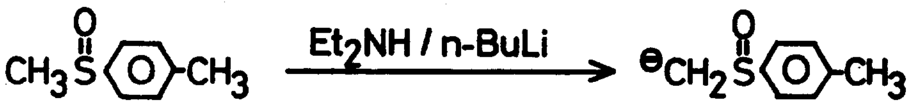
(Received in Japan 20 September 1972; received in UK for publication 3 October 1972)

We have found that *p*-tolylsulfinylcarbanion(2) is quantitatively generated from methyl *p*-tolyl sulfoxide(1) by the action of lithium diethylamide[1)] and reacts with aldehydes, ketones, or oxiranes to produce a diastereomeric mixture of β- or γ-hydroxysulfoxides.[2)] Utilizing these reactions we have carried out the asymmetric synthesis of alcohols using the optically active sulfoxide.[3)] By this method, 1-phenylethanol, 1-hydroxy-1-methyl-1,2,3,4-tetrahydronaphthalene, and *trans*-2-methylcyclohexanol have been obtained in high optical purity.



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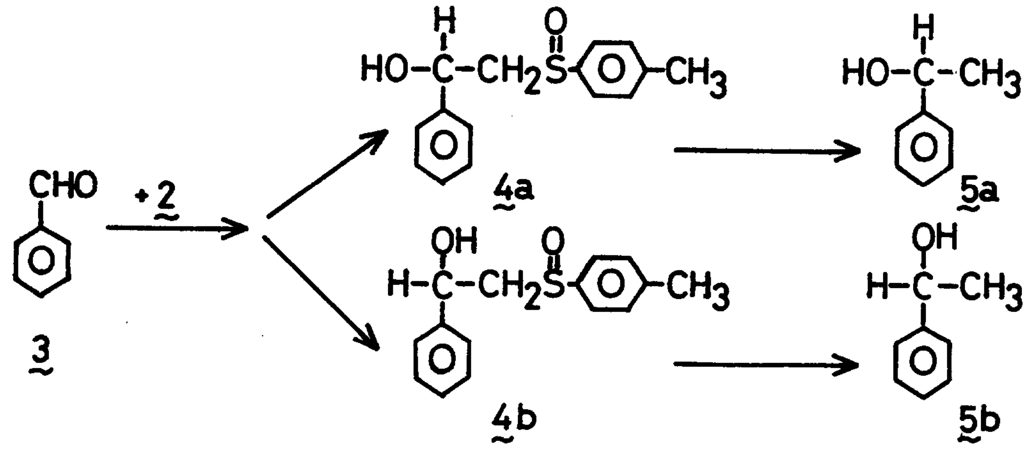
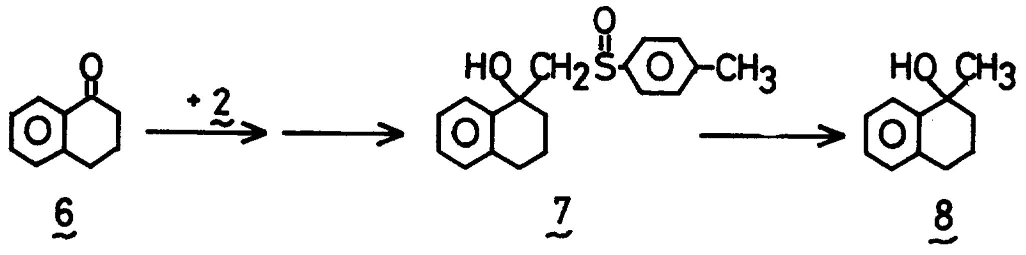
Addition of benzaldehyde(3) to a solution of *p*-tolylsulfinylcarbanion(2) prepared from optically active (R)-methyl *p*-tolyl sulfoxide(1), $[\alpha]_D$ +188.3° (c 1, $CHCl_3$),[4)] by the action of lithium diethylamide in tetrahydrofuran at ice-salt temperature produced a (1:1) diastereomeric mixture of 2-hydroxy-2-phenylethyl *p*-tolyl sulfoxides(4a and 4b) in 84% yield. Separation of the diastereomers was effected by silica gel chromatography and fractional crystallizations from methanol-water to afford (R_c, R_s)-isomer(4a), mp 141-142°C, $[\alpha]_D$ +91.7°, in 17% yield, and (S_c, R_s)-isomer(4b), mp 94-95°C, $[\alpha]_D$ +202.8°, in 15.5% yield. Reductive desulfurization of 4a and 4b with Raney-nickel followed by chromatography gave (S)-(-)-1-phenylethanol(5a), $[\alpha]_D$ -42.6°(c 0.27, ether), and (R)-(+)-1-phenylethanol(5b), $[\alpha]_D$ +42.1°(c 0.14, ether), in approximately 60% yields, respectively. Since the specific rotation of optically pure 1-phenylethanol is reported to be $[\alpha]_D$ 43.5°(neat),$^{5)}$ the alcohols of high optical purity have been obtained by this method.

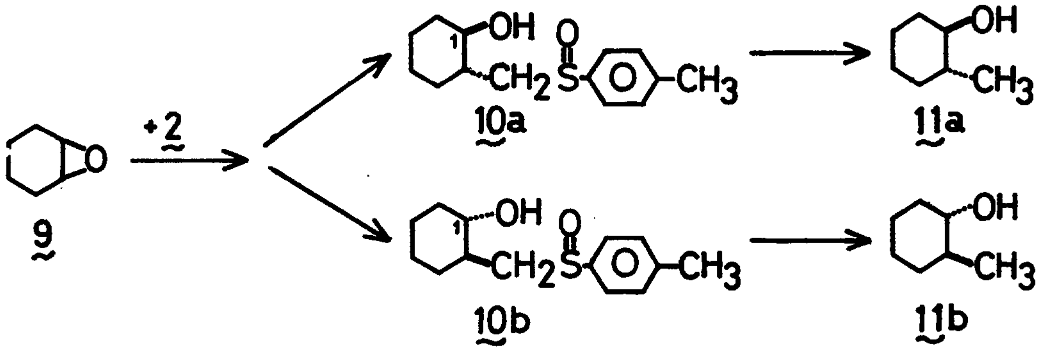


Reaction of p-tolylsulfinylcarbanion from the corresponding sulfoxide ($[\alpha]_D$ +189.1°) with α-tetralone(6) produced a (1.8 : 1) diastereomeric mixture of 1-hydroxy-1-(p-tolylsulfinylmethyl)-1,2,3,4-tetrahydronaphthalenes(7) quantitatively. A major isomer, mp 112-113°C, $[\alpha]_D$ +77.6°, was easily isolated in 45.5% yield by chromatography. Desulfurization with Raney-nickel gave



(-)-1-hydroxy-1-methyl-1,2,3,4-tetrahydronaphthalene(8), mp 68.5-69.0°C, $[\alpha]_D$ -31.0°(c 0.5, hexane), in 68% yield. To our best knowledge, the optically active form of this *tertiary* alcohol(8) has not been known. Accordingly we cannot know the optical purity of our product(8). However, as this method using the anion(2) generally gives the product of the high optical purity (see below), 8 is expected to be obtained also in high optical purity. Consequently this reaction furnishes a general method for the synthesis from ketones of optically active *tertiary* methylcarbinols which are hardly obtained by the conventional way of resolution using phthalic or succinic half-ester.

Reaction of *p*-tolylsulfinylcarbanion($[\alpha]_D$ +185.7°) with 1,2-epoxycyclohexane(9) in dimethoxyethane at reflux temperature gave a (1.5-2 : 1) mixture of 2-(*p*-tolylsulfinylmethyl)cyclohexanol(10a and 10b) in 63.5% yield.[6]



Chromatography followed by fractional crystallizations from methanol-water furnished (R_c, R_c, R_s)-isomer(10a), mp 141-141.5°C, $[\alpha]_D$ +118.2°, in 13.5% yield, and (S_c, S_c, R_s)-isomer(10b), mp 122-124°C, $[\alpha]_D$ +225.3°, in 13% yield. In the NMR spectra of both 10a and 10b, *H*-C_1 was observed as axial. This fact indicates that the epoxide ring is opened in *trans* manner to give *trans*-substituted 10a and 10b when the anion(2) attacks 9. Desulfurization with Raney-nickel gave (R, R)-(-)-*trans*-2-methylcyclohexanol(11a),[7] $[\alpha]_D$ -39.5°(c 0.43, methanol), in 62% yield,[8] and (S, S)-(+)-*trans*-2-methylcyclohexanol(11b),[7] $[\alpha]_D$ +40.7°(c 0.46, methanol), in 77% yield,[8] respectively. As the specific rotation of optically pure *trans*-2-methylcyclohexanol is reported to be $[\alpha]_D$ 42.9°(c 1, methanol),[9] the alcohols(11) of high optical purity have been obtained.

Thus, the optically active *p*-tolylsulfinylcarbanion which is easily prepared from the corresponding sulfoxide by the action of lithium diethylamide is a versatile reagent for the synthesis of optically active methyl-substituted alcohols. Application of this method to the synthesis of the natural products will be an interesting subject.

Studies on the other α-sulfinylcarbanions and their reactions to the other substrates such as nitriles, esters, and imines are in progress.

Acknowledgement: The partial support of this work by the Kawakami Memorial Foundation is gratefully acknowledged.

REFERENCES and REMARKS

1. Lithium diethylamide was prepared in situ in tetrahydrofuran from diethylamine and n-butyllithium.
2. n-Butyllithium is commonly employed to generate α-sulfinylcarbanions. However, when it was used for the generation of p-tolylsulfinylcarbanion from methyl p-tolyl sulfoxide and the present reactions were carried out, the formation of by-products took place inevitably. For example, in the reaction with benzaldehyde, 2-hydroxy-2-phenylethyl butyl sulfoxides were obtained in ~16% yield.
3. Asymmetric synthesis of oxiranes using optically active sulfoxides was reported recently. a) C.R. Johnson and C.W. Schroeck, J. Amer. Chem. Soc., 93, 5303(1971). b) T. Durst, R. Viau, R. Van Den Elzen, and C.H. Nguyen, Chem. Commun., 1334(1971).
4. $[\alpha]_D$ +189.1°(c 1.11, $CHCl_3$) was the highest rotation of the optically active sulfoxide(1) which we obtained according to the method of Andersen. see K.K. Andersen, Tetrahedron Lett., 93(1962).
5. R. MacLeod, F.J. Welch, and H.S. Mosher, J. Amer. Chem. Soc., 82, 876(1960).
6. In only one experiment. Preliminary reaction using the optically inactive sulfoxide gave the product in 77% yield.
7. C. Beard, C. Djerassi, T. Elliot, and R.C.C. Tao, J. Amer. Chem. Soc., 84, 874(1962).
8. The yields were based on gas-chromatographic analysis using 20% nitrile silicone.
9. R. Backstrom and B. Sjoberg, Ark. Kemi, 26, 549(1966).