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THE PRACTICAL PROCEDURE FOR A PREPARATION OF 1-CHLOROALKYL p-TOLYL SULFOXIDES IN HIGH OPTICALLY ACTIVE FORM: A VERY SHORT SYNTHESIS OF OPTICALLY ACTIVE DISPARLURE[1]

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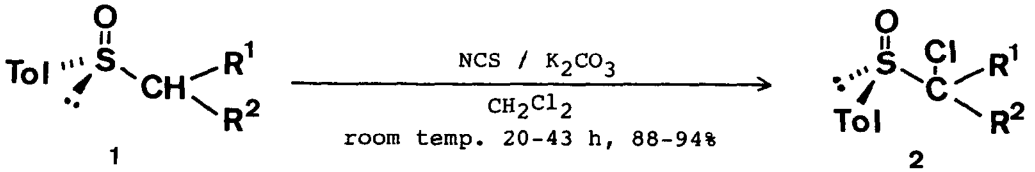
<u>Summary</u> A chlorination of optically active alkyl p-tolyl sulfoxides with N-chlorosuccinimide in dichloromethane in the presence of potassium carbonate afforded optically active 1-chloroalkyl p-tolyl sulfoxides in 87-94% ee (88-94% chemical yields). The optically active chloroalkyl sulfoxide was applied to a synthesis of optically active (+)-disparlure.

One of the most important problem in modern synthetic organic chemistry is asymmetric synthesis. Recently, the synthesis of optically active compounds by the use of optically active sulfur compounds as a chiral auxiliary has received much attention.[2] On the other hand, since the pioneering work of Durst,[3] Reutrakul,[4] ours,[5] and others,[6] it is recognized that 1-chloroalkyl aryl sulfoxides are quite useful compounds in synthetic organic chemistry. The asymmetric synthesis using optically active 1-chloroalkyl aryl sulfoxides could be thought to be quite promising; however, none of the report has been appeared so far. One of the primary reason must be lack of the reliable practical procedure for preparing 1-chloroalkyl aryl sulfoxides having high optical purity.

In this paper, we report the practical, less expensive procedure for a preparation of 1-chloroalkyl p-tolyl sulfoxides in high optically active form (Scheme 1) and an application of the procedure to the very short synthesis of optically active (+)-disparlure.



a $R^1=R^2=H$ c $R^1=H$, $R^2=CH_2Ph$
b $R^1=H$, $R^2=CH_3$ d $R^1=R^2=CH_3$

87-94% ee
(on sulfur chiral center)

Scheme 1.

Direct chlorination of alkyl aryl sulfoxides has been reported by using N-chlorosuccinimide (NCS),[7] iodobenzene dichloride,[8] sulfuryl chloride,[9] or other chlorinating agents.[10] Chlorination of the optically active alkyl aryl sulfoxides for obtaining optically active 1-chloroalkyl aryl sulfoxides, however, has been report to be quite difficult owing to racemization. Two methods were reported to be effective for preparation of optically active 1-chloroalkyl aryl sulfoxides. One was the chlorination of optically active alkyl aryl sulfoxides with $PhICl_2$-$AgNO_3$[8d] and the other was with NCS on silica gel.[11] These reactions themselves are quite interesting; however, optical yields were rather low and quite expensive in the former method. We studied the chlorination of optically active alkyl p-tolyl sulfoxides with wide variety of reagents and found that NCS-K_2CO_3 was the reagent of choice for the chlorination.

Optically pure alkyl p-tolyl sulfoxides (1) were easily synthesized according to the procedure reported by Solladie[2a] with slight modification.[12] (+)-Methyl p-tolyl sulfoxide (1a) was treated with 2 equivalents of NCS in CH_2Cl_2 in the presence of K_2CO_3 at room temperature for 40 h to give chloromethyl p-tolyl sulfoxide (2a) as a colorless solid.[13] This showed quite high value of specific rotation ($[\alpha]_D^{25}$ -207.9°; c 1.0, acetone) compared to that from formerly reported methods.[8c,11] Several recrystallization of the crystals from AcOEt-hexane gave colorless plates having highest value of specific rotation ($[\alpha]_D^{25}$ -239.0°; c 1.0, acetone; mp 88.5-89 °C),[14] which was much higher than that reported (+213.9°).[8c]

Parallel to this reaction, optically pure (+)-1b, (+)-1c, and (+)-1d were subjected to the same conditions to afford the results shown in Table 1.[14,15]

Table 1.

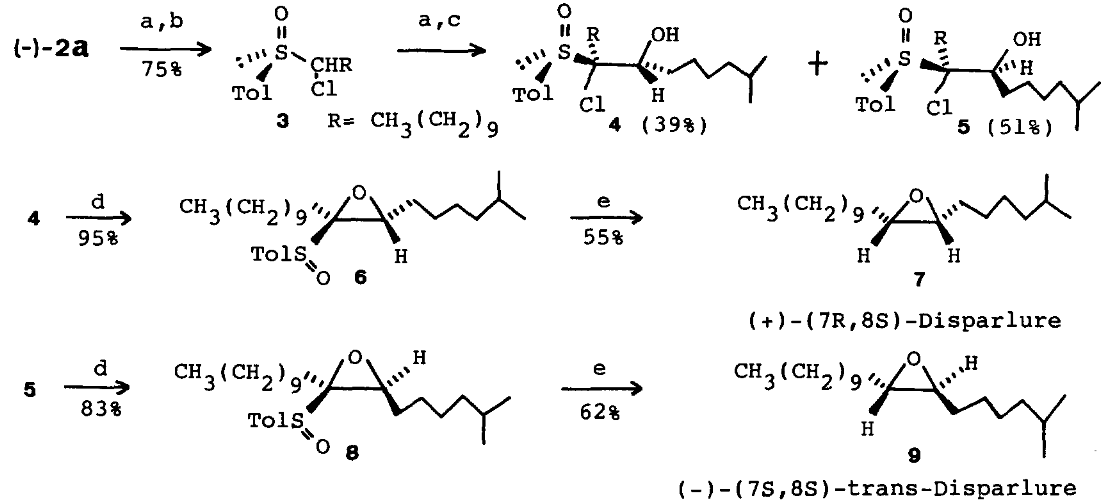
Chlorination of optically pure alkyl p-tolyl sulfoxides (1) with NCS-K_2CO_3

	1		Reaction Time (h)	Chemical Yield (%)	2	% ee b)	Highest $[\alpha]_D$
	R^1	R^2			$[\alpha]_D$ a)		
1a	H	H	40	91	-207.9°	87 c) 89 d)	-239.0°
1b	H	CH_3	20	94	-154.1°	93 d)	--- e)
1c	H	CH_2Ph	43	88	-85.1°	87 d)	--- f)
1d	CH_3	CH_3	40	92	-115.2°	94 C)	-122.6°

a) All specific rotations were measured in acetone at 25 °C b) Enantiomeric excess with respect to the sulfur chiral center. c) Calculated based on the highest value of specific rotation obtained in this study. d) Calculated from NMR (the adduct with acetone in the presence of $Eu(hfc)_3$). e) 3:1 Diastereomeric mixture. f) 6.6:1 Diastereomeric mixture.

To demonstrate the usefulness of the optically active 1-chloroalkyl p-tolyl sulfoxides in asymmetric synthesis, we planned to use optically pure (-)-2a to a synthesis of optically active compounds whose absolute stereochemistry was known. (+)-Disparlure,[16] the sex attractant of female gypsy moth, was the compound of choice.

Durst[3] and also we have already observed that the alkylation of a diastereomeric mixture of 1-chloroalkyl phenyl sulfoxide with symmetric ketone (such as acetone, cyclohexanone) with LDA as a base at below -40 °C gave single isomer of chlorohydrin. This result means that the stereochemistry of this reaction was completely controlled by the chirality of the sulfur.



a: LDA, THF, -50 °C b: 1-Iododecane c: 6-Methyl-1-heptanal d: t-BuOK, t-BuOH e: n-BuLi, THF, -100 °C.

Scheme 2.

Alkylation of optically pure (-)-2a with 1-iododecane with LDA as a base gave diastereomeric mixture of 3 in 75% yield. The mixture of 3 was again treated with LDA at -50 °C then 6-methyl-1-heptanal was added to afford the chlorohydrins (4 and 5) in 90% yield, which were quite easily separated by silica gel column chromatography. Only two products were observed; this fact means that the stereochemistry of the carbon bearing the sulfoxide group was controled by the chirality of the sulfur (1,2-asymmetric induction). Both chlorohydrins were treated with t-BuOK in t-BuOH at room temperature to afford the α,β-epoxy sulfoxides (6; $[\alpha]_D^{25}$ -1.6°, C 0.4, CCl_4; and 8; $[\alpha]_D^{25}$ -8.8°, C 0.4, CCl_4) in good yields. The α,β-epoxy sulfoxide (6) was treated with one equivalent of n-BuLi at -100 °C[17] to give 55% yield of (+)-(7R,8S)-disparlure (7),[18] which showed $[\alpha]_D^{25}$ +0.87°, C 1.2, CCl_4 (lit.[16a] $[\alpha]_D^{25}$+0.6±0.4°; lit.[16b] $[\alpha]_D^{23}$ +0.8±0.2°). The similar treatment of 8 with n-BuLi gave (-)-(7S,8S)-trans-disparlure (9)[18] in 62% yield ($[\alpha]_D^{25}$ -28.7°, C 0.3, CCl_4; lit.[16a] $[\alpha]_D^{25}$ -26.6±0.8°).

In conclusion, these results contribute to a chemistry of optically active sulfoxides and also to new type of asymmetric synthesis by using optically active sulfoxides as a chiral auxiliary.

Acknowledgement We are grateful to Professor Kenji Mori, The University of Tokyo, for providing us copies of the NMR and IR spectra of (+)-disparlure and (±)-trans-disparlure.

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12. 2.5 equivalents of Grignard reagent and toluene as the solvent were used at -50 °C. We are grateful to Dr. Hiroshi Kosugi of Chemical Research Institute of Non-aqueous Solution, Tohoku University for his kind suggestion of this procedure and general discussion in these chemistry.
13. A suspension of (+)-1a (1.54 g; 10 mmol), K_2CO_3 (800 mg) and NCS (2.67 g; 20 mmol) in 10 ml of dry CH_2Cl_2 was stirred at room temperature for 40 h. The reaction mixture was diluted with ether and washed successively with 4% NaI followed by 10% $Na_2S_2O_3$ to destroy the excess NCS. The product was purified by silica gel column chromatography to afford 1.71 g (91%) of 2a as a colorless solid, which was recrystallized once from AcOEt-hexane to give 1.36 g (72%) of colorless plates ($[\alpha]_D^{25}$ -233.7°; 98% ee).
14. We claim that optically pure 2a and 2d have $[\alpha]_D^{25}$ -239.0° and $[\alpha]_D^{25}$ -122.6°, respectively.
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18. Gas chromatographically pure products, whose IR and NMR spectra were identical with those of Professor K. Mori.

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