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A CHIRAL AMINATION REAGENT AND AN EFFICIENT SYNTHESIS OF (S)-METHYL p-TOLYL SULPHOXIDE

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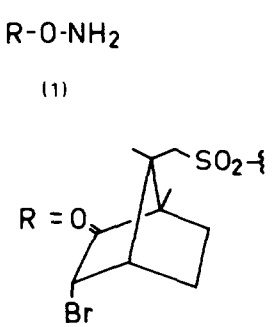
Summary (+)-O-(α-Bromocamphor-π-sulphonyl)-hydroxylamine, (1), a chiral amination reagent, converts prochiral sulphides into diastereomeric aminosulphonium α-bromocamphor-π-sulphonates. This reaction forms the basis of a convenient synthesis of enantiomerically homogeneous (S)-methyl-p-tolyl sulphoxide, a key compound in sulphur stereochemistry.

Synthesis of enantiomerically homogeneous sulphoxides is a task often beset with considerable difficulties. It occurred to us that resolution of diastereomeric aminosulphonium salts, produced from prochiral sulphides by chiral amination, followed by conversion of the salts into individual sulphoxide enantiomers, might be a useful adjunct to existing methods. Hence, we synthesized[1] (+)-(α-bromocamphor-π-sulphonyl)-hydroxylamine (1), a chiral amination reagent modelled after Tamura's reagent, O-mesitylenesulphonylhydroxylamine, widely adopted for the amination of various nucleophiles including sulphides and sulphoxides.[2] The reagent (1) proved quite stable and was characterized as the oxime (2),[3] formed upon reaction with acetone, and identical with a specimen produced by treating acetoneoxime with

(+)-α-bromocamphor-π-sulphonyl chloride.

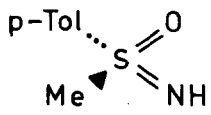


(3): A = Me; B = p-Tolyl

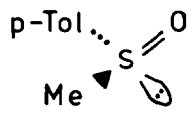
(4): A = p-Tolyl; B = Me

Optically active methyl p-tolyl sulphoxide is a key compound in stereochemical correlations within the series of tri- and tetra-coordinate sulphur compounds,[4] but also serves as a starting material for the synthesis of otherwise difficultly available alkyl methyl sulphoxide enantiomers.[5] Hence, we treated methyl p-tolyl sulphide with an equimolar amount of the reagent (1) in ether. A quantitative yield of a mixture of the two amino methyl p-tolyl sulphonium α-bromocamphor-π-sulphonates, (3) and (4), separated instantaneously. In order to assess the extent of asymmetric induction in the reaction, the sulphimides were set free from the non-fractionated salt mixture and subjected to tosylation.[6] The rotation $[\alpha]_D^{25} = +10.2^o$ (Me_2CO), compared with that of the enantiomerically homogeneous (R)-N-p-toluenesulphonyl methyl p-tolyl sulphimide, $[\alpha]_D^{25} = +267^o$ (Me_2CO),[7] reveals an excess of the (R)-enantiomer of only a few per cent. Even when the asymmetric induction thus is low the reaction is preparatively useful, because the less soluble salt (3) becomes homogeneous after only three recrystallizations from water.[8] Alternative utilization of the enantiomeric amination reagent, similarly prepared from commercially available ammonium (-)-α-bromocamphor-π-sulphonate, renders the salt (4) equally available.

Acid hydrolysis of the salt (3) to methyl p-tolyl sulphoxide proceeded readily, but was accompanied by extensive racemization, whereas alkali caused rapid decomposition of the free sulphimides formed on deprotonation. Hence, recourse was taken to oxidation of (3) to the sulphoximide (5),[9] followed by quantitative deimination[11] of the latter to (S)-methyl p-tolyl sulph-



(5)



(6)

oxide (6), both reactions known to proceed with retention. The sulphoxide (6) obtained had m. p. 74.5-75.5°C and $[\alpha]_D^{25} = -145.3^\circ$ (c 0.8, Me_2CO), matching the values, m. p. 74.5 - 75.5°C, $[\alpha]_D^{25} = +145.3^\circ$ (c 0.795, Me_2CO) for the supposedly enantiomerically homogeneous (R)-enantiomer.[10] We believe that the here described method provides the easiest access to enantiomerically homogeneous p-tolyl methyl sulphoxides.

Unfortunately, the method is not generally applicable. Quantitative yields were obtained of salts of type (3) and (4) from (1) and butyl methyl sulphide, methyl phenyl sulphide, phenyl p-tolyl sulphide, and o-methoxyphenyl phenyl sulphide, but efficient separation by fractional recrystallization proved unsuccessful in all the cases.

Acknowledgement

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References and Notes

1. The sulphonyl chloride (46 mM), produced from commercial (+)-ammonium α-bromocamphor-π-sulphonate was added to a cooled and stirred solution of ethyl N-hydroxyiminoacetate (46 mM) and TEA (46 mM) in DMF (15 ml) to give ethyl N-(α-bromocamphor-π-sulphonyloxy)-acetimidate (88%), m. p. 130-131°C, $[\alpha]_D^{25} = +57.2^\circ$ (c 1, $CHCl_3$); one stereoisomer according to ^1H NMR. The protected hydroxylamine ester (10 mM)

was kept in 80 % H_2SO_4 (40 ml) at 0°C for 4 h. The solution was then poured into ice-water (150 ml), stirred for 30 sec, and extracted with ether (4 x 50 ml). The dried ether solution was used as such; the contents of (1) were determined iodometrically.

2. Y. Tamura, J. Minamikawa and M. Ikeda, Synthesis, 1977, 1.

3. Produced from ethyl (α-bromocamphor-π-sulphonyloxy)-acetimidate[1] (2.5 ml) and acetone (2 ml), dissolved in dioxane (0.5 ml) at 0°C, by adding 80 % H_2SO_4 (0.25 ml) in the course of 10 min. The oxime (85 %) was isolated by dilution with water and ether extraction. It was recrystallized from EtOAc:hexane, m.p. 81°C, $[\alpha]_D^{25} = +90.3^\circ$ (c 1, $CHCl_3$). A specimen, alternatively produced from (+)-α-bromocamphor-π-sulphonyl chloride and acetoneoxime in benzene, containing TEA, possessed identical physical data.

4. For a review, see D. J. Cram and J. M. Cram, Fortschr. Chem. Forsch., 1972, 31, 1.

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

6. The salt mixture (1 mM) was suspended in water (10 ml) at 0°C. 1 N NaOH (1.2 ml) was added and the mixture was quickly extracted with $CHCl_3$ (3 x 10 ml). The extract was dried, concentrated to 3 ml, and subjected to tosylation by adding pyridine and p-toluene sulphonyl chloride. The product was non-fractionally purified by flash chromatography (EtOAc). Yield 42 %.

7. B. W. Christensen and A. Kjær, J. Chem. Soc., Chem. Commun., 1975, 784.

8. After three recrystallizations from water, a 40 % yield of the pure salt (3) was obtained, m.p. 203-204°C, $[\alpha]_D^{25} = +57.4^\circ$ (c 1, H_2O).

9. A solution of the sulphimide in dichloromethane, produced from (3) by alkali addition at 0°C and rapid extraction, was oxidized with $KMnO_4$ at 20°C in aqueous dioxane solution. After filtration of MnO_2, the sulphoximide (5) was isolated by extraction with dichloromethane as a hygroscopic solid, m.p. 58-60°C, $[\alpha]_D^{25} = +32.6^\circ$ (c 0.9, Me_2CO) (previously reported:[10] m.p. 59-61°C, $[\alpha]_D^{25} = -32.4^\circ$ (c 0.885, Me_2CO) for the (R)-enantiomer).

10. D. J. Cram, J. Day, D. R. Rayner, D. M. vonSchriltz, D. J. Duchamp and D. C. Garwood, J. Am. Chem. Soc., 1970, 92, 7369.

11. The deimidation of (5) was performed in 4 N H_2SO_4 to which 2 mol. equiv. of $NaNO_2$ in water was added at 20°C. The resulting sulphoxide (6) was extracted with $CHCl_3$ (96 % yield).

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