



0957-4166(95)00253-7

A New Synthesis of Enantiomerically Pure *n*-Alkyl 4-Bromobenzenesulfonates and their Configurational Assignment

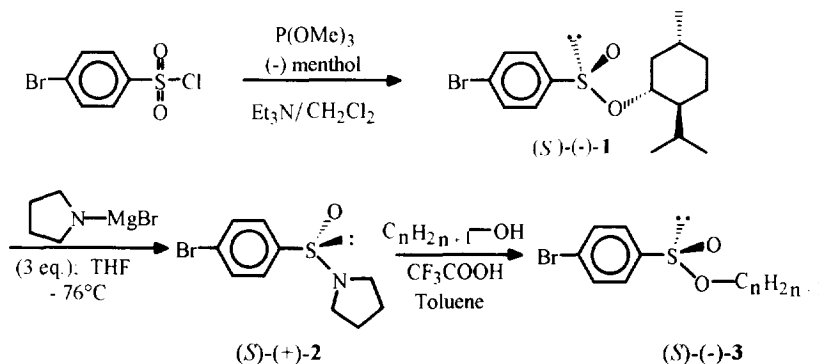
Jean-François Nicoud* and Mohammed Zoubair Cherkaoui

Institut de Physique et Chimie des Matériaux de Strasbourg, Unité Mixte 380046 - CNRS - ULP - EIHCS,
Groupe des Matériaux Organiques, 23, rue du Loess - B.P. 20 CR - 67037 Strasbourg Cedex, France

Abstract : (*S*)-(-)- α,α -diphenyl-2-pyrrolidinemethanol reacts with 4-bromobenzenesulfinyl chloride to give a single diastereomer of the corresponding sulfinamide in high yield. By an acidic alcoholysis of the sulfinamide with primary alcohols one obtains enantiomerically pure new (*R*)-(+)-*n*-alkyl 4-bromobenzenesulfonates. The configurations of the sulfinamide and the sulfonates derived from it have been determined by ¹H-NMR and molecular modeling.

Introduction

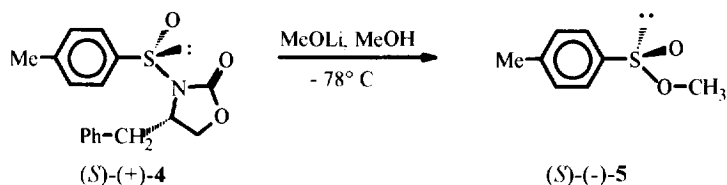
In the course of our present interest in new chiral smectic C (S_C^*) ferroelectric liquid crystals (FLC), we have been involved in the synthesis of optically active *n*-alkyl arenesulfonates.¹ The chemistry of chiral sulfinic acid derivatives has been well developed recently; in addition to their interesting properties as model molecules for the study of nucleophilic substitution at sulfur, they have been found to be useful intermediates in stereoselective syntheses of many other chiral sulfur derivatives.² Thus *p*-toluenesulfonate esters have been widely exploited as starting materials in the synthesis of optically active sulfoxides. However, only a few methods for the asymmetric synthesis of sulfonates have been reported. The first method initiated by Mikolajczyk involved the preparation of sulfinamide intermediates;³ this method has been recently revived in our laboratory for the synthesis of essentially enantiomerically pure *n*-alkyl 4-bromobenzenesulfonates bearing a long alkyl chain (Scheme 1).⁴



The bromine atom in position 4 on the benzene ring permits a straightforward access to several kinds of aromatic rigid cores of the targeted liquid crystals.^{1,5} The pure crystalline epimer (*S*)-(-)-1, which is easily obtained from 4-bromobenzenesulfonyl chloride and (-)-menthol, is first converted into the corresponding

sulfinamide (*S*)-(+)-**2**, by nucleophilic displacement with bromomagnesium diethylamide or pyrrolidinylamide, in excellent yield and enantioselectivity. Finally, *n*-alkyl 4-bromobenzenesulfonates (*S*)-(-)-**3** are obtained by reaction of primary alcohols with sulfinamides **2** at low temperature under acidic conditions (CF₃COOH, toluene, -78°C). The (*S*) configuration at sulfur in sulfonates (*S*)-(-)-**3** is deduced from (*S*)-(-)-**1** by considering two successive inversions of configuration.⁴

Three years ago Evans *et al.* described the use of *N*-arylsulfinyloxazolidones derived from (*S*)-phenylalanine as a new class of chiral sulfinyl transfer reagents for the asymmetric synthesis of chiral organosulfur compounds.⁶ For example (*S*)-(-)-methyl *p*-toluenesulfinate (**5**) can be obtained by the reaction of lithium methoxide with *N*-*p*-toluenesulfinyloxazolinone (*S*)-(+)-**4** (excess MeOH, -78°C) in high yield and enantiomeric excess (e.e. > 95%) (Scheme 2).



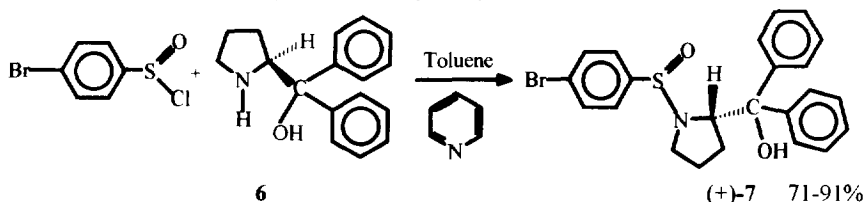
Scheme 2

More recently Whitesell and Wong described a new asymmetric synthesis of chiral sulfinate esters by using *trans*-2-phenylcyclohexanol as a chiral auxiliary, but the method did not seem useful for our targeted *n*-alkyl arenesulfonates.⁷ In particular all the above methods involve several steps. The overall yield in the preparation of pure (*S*)-(-)-**1** and (*S*)-(+)-**4** starting from (-)-menthol and (*S*)-(+)-phenylalanine is not so high, since it implies the separation of diastereomeric mixtures. The scheme 1 method, though giving sulfonates (*S*)-(-)-**3** with high e.e.¹ involved the preparation of the sulfinamides (*S*)-(+)-**2** from (*S*)-(-)-**1** as an additional step since the *trans*-esterification reaction of (*S*)-(-)-**1** with a primary alcohol leads to nearly complete racemization.⁸ So we decided to explore a synthetic method leading directly to one enantiomerically pure sulfinamide of type **2** by using an enantiomerically pure amine, that would leave only one step to get the 4-bromobenzenesulfinate esters of type **3**.

We wish to report here such a new method for the asymmetric synthesis of *n*-alkyl 4-bromobenzenesulfinate esters that uses the commercially available (*S*)-(-)- α,α -diphenyl-2-pyrrolidinemethanol (**6**) as the chiral auxiliary. The method necessitates only two steps from 4-bromobenzenesulfinyl chloride to get 4-bromobenzenesulfinate esters (*R*)-(+)-**3**, $n \geq 8$ with good yields and high enantiomeric purities (93% / 100%).

Results and Discussion

In the early phase of our study we tried to prepare the sulfinamides by reaction of 4-bromobenzenesulfinic acid with (*S*)-(+)-2-methylpiperidine. However we were not able to isolate a pure diastereomer from the crude oily diastereomeric mixture so obtained. Then we chose the chiral pyrrolidine derivative **6**, bearing a more hindered stereogenic center, and leading more probably to crystalline sulfinamides.



Scheme 3

^1H NMR spectra in the presence of chiral shift reagent, as shown in figure 1, we were able to assign clearly the (*R*) configuration to the *n*-octyl sulfinate (+)-**3** obtained by reaction of scheme 4. Indeed, in comparison with the optically active *n*-octyl 4-bromobenzenesulfinate (*S*)-(-)-**3**, *n*=8 obtained following scheme 1 synthesis, for which the sulfur absolute configuration (*S*) has been unambiguously deduced from the X-ray crystal structure of (*S*)-(-)-**1**,⁴ we obtained the dextrorotatory sulfinate (+)-**3**, *n* = 8, thus having the (*R*) configuration. Then, considering that the alcoholysis occurred with inversion of configuration,^{2,3} the sulfur must possess the (*R*) configuration in the sulfinamide (+)-**7**.

In addition to this first absolute configuration assignment, we investigated another method of stereochemical assignment for the sulfur atom of sulfinamide (+)-**7**, by molecular modeling. By using the SYBYL software (Tripos Associates, Inc.), we have established the most stable structure for each possible epimer of the sulfinamides **7**. Knowing that the asymmetric carbon atom derived from natural proline is of (*S*) configuration, both these structures are represented in figures 2 (C_SS_R -**7** in fig. 2a and C_SS_S -**7** in fig. 2b).

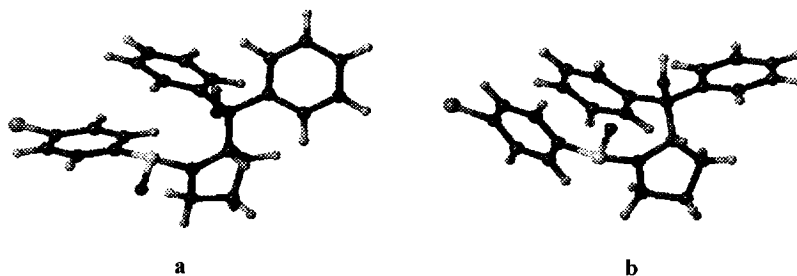


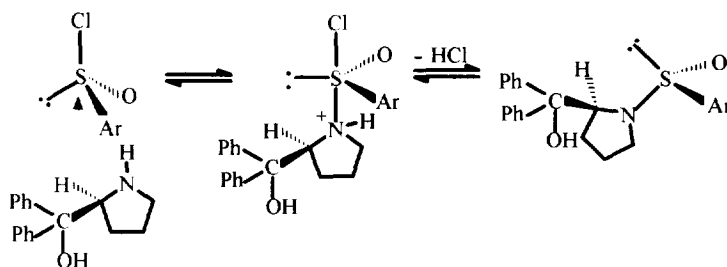
Figure 2. Structures of C_SS_R -**7** (fig. 2a) and C_SS_S -**7** (fig. 2b) obtained by molecular modeling.

We note easily from figure 2b that when the sulfur is of (*S*) configuration, the S=O bond is directed toward one of the phenyl groups, whilst in the other case (figure 2a) the S=O bond is directed distinctly outside of the rest of the molecule, a little toward the methylene group of the pyrrolidinyl ring, and thus is much less hindered. No intramolecular H-bonding between S=O and the hydroxyl group could be evidenced by the molecular modeling. If we assume a thermodynamic control for the reaction shown in scheme 3, the single epimeric sulfinamide obtained must be the one of figure 2a, therefore (*R*)-(+)-**7**.

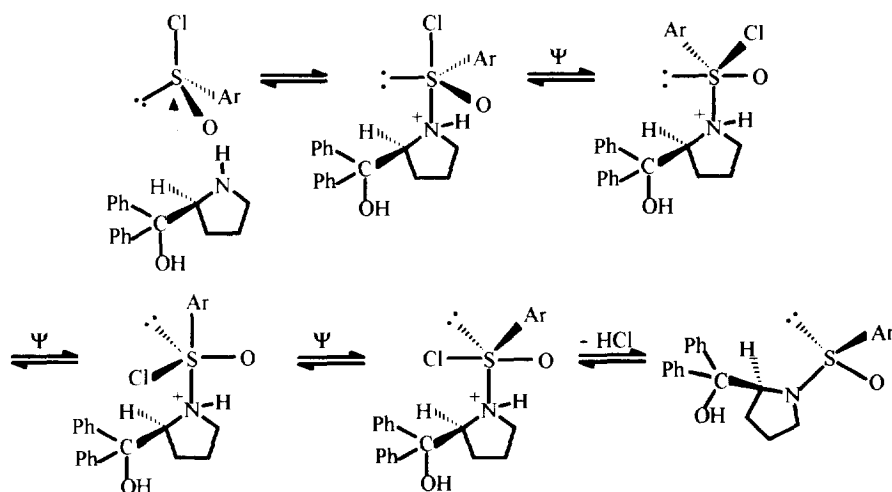
Such a quasi total asymmetric induction observed during the formation of the single epimer (*R*)-(+)-**7** must have an explanation. If we assume that the sulfinyl chloride starting reagent is a stable not labile racemic mixture, then since we obtained (*R*)-(+)-**7** in 71-91 % yield, the reaction is not a kinetic resolution. To account for our results the reaction mechanism for each enantiomer must be examined separately. We can propose the following addition-elimination reaction mechanisms for reaction of scheme 3 (schemes 5a, 5b). In scheme 5a we consider the reaction of the (*R*)-sulfinyl chloride; an apical attack of the prolinol derivative leads to a sulfurane intermediate that undergoes a rapid elimination of HCl leading to the sulfinamide **7** with (*R*) configuration at sulfur, though it is with an inversion of configuration.

Following the same mechanism, the (*S*)-sulfinyl chloride should lead to (*S*)-**7**, but this reaction is highly unfavorable as seen in figure 2b. Thus the sulfurane intermediate obtained after the apical attack of the amine undergoes three rapid pseudorotations (Ψ) leading finally to a retention of configuration at the sulfur center, as shown in scheme 5b. In this way (*R*)-**7** is obtained from both enantiomers of the sulfinyl chloride. The observation of such a retention of configuration, attributed to the pseudorotation on a sulfurane derivative, has been reviewed by Mikolajczyk.¹⁰

Scheme 5a



Scheme 5b



Conclusion

We presented a new synthesis of enantiomerically pure (*R*)-(+)-*n*-alkyl 4-bromobenzenesulfonates that requires only two steps from readily available starting materials. The chiral auxiliary (*S*)-(-)- α,α -diphenyl-2-pyrrolidine-methanol (**6**) is not destroyed during the reaction thus is theoretically recoverable. The quasi total asymmetric induction observed during the formation of the single epimer (*R*)-(+)-**7**, the first time for such a sulfinyl derivative, may be attributed to the steric effect caused by the diphenylcarbinol group bonded to the asymmetric carbon atom on the pyrrolidinyl group. Such an effect, evidenced by molecular modeling, could be further studied by using other prolinol or chiral aminoalcohol derivatives, to get new sulfinamides of type **2**.

Experimental Procedures

Synthesis of (*R*)-(-)-1-[(4-bromobenzenesulfinyl)]-(2*S*)-(diphenylhydroxymethyl)pyrrolidine [(*R*)-(+)-**7**]

4-bromobenzenesulfinic acid was prepared as previously reported.^{1,9} The sulfinic acid (1.0g, 4.52mmol) was stirred in freshly distilled thionyl chloride (10 ml) under reflux for 1 hour. After evaporation of the excess thionyl chloride, the residue was dried under vacuum, then dissolved in dry toluene (15 ml); then 1.37g (5.42mmol) of (*S*)-(-)- α,α -diphenyl-2-pyrrolidinemethanol (Lancaster) in 15 ml of dry toluene was added and the mixture is stirred at 0° C. A white precipitate of sulfinylammonium salt immediately occurred, after what 10 ml of anhydrous pyridine were added, and the mixture was stirred at room temperature during 2 hours. Then the reaction mixture was treated with 100ml of dichloromethane, and the pyridine hydrochloride was extracted with brine and water (3 x 100ml). The organic layer was dried over Na₂SO₄, filtered and evaporated to yield a

white solid giving a single spot in TLC analysis (SiO₂, eluent CH₂Cl₂/CH₃CN : 95/5, R_F = 0.30). A crystallization from a mixture CHCl₃/hexane afforded white crystals. The yield of (*R*)-(+)-7 was 1.6g (80%). [α]_D²² +82.3 (c 1.30, DMSO). Found, C 60.5, H 4.8, N 2.9, O 7.25, S 7.15 %; C₂₃H₂₂BrNO₂S requires C 60.5, H 4.9, N 3.1, O 7.0, S 7.0 %. δ_H (200MHz, CDCl₃) 7.74-7.02 (14H, m, H-Ar), 5.14 (1H, dd, J = 5.10Hz), 3.50 (1H, dtd, J = 10.7 and 7Hz), 2.50 (1H, dt, J = 10.7 and 7Hz), 2.09 (1H, mc), 1.95 (1H, mc), 1.80 (2H, mc). m/z (C.I., NH₃) (only peaks from ⁸¹Br are reported) 475[(⁸¹M + 18)]⁺, 1%; 458 [(⁸¹M + 1)]⁺, 1%; 276, 2%; 252, 2%; 236, 32%; 183, 55%; 70, 100%.

Synthesis of optically active n-octyl 4-bromobenzenesulfinate [(R)-(+)-3, n=8]

The synthesis of the (*R*)-(+)-*n*-octyl 4-bromobenzenesulfinate is described as a representative procedure for the whole series. A suspension of the sulfinamide (*R*)-(+)-7 (0.6g, 1.31mmol) in dry toluene was stirred during 6 h at 0° C in the presence of 1-octanol (1.03g, 7.90mmol) and trifluoroacetic acid (0.3g, 2.62mmol). The reaction was monitored by TLC (SiO₂, eluent : Et₂O/pentane: 1/3, R_F = 0.60 for 3); After completion of the reaction, the mixture was quenched with saturated aqueous NaHCO₃ which made it clear, then was extracted with diethylether. The combined organic extracts were washed with saturated aqueous NaCl, dried over Na₂SO₄ and the solvent evaporated. The resulting crude yellow oil was purified by column chromatography on silica (Et₂O/pentane : 1/3) to give (*R*)-(+)-3 as colorless oil (yield 84%); [α]_D²⁵ +108.3 (c 1.03, EtOH); e.e. = 96% by ¹H NMR using Eu(hfc)₃, see figure 1. IR ν_{max}: 3040, 2920, 2900, 2860, 1590, 1470, 1390, 1130 (S=O), 1070 and 1010 cm⁻¹. Found, C 50.58, H 6.41, O 9.55, S 9.57 %; C₁₄H₂₁BrO₂S requires C 50.45, H 6.35, O 9.60, S 9.62 %. δ_H (200MHz, CDCl₃) 7.69 and 7.58 (2H, dd, J = 8.60Hz, H-Ar), 4.04 and 3.61 [1H, dt(ABX₂); J=9.76 and 6.62Hz, -SOO-CH₂], 1.62 (2H, mc, -SOO-CH₂-CH₂), 1.25 (10H, m, (-CH₂-)aliph), 0.88 (3H, t, J=6.33Hz, CH₃-CH₂-). m/z (70eV) (only peaks from ⁸¹Br are reported) 43 (72%), 57(100%), 71(84%), 71(11%), 96(11%), 157(9%), 205(17%), 223(14%), 317(28%), 335([M+H]⁺, 34%).

Similarly were obtained the *n*-decyl 4-bromobenzenesulfinate [(*R*)-(+)-3, n=10], colorless oil : [α]_D²³ +111 (c 1.4, EtOH), e.e. = 100% (the (*S*) enantiomer was not detected by using the NMR method shown in figure 1), and *n*-dodecyl 4-bromobenzenesulfinate [(*R*)-(+)-3, n=12], white crystals, m.p. = 32° C; [α]_D²⁵ +89.2 (c 1.02, EtOH); e.e. = 93%.

Acknowledgements. We thank Pr. Jean-Claude Fiaud and Dr. Stéphane Méry for helpful discussions.

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