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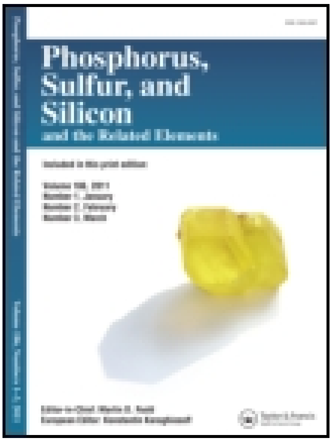

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Synthesis of Chiral Aminosulfite and Sulfite from Optically Active 2-Naphthol Derivatives

Professor Jozef Drabowicz [a] [b] , Miss Dorota Krasowska [a] , Miss Anna Aftyka [a] , Dr Bernard Marciniak [b] & Dr Ewa Rozycka-Sokolowska [b]
[a] Center of Molecular and Macromolecular Studies, Polish Academy of Sciences , Łodz, Poland
[b] Jan Dlugosz University in Czestochowa , Czestochowa, Poland
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SYNTHESIS OF CHIRAL AMINOSULFITE AND SULFITE FROM OPTICALLY ACTIVE 2-NAPHTHOL DERIVATIVES

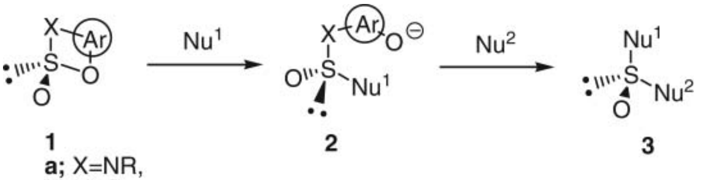
Jozef Drabowicz,[1,2] Dorota Krasowska,[1] Anna Aftyka,[1] Bernard Marciniak,[2] and Ewa Rozycka-Sokolowska[2]
[1]Center of Molecular and Macromolecular Studies, Polish Academy of Sciences, Łodz, Poland
[2]Jan Dlugosz University in Czestochowa, Czestochowa, Poland

Abstract *Preparation of chiral cyclic aminosulfite and sulfite derived from diastereomerically pure 1-[α-N-1-phenylethyl]benzyl-2-naphthol and 1,1′-bi-2′-naphthol, respectively, are reported. The nucleophilic substitution on the sulfite substrate by using some selected nucleophiles is also discussed.*

Keywords Aminosulfites; BINOL; chiral cyclic sulfinyl derivatives; nucleophilic substitution; sulfites

INTRODUCTION

An approach based on the two consecutive reactions between the chiral cyclic sulfinylating agents **1a**,**b** and two different nucleophiles constitutes an efficient way to afford chiral sulfinyl derivatives (diastereomerically pure **2** and enantiomerically pure **3**, respectively).[1]



Because a phenolate is known as a very efficient leaving group, cyclic aminosulfite or sulfite structures derived respectively from aminophenols or biphenols should be expected to be more efficient sulfinylating agents as the aliphatic aminoalcohols or diols derivatives. Thus, we decided to synthesize as the model structures an aminosulfite derived from

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Address correspondence to Jozef Drabowicz, Center of Molecular and Macromolecular Studies, Polish Academy of Sciences, Sienkiewicza 112 90-363, Łodz, Poland. E-mail: draj@cbmm.lodz.pl

diastereomeric, enantiopure 1-[α-*N*-1-phenylethyl]benzyl-2-naphthol[2] and sulfite derived from 1,1′-bi-2-naphthol[3] (racemic or enantiopure) and to study the reactivity of the later towards some selected nucleophilic reagents. The outcome of these preliminary experiments will be presented below.

RESULTS AND DISCUSSION

Aminosulfites Derived from Enantiopure 1-[α−*N*-1-Phenylethyl]benzyl-2-naphthol

Earlier, small scale reactions of thionyl chloride with the (*R,R*) enantiomer of aminonaphthol **4** performed in the presence of a tertiary amine at temperatures from −70°C to room temperature in diethyl ether, were found to give the expected aminosulfite **5** as a mixtures of diastereomers in yields above 90% and with diastereomeric excesses (*de*) below 30%. All attempts to isolate a pure diastereoisomer from these mixtures (or a mixture strongly enriched in a particular diastereomer) by typical crystallization have been unsuccessful. However, it was possible to isolate, in some experiments, the pure diastereomers by partition of the diastereomers in petroleum ether (due to the different solubility) occurring effectively during a few hours stirring of their suspensions in this solvent.[4] We were able to carry out an X-ray structural analysis for the pure diastereomer having optical rotation equal to $[\alpha]_D = -75.2$ (CH_2Cl_2). It showed a slightly distorted tetrahedral rearrangement of the substituents (two oxygens, one nitrogen, and a lone electron pair) and the (*S*) absolute configuration at the sulfinyl sulfur atom.[5] To isolate the pure diastereomer having the (*R*) absolute configuration at the sulfinyl sulfur atom, we carried out reactions of thionyl chloride with the (*S,S*) enantiomer of aminonaphthol **4** under various reaction conditions (given in Table 1). In this case, the expected amidosulfite **5** was formed now as a mixture of diastereomers with, again, diastereomeric excesses (*de*) below 30% (see Table 1). The almost pure diastereomer S,S,S_S-**5** (*de* > 95%) having optical rotation equal to $[\alpha]_D = +289.8$ (CH_2Cl_2) was isolated in 19% yield by column chromatography of the crude sample having 24% *de* (Scheme 1).

The Sulfite Derived from Binol and Its Reactions with Selected Nucleophiles

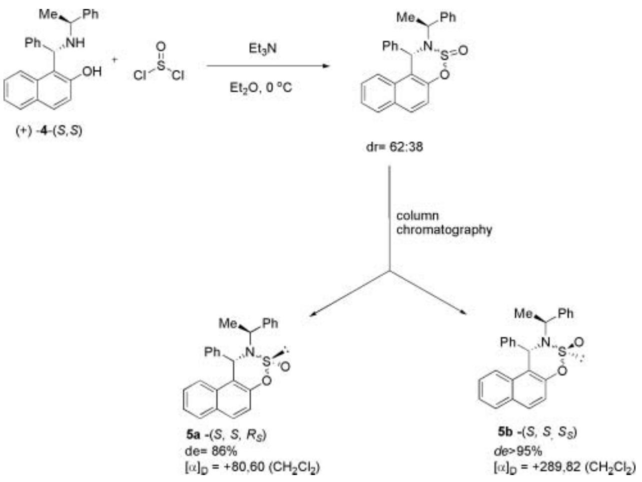
The cyclic sulfite derived from enantiopure BINOL can be envisioned as a good substrate for the generation of acyclic, diasteromeric sulfinyl derivative *via* the stereoselective nucleophilic substitution at the sulfinyl sulfur atom due to good leaving ability of

Table 1 Reactions of thionyl chloride with the (*S,S*) enantiomer of aminonaphthol **4** under various reaction conditions

Base	Temp (°C)	Yield[a] (%)	dr[b]
i-PrMgBr	0°C	12	55:45
$NaH:Et_3N$ 1:1,05	0°C	72	55:45
$NaH:Et_3N$ 1:1,05	−78°C	65	57:43
Et_3N (4 eq mol)	0°C	79	62:38

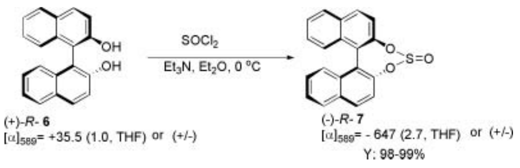
[a] For a crude product.

[b] From the ^{1}H NMR recorded for a crude product.



Scheme 1

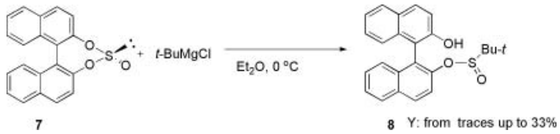
a naphthoxy residue. In order to verify this expectation, we worked out an independent protocol for the preparation 1,1′-binaphthyl-2,2′-diyl sulfite **7** starting from racemic and enantipure (+)-(*R*)-BINOL-**6** and carried out the model nucleophilic substitution reactions. The synthesis of 1,1′-binaphthyl-2,2’-diyl sulfite **7** as (+)-isomer (from (-)-(*S*)-BINOL) was described in the literature by Zhang et al.[5] However, the product was obtained in poor yield (18%) and only after column chromatography. It should be noted here that information on that synthesis (published in Chinese) is still not available in the Beilstein database, though we did find it in the SciFinder scholar database unexpectedly, only after working out our procedure, in which we used diethyl ether as a solvent and triethylamine as a base (insead of methylene chloride and pyridine). Our procedure gave both racemic and optically active (*R*)-(-)- isomer almost quantitatively (Scheme 2). Racemic and optically active derivatives are stable and could be stored at ambient temperature for months. We were able to redetermine the crystal structure of the optically active (*R*)-(-) sulfite isomer with an optical rotation $[\alpha]_D = -647$ (2.7, THF).



Scheme 2

Reactions of the Sulfite 7 with Selected Nucleophiles

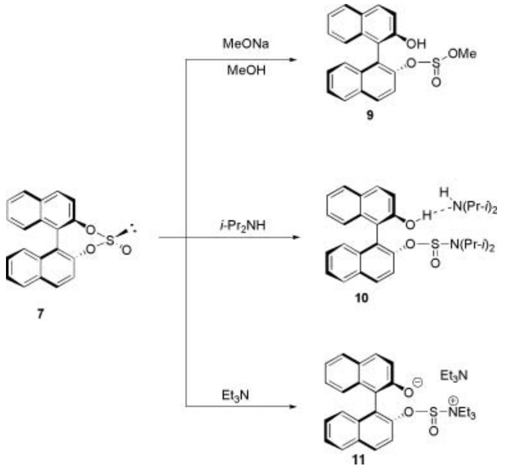
Knowing from our previous work[6] that it is possible to stop the reaction of dialkyl sulfites with Grignard reagents at the stage of a sulfinate formation if tertiary Grignard reagents are used, we decided to find the reaction of sulfite **7** with *tert*-butylmagnesium chloride, hoping that it will result in the highly diastereoseletive formation of the corresponding *O*-aryloxy *tert*-butanesulfinate **8** (Scheme 3). The presence of the expected *tert*-butylsulfinate



Scheme 3

8 (from traces to 33% yield) was confirmed by ^{1}H NMR and MS spectra in crude reaction products of all reactions which were carried out with two (or more) equivalents of *tert*-butylmagnesium chloride. Unfortunately, all attempts to isolate and fully characterize this sulfinate were until now unsuccessful. Very low yields of the desired sulfinate **8** in crude reaction mixtures are undoubtedly due to its greater reactivity towards *tert*-butylmagnesium chloride as compared with that of the starting sulfite. This should lead to the formation of di-*tert*-butylsulfoxide, the presence of which in the crude reaction mixtures was supported by their ^{1}H NMR spectra.

Sodium methoxide, diisopropylamine, and triethylamine were also checked as nucleophiles in the reaction with the sulfite **7**. The reaction courses followed by ^{1}H NMR and polarymetry (based on analyzing the chemical shifts of selected aromatic absorption and dramatic changes in the observed optical rotations of the sample solutions) suggested the very rapid formation of acyclic, diastereomeric sulfinyl derivatives **9–11** as reaction intermediates (Scheme 4).



Scheme 4

CONCLUSIONS

The reactions of diastereiomeric enantiopure 1-[α-*N*-1-phenylethyl]benzyl-2-naphthols or the racemic or enantipure BINOL with thionyl chloride led to the corresponding aminosulfite or sulfite diastereomers, respectively. The sulfite was found to be very reactive towards selected nucleophilic reagents. The reaction courses that were followed by means of ^{1}H NMR and polarimetry revealed very rapid formation of acyclic, diasteomeric sulfinyl derivatives **9–11** as the reaction intermediates.

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