J. Braz. Chem. Soc., Vol. 21, No. 11, 2023-2026, 2010.
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0103 - 5053 $6.00+0.00

Communication

Enantiomeric Excess Detection with (*S*)-3-Phenyl-2-(selenophenyl)propan-1-ol Derivatizing Agent via Mix and Shake ^{77}Se NMR

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Neste artigo demonstramos que o composto (*S*)-3-fenil-2-(selenofenil)propan-1-ol pode ser empregado com sucesso como agente de derivatização quiral na determinação de excesso enantiomérico de substratos ácidos carboxílicos quirais via RMN de ^{77}Se. Os derivados diastereoméricos são obtidos através da mistura do agente de derivatização quiral com um substrato ácido não racêmico no próprio tubo de RMN e o excesso enantiomérico é determinado com apenas um espectro. Os melhores resultados foram os obtidos com o emprego do *(S)*-3-fenil-2-(selenofenil) propan-1-ol, que apresentou boas anisocronias para os sinais de selênio, variando entre $\Delta\delta$ = 22 Hz a $\Delta\delta$ = 211 Hz, mesmo com até 5 ligações separando o estereocentro do átomo de selênio.

In this article, we demonstrate that (*S*)-3-phenyl-2-(selenophenyl)propan-1-ol can be successfully employed as chiral derivatizing agent for enantiomeric excess determination of chiral carboxylic acid substrates via ^{77}Se NMR. The required derivatives are obtained by mixing the chiral derivatizing agent with the non racemic carboxylic acid substrate directly in the NMR tube and determining the enantiomeric excess with just one spectrum. The best results were obtained with *(S)*-3-phenyl-2- (selenophenyl)propan-1-ol, which showed good anysochronies of the selenium signals, ranging from $\Delta\delta$ = 22 Hz to $\Delta\delta$ = 211 Hz, even with the stereocenter and the selenium atom five bonds apart.

Keywords: enantiomeric excess, derivatizing agent, selenium NMR, chiral non racemic substrates

Introduction

The increased development of single-enantiomer pharmaceuticals and the interest in enantioselective synthesis has enhanced the need for methods for determination of enantiomeric excess, ee, of chiral compounds.[1-3]

NMR spectroscopy continues to be one of the most important techniques for analyzing chiral molecules. A wide variety of optically pure discriminating agents have been developed to facilitate the determination of ee.[4,5] One of the main procedures is based on the covalent attachment of an enantiopure chiral derivatizing agent (CDA) to the chiral substrate to be analyzed. Therefore, a pair of enantiomers attached to a CDA, yields diastereomers, which are expected to have different chemical shifts in the NMR spectrum.

Some techniques have already been described for the determination of ee via ^{77}Se NMR spectroscopy. The natural abundance, 7.63%, of selenium-77 nucleus, its large chemical shift range (near 3400 ppm) and enhanced sensitivity to its electronic environment, make ^{77}Se an excellent nucleus of choice.[6-8]

Our objective was to design and synthesize new chiral derivatizing agents that would add to the currently existing ones, by incorporating a more sensitive NMR active nucleus. In this way it became interesting to evaluate the potentiality of ^{77}Se NMR as a chiral discrimination methodology.

Ideally, the new selenium chiral auxiliaries, that would incorporate the advantageous features described above, should be obtained by a simple enantioselective route, yielding air stable products that would react with the substrate directly in an NMR tube, allowing for a micro scale and rapid method of detection.

Results and Discussion

Our strategy was based on the synthesis of *(S)*-3-phenyl-2-(selenophenyl)propan-1-ol (**1**), which was obtained in a two step procedure shown in Scheme 1.

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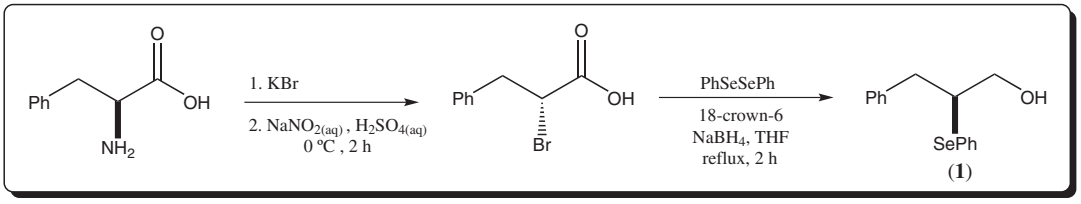
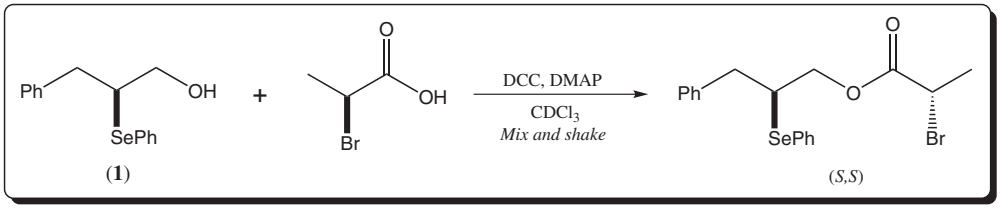


Scheme 1.



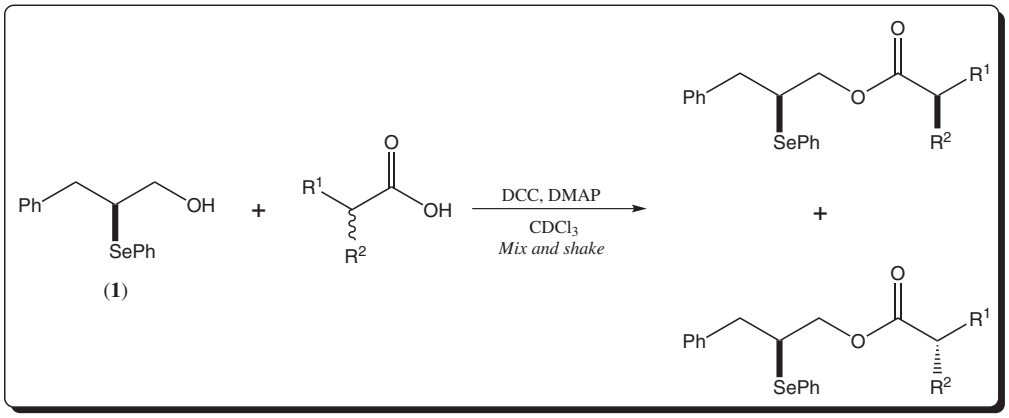
Scheme 2.

The α-bromoacid was readily prepared from the corresponding natural aminoacid in a one pot reaction.[9] In the next step, the corresponding α-bromoacid was made to react with the nucleophilic phenylselenolate anion, generated *in situ* from diphenyl diselenide and sodium borohydride in excess, plus the addition of a catalytic amount of 18-C-6 ether. The reduction of the carboxylic acid group occurred concomitantly. After purification, *(S)*-3-phenyl-2- (selenophenyl)propan-1-ol, **1** was isolated with an overall yield of 55%.[10,11] It is worth mentioning that the α-selenoalcohol is quite stable and can be stored at 10 °C for more than six months.

As for the optical purity of compound **1**, it could be evaluated by reacting the α-selenoalcohol with commercial *(S)*-2-bromopropionic acid in the presence of DCC and DMAP, in $CDCl_3$ as solvent (Scheme 2). For the obtained product, only one ^{77}Se resonance signal was observed. Accordingly, the same reaction was performed with the bromoacid of R configuration, affording an optically pure ester. As expected, the diastereomeric esters of (*S*,*S*) and (*S*,*R*) configuration presented different chemical shifts.

The procedure to evaluate the performance of the synthesized α-selenoalcohol as CDA was accomplished by preparing samples of **1** and by reacting them in the NMR tube with the racemic carboxylic acids, corresponding to entries 1-3 (Table 1) as follows. In an NMR tube, containing CDCl3, the racemic carboxylic acid (0.5 mmol) was added to the α-selenoalcohol, followed by DCC (0.6 mmol) and a catalytic amount of DMAP. The heterogeneous mixture was gently shaken for a couple of minutes. Without any further manipulation, the ^{77}Se NMR spectrum was recorded in the usual way, immediately after the sample preparation. In all cases tested, the derivatizations were shown to be quantitative (Scheme 3).

Table 1 presents spectroscopic results for the racemic acids **2**, **3** and **4**, in admixture with the chiral discriminating agent **1**. For all cases, the ^{77}Se NMR spectra allowed for an easy identification of selenium resonances for both diastereomeric esters. The values of the observed $\Delta\delta$ ranged from 22 to 211 ppm, the largest value being attributable to the anysotropy of the phenyl ring that is attached to C-2 of **4**, but absent in the molecular structure of **2** and **3**.



Scheme 3.

Table 1. Results of ^{77}Se NMR experiments for the diastereomeric esters prepared *in situ* from α-selenoalcohol (**1**) and racemic carboxylic acids (**2**, **3** and **4**)

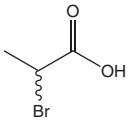
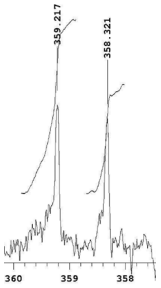
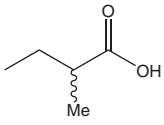
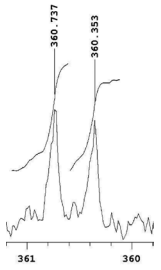
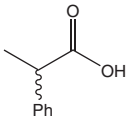
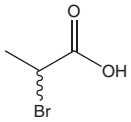
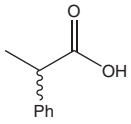
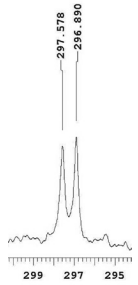
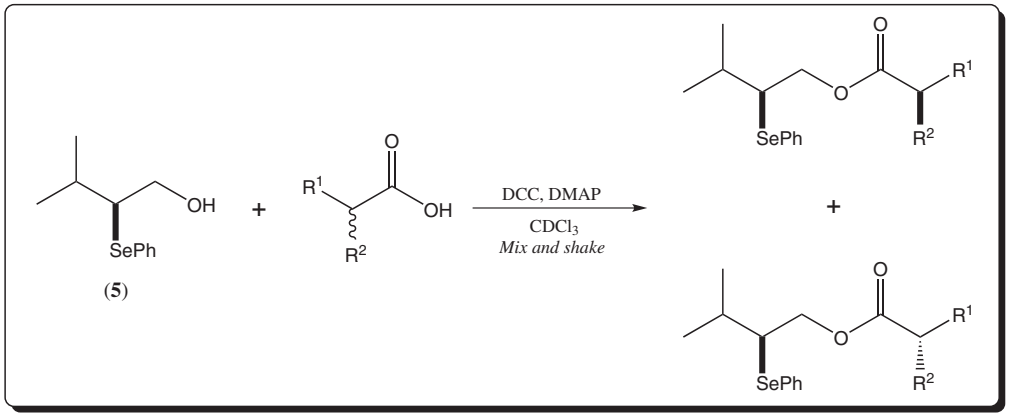
entry	Acid	Δδ ^{77}Se (Hz)	Partial spectra
1	 (**2**)	51	
2	 (**3**)	22	
3	 (**4**)	211	

Table 2. Results of the experiments of ^{77}Se NMR of the diastereomeric esters obtained from α-selenoalcohol (**5**) and the corresponding racemic carboxylic acids (**2** and **4**)

entry	Acids	Δδ ^{77}Se (Hz)	Partial spectra
1	 (**2**)	0	
2	 (**4**)	40	

In order to verify the extension of the anisotropic effect due to the phenyl group attached to C-3 of the chiral auxiliary, we decided to synthesize the selenoalcohol, *(S)*-3-methyl-2-(selenophenyl)butan-1-ol **5**. We followed the same experimental procedure, and compound **5** was obtained after purification, in 50% yield. Table 2 presents the ^{77}Se NMR results for two derivatization reactions using **5** as CDA (Scheme 4).

The importance of the presence of an aryl group in the molecular structure of the α-selenoalcohol is highlighted by the results reported in Tables 1 and 2. In fact, when CDA **5** reacted with racemic acids **2** and **4**, a significant smaller Δδ value was observed, when compared to results for the reaction of the same acids with CDA **1**. It is worth mentioning that when the chiral auxiliary *(S)*-3-phenyl-2-(selenophenyl)propan-1-ol was employed with a substrate having two similar alkyl moieties attached to the stereocenter, it was still possible to achieve good separation between the selenium resonances for the two diastereomeric



Scheme 4.

esters, even when, as in this case, the stereocenter and the selenium nucleus are five bonds apart.

Conclusions

We have thus demonstrated that *(S)*-3-phenyl-2-(selenophenyl)propan-1-ol **1** can be successfully employed as CDA for enantiomeric excess determination of chiral carboxylic acid substrates. This optically pure compound is easily prepared by a simple enantioselective route, and is stable when exposed to air at room temperature. The presence of the very sensitive 77-selenium nucleus allows for the determination of the enantiomeric excess of diastereomeric esters having both estereocenters up to five bonds apart. On the other hand, the described method consists of a very simple procedure for performing an esterification reaction directly in an NMR tube. Such transformation is quantitative and is completed after mixing and shaking for a very short time.

Acknowledgments

The authors gratefully acknowledge CNPq, CAPES and FACEPE (PRONEX) for financial support.

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Submitted: June 1, 2010
Published online: August 31, 2010