Revista de la Sociedad Química de México, Vol. **47***, Núm. 2 (2003) 127-129*

Investigación

The Use of *N,N'*-Di[α-phenylethyl]-diamines as Phosphorylated Chiral Derivatizing Agents for the Determination of the Enantiomeric Purity of Chiral Secondary Alcohols

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Recibido el 17 de febrero del 2003; aceptado el 26 de marzo del 2003

This paper is dedicated to Dr. Alfonso Romo de Vivar in appreciation of his contributions to chemistry

Abstract: The influence of the framework structure in C_2-symmetric *N,N'*-di[α-phenylethyl]diamines as chiral derivatizing agents, on their effectiveness for the determination of the enantiomeric composition of chiral secondary alcohols by ^{31}P-NMR spectroscopy of derived diastereomeric phosphonamides, is described.
Key words: chiral derivatizing agents, enantiomeric composition, C_2-symmetric diamines, ^{31}P-NMR spectroscopy.

Resumen: Se describe la influencia de la estructura de *N,N'*-di[α-feniletil]-diaminas con eje de simetría C_2, como agentes derivatizantes quirales en la determinación de la composición enantiomérica de alcoholes secundarios quirales empleando RMN de ^{31}P.
Palabras clave: Agente derivatizante quiral, composición enantiomérica, diaminas con simetría C_2, RMN de ^{31}P.

Introduction

Chiral derivatizing agents (CDAs) for NMR spectroscopy represent one of the most effective tools to satisfy the great demand for rapid and reliable methods for the determination of the enantiomeric composition of chiral substrates [1]. Their use involves the derivatization reaction of an enantiomerically pure chiral auxiliary with the substrates to be analyzed, in order to obtain diastereoisomeric products presenting anisochronous absorptions in their NMR spectra. Efforts directed to the development of fast and reliable CDAs continue [2]. In this context, the high sensitivity afforded by ^{31}P NMR spectroscopic methods makes attractive the use of phosphorus-containing derivatives towards this goal [3].

Chiral diamines have been shown to be useful chiral reagents and ligands for chemical catalysis, with especial application in asymmetric synthesis [4]. By the same token, (*R*)- and (*S*)-α-phenylethylamine are simple, yet powerful stereodifferentiating auxiliaries in organic transformations [5].

Presently, there exist several reports in the literature describing the use of diamines containing diverse *N*-substituents as CDAs, which are based on the synthesis of chiral phospholidines for the determination of enantiomeric composition of chiral alcohols, amines, carboxylic acids, halohydrins and thiols. In particular, *N,N'*-di[(*S*)-α-phenylethyl]ethane-1,2-diamine, **A**, and *N,N'*-di[(*S*)-α-phenylethyl]propane-1,3-diamine, **B**, (Fig. 1) have been reported as effective and inexpensive CDAs [6]. In addition, the use of chiral diamines based on enantiopure *trans*-1,2-diaminocyclohexane as CDAs, such as **C** has been demonstrated [7]. Furthermore, our group also reported the use of *trans-N,N'*-di-[(*S*)-α-phenylethyl]-cyclohexane-1,2-diamines, **D** and **E** as convenient CDAs [8].

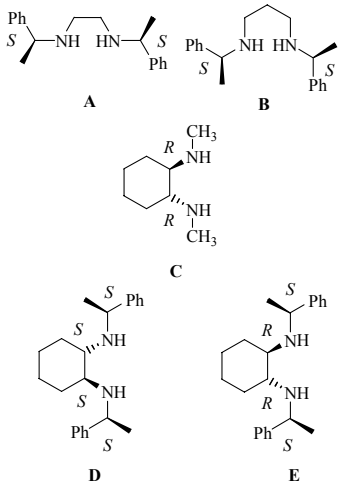


Figure 1.

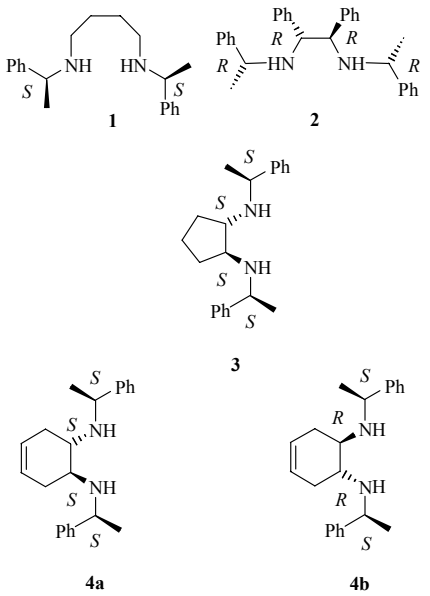


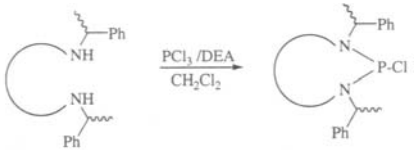
Figure 2.

Results and discussion

The use of C_2-symmetric *N,N'*-di[α-phenylethyl]-diamines 1, **2**, **3**, **4a** and **4b** as chiral ligands (Fig. 2) will be reported [9]. In the present work their application as chiral derivatizing agents (CDAs), via the formation of the corresponding *P*-chloro-1,3-diazaphospholidines is described. These CDAs can be prepared directly in the NMR tube employed for ^{31}P NMR analysis [8].

To this end, each diamine in $CDCl_3$ solvent was treated with one equivalent of PCl_3 in CH_2Cl_2 at room temperature to give the corresponding phospholidines as intermediates. The formation of the *P*-chloro-1,3-diazaphospholidines of interest was very fast and quantitative with diamines **1**, **2**, **4a**, and **4b**, but rather slow and incomplete with diamine **3** (Table 1). Apparently, the reaction of diamine **3** with PCl_3 is also unfavorable, because of strain in the *trans*-fused five-membered bicyclic phospholidine formed.

Table 1. Synthesis of *P*-chloro-1,3-diazaphospholidines.



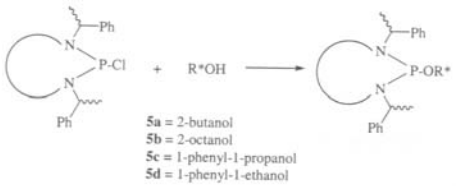
Entry	Diamine	Reaction time, h	Conversion %[a]	δ (ppm) ^{31}P-NMR of Phospholidine
1	1	0.5	100	165.21
2	2	0.5	100	168.93
3	3	24	23	166.50
4	4a	0.5	100	177.40
5	4b	0.5	100	175.25

[a] The percent of conversion were determined from the ^{31}P-NMR spectra in relation to the amount of PCl_3.

Gratifyingly, the *P*-Cl bond of the phospholidines **2**, **4a** and **4b** were readily cleaved, upon treatment with the carbinols of interest. So, derivatization was carried out by addition of 0.8 equiv of the racemic secondary alcohols, **5a-d**, to afford the respective *P*-alkoxy-1,3-diazaphosphonamides (Table 2). The *all*-(*S*) diamine **4a** afforded the largest differences of chemical shifts (Δδ) in the ^{31}P NMR spectra of the diastereomeric phosphonamides. Nevertheless, the *P*-Cl bond of the P-chloro-1,3-diazaphospholidine derived from **1** was specially resistant upon treatment with carbinols. Thus, diamines **1** and **3** were not useful as CDAs.

In summary, the *P*-chloro-1,3-diazaphospholidines derived from chiral diamines **2**, **4a**, and **4b**, incorporating *N*-(α-phenylethyl) substituents, are convenient chiral derivatizing agents for the determination of the enantiomeric purity of chiral alcohols. The quantitative and fast P-Cl bond cleavage upon alcoholysis leads to phosphonamide formation, directly in the NMR tube prior to measurement. Large differences in

Table 2. ^{31}P NMR data of *P*-alkoxy-1,3-diazaphospholidines derived from secondary alcohols **5a-d** recorded in $CDCl_3$.



Entry	Diamine	R*OH	Diastereoisomeric P-OR, Δδ	**A** lit.[6] Δδ	**B** lit.[6] Δδ	**C** lit.[7a] Δδ	**D** lit.[8] Δδ	**E** lit.[8] Δδ
1	**4a**	**5a**	1.48	—	2.73	0.27	1.07	0.38
2	**4b**		0.44					
3	**4a**	**5b**	1.61	—	—	0.27	0.98	0.31
4	**4b**		0.37					
5	**4a**	**5c**	2.79	0.39	3.69	—	6.34	1.01
6	**4b**		0.21					
7	**2**		0.44					
8	**4a**	**5d**	1.21	0.20	1.38	0.40	4.71	0.58
9	**4b**		0.18					

the ^{31}P NMR chemical shifts ($\Delta\delta$) for the diastereomeric phosphonamides were observed, allowing accurate integration and quantitative determination of the diastereomeric ratios.

Experimental section

^{31}P NMR spectra were measured on a Varian Mercury-200 MHz spectrometer. Chemical shifts are given as δ values (ppm). All reagents were purchased from Aldrich Chemical Co.

General Procedure for Chiral Alcohol Derivatization

In an NMR tube are placed with vigorous stirring 0.16 mmol of free diamine, 0.5 mL of $CDCl_3$, 119 mg (0.80 mmol) of diethylaniline, and 23 mg (0.16 mmol) of PCl_3 previously dissolved in 50 μL of CH_2Cl_2, affording the chlorodiazaphospholidine and the ^{31}P NMR spectra are recorded (Table I). Immediately after, 0.13 mmol of racemic secondary alcohols is added, and the resulting mixture is stirred for 30 minutes before ^{31}P NMR spectra are recorded at room temperature (Table 2).

Acknowledgment

We thank CONACyT for financial support (Projects No. 32202-E and 33023-E, and Grants No. 91275 and 144937).

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