Optically Active Diazacyclophosphamides: Novel Efficient Reagents for the Determination of the Absolute Configuration of Amines and Alcohols

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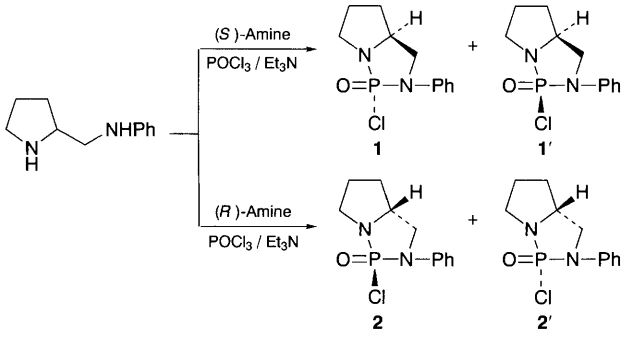
Various amines and alcohols are converted into the corresponding phosphamides by the action of optically active diazacyclophosphamidic chlorides and absolute configurations of amines and alcohols are readily determined by proton and phosphorus NMR of the cyclophosphamides that are formed.

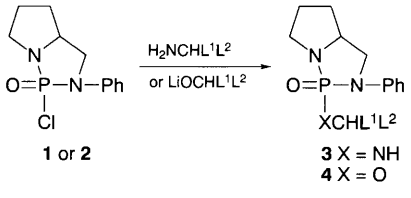
Mosher's method for determining absolute configurations using (*R*)- and (*S*)-MTPA has been used frequently.[1–3] While several methods have been developed for determining enantiomeric excesses of alcohols and amines using ^{31}P NMR,[4] chiral phosphorus reagents for determining both absolute configuration and the e.e. of protic compounds such as amines and alcohols are unknown.

We report here the diastereoselective preparation of (2*R*, 5*S*)- and (2*S*, 5*R*)-2-chloro-3-phenyl-1,3,2-diazaphosphabicyclo[3.3.0]octane 2-oxides **1** and **2** from (*S*)- and (*R*)-2-(anilinomethyl)pyrrolidines, and the efficient diastereoselective preparation of cyclophosphamide derivatives of amines and alcohols as well as the determination of their absolute configuration by ^1H and ^{31}P NMR spectroscopy.

Cyclophosphamidic chlorides **1** and **2** were easily prepared by diastereoselective reactions of corresponding chiral diamines with $POCl_3$ in the presence of Et_3N at −78 °C in quantitative yield (Scheme 1) and crude products **1** and **1′** (chemical shifts were δ 19.13 and 26.13 on ^{31}P NMR, respectively; ratio of **1** : **1′** = 92 : 8)† or **2** and **2′** (chemical shifts were δ 19.13 and 26.13 on ^{31}P NMR, respectively; ratio of **2** : **2′** = 91 : 9) were easily separated by column chromatography on silica gel. The precise stereochemistrics at phosphorus of purified **1** and **2** were determined on the basis of the ^1H NMR (400 MHz) where C^5-H of compound **1** showed a high field chemical shift (δ 4.02) compared with C^5-H of compound **1′** (δ 4.28).[5] Phosphamides **3** and esters **4** were obtained in good yields by the reaction of diazacyclophosphamidic chlorides **1** and **2** with appropriate racemic amines in the presence of Et_3N, or with lithiated racemic alcohols by treatment with Bu^nLi at room temperature (Scheme 2). In all of these synthetic reactions to prepare **3** and **4**, the stereochemistry at phosphorus was retained judging from the chemical shifts of C^5-H of **3** and **4** which were not moved downfield in the ^1H NMR by 1,3-diaxial effects.[6] In general, substitution reactions of halide in these five-membered cyclic systems are known to proceed with complete retention of configuration at phosphorus.[7] Table 1 shows summarized results of ^{31}P NMR chemical shifts, diastereoisomer ratios and chemical shift differences (Δδ) on ^1H NMR. The nonequivalence of the observed chemical shifts of the groups (protons underlined in Table 1) attached to the cyclophosphamide moiety could be used to assign the absolute configurations of the stereogenic centres. All products **3** and **4** given by reactions of **1** and **2** with corresponding optically active amines and alcohols were compared. The assumed configurations upon which these models depend are illustrated by structures **A** and **B** in Fig. 1. The protons of the substituents that are retained in the eclipsed configuration with the phenyl ring of *N*-phenyl group always show higher field shifts presumably due to the shielding effect of the phenyl ring. As shown in Table 1, the ^1H NMR signal of group L^1 in structure **A** appears consistently at the higher field than that of L^1 in structure **B**, whereas the signal of L^2 in structure **A** appears at the lower field than that of L^2 in structure **B**. Therefore, structures **A** and **B** possess (R_P, *R*)- and (R_P, *S*)-configurations, respectively. Diazacyclophosphamidic chloride **2** derived from (*R*)-2-(anilinomethyl)-pyrrolidine is distinctly suggested to have the opposite configuration to that of **1** on the basis of ^1H NMR of **A** and **B** (Table 1, entry 9). Even the remote stereogenic



Scheme 1



Scheme 2

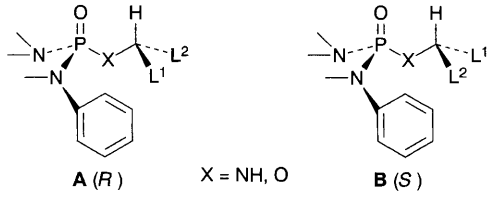


Fig. 1 Configurations of **A** and **B** ($L^1 > L^2$)

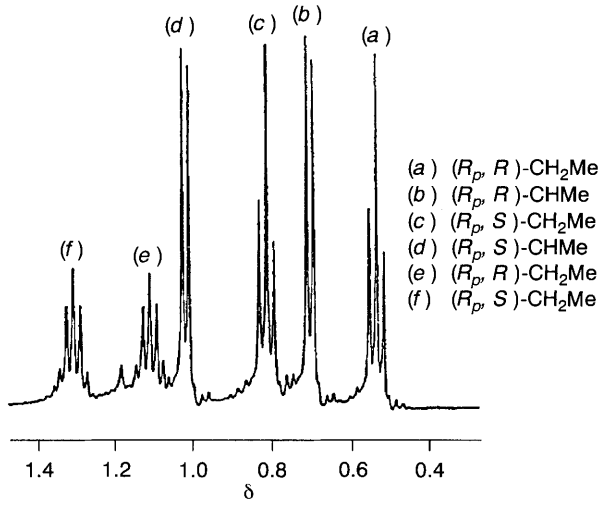
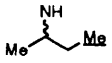
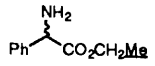
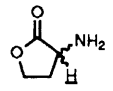
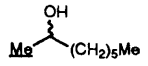
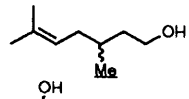
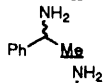
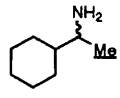


Fig. 2 ^1H NMR Spectrum of diastereoisomeric mixtures (**A** and **B**) of **3b**

Table 1 Chemical shifts and ratios of diastereoisomers on ^{31}P NMR, and chemical shift differences between the signals (protons underlined) on ^{1}H NMR of the diastereoisomers **3** and **4**[a]

Entry	Amines or[b] alcohols	Product	^{31}P NMR[c] δ A (*R*)	B (*S*)	Peak ratio (*R*)/(*S*)	^{1}H NMR Δδ B (*S*)–A (*R*)
1		**3a**	28.88	18.64	50/50	−0.17
2		**3b**	24.47	20.98	50/50	−0.28
3		**3c**	20.10	18.45	50/50	−0.13
4		**3d**				(0.25)[d]
5		**3e**	20.89	19.52	50/50	−0.10
6		**4a**	15.92	16.70	50.5/49.5	−0.01
7		**4b**	21.26	20.88	50/50	−0.05
8		**4c**	15.95	20.88	51.1/48.9	−0.97
9		**3f**	18.55	20.78	50/50	+0.17
10		**3g**	20.01	26.60	50/50	+0.32

[a] Entries 1–8 show the results of reaction with chloride **1**. Entries 9 and 10 show reaction with chloride **2**. [b] The NMR chemical shifts of **3** and **4** were compared with those of the optically active authentic reagents. [c] All spectra measured at 36.10 MHz. Chemical shift values were given with 85% phosphoric acid (δ 0.0) as the external standard with proton decoupling. Ratios were calculated based on the integrated area. [d] Chemical shift difference of the nonequivalent methyl groups of isopropyl group.

centre from the hydroxy group such as (±)-citronellol (Table 1, entry 7), structures **A** and **B** of product **4b** could be clearly discriminated and easily assigned (*R*) and (*S*) forms by the differences of chemical shifts of ^{1}H NMR of methyl groups on the stereogenic centres.

Phosphamide **3d** (Table 1, entry 4) synthesized from reaction of diazacyclophosphamidic chloride **1** with isopropylamine was subjected to measurements of ^{1}H NMR. The nonequivalent methyl groups of isopropyl group exhibited two kinds of doublets (δ 0.85 and 1.10, J_{HH} 6.8 Hz). These spectral data may be explained as follows: phosphamide **3d** forms rigid conformations and the isopropyl group shows restricted free rotation in $CDCl_3$, therefore, the shielding effect of phenyl group of diazacyclophosphamide is brought out clearly.[8] ^{1}H NMR spectrum (400 MHz) of **3b** (Table 1, entry 2) derived from chloride **1** and (±)-*sec*-butylamine, shown in Fig. 2, shows the existence of the 1 : 1 diastereoisomers.

The present results clearly demonstrate that during the reaction of diazacyclophosphamidic chlorides **1** and **2** with protic reagents forming products **3** and **4** racemization at phosphorus did not occur at all.[7]

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Footnote

† The following preparation of diazacyclophosphamide **1** is described as a typical procedure. To a solution of 2(*S*)-(anilinomethyl)pyrrolidine (5.0 g, 28.0 mmol) and triethylamine (6.0 g, 60.0 mmol) in CH_2Cl_2 (30 ml) at −78 °C was added solution of phosphorus oxychloride (4.3 g, 28.0 mmol) in CH_2Cl_2 (30 ml). The reaction mixture was stirred for 2 h and was then filtered by suction, and concentrated *in vacuo*. The resultant residue was chromatographed on a silica-gel column using ethyl acetate/hexane (1/2 *v/v*) as eluent to give analytically pure chloride **1** in 93% yield. Diazacyclophosphamidic chloride **1**: mp 117–118 °C and $[\alpha]_D^{20}$ + 117.3 (*c* 0.80, $CHCl_3$) and diazacyclophosphamidic chloride **2**: mp 117–118 °C and $[\alpha]_D^{20}$ − 117.4 (*c* 0.72, $CHCl_3$). Favoured stereochemistries at phosphorus of diazacyclophosphamidic chlorides **1** and **2** were revealed to be (R_P) by computational program PM3 of MOPAC (Stuart) and the results were further confirmed by X-ray crystallographic analyses.

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