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Synthesis of Chiral 2-Oxo- and 2-Thio-1,3,2-oxazaphospholidines via the Asymmetric Cyclization of L-Serinoates with (Thio)phosphoryl Dichlorides

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ABSTRACT: *In this article, we have described the asymmetric cyclization of L-serinoates and N-benzyl L-serinoate with phosphoro(no-)dichloridates or their thio-analog, respectively, and we have investigated the asymmetric induction effect of the chiral carbon center on the forming of a chiral phosphorus center. The diastereomeric excess percentages (de%) of the desired products 2-oxo- and 2-thio-1,3,2-oxazaphospholidines, are obtained based on their ^{31}P NMR data. In some cases, the cyclization products have been separated as pure diastereomers by column chromatography. Their configuration is preliminarily discussed.*
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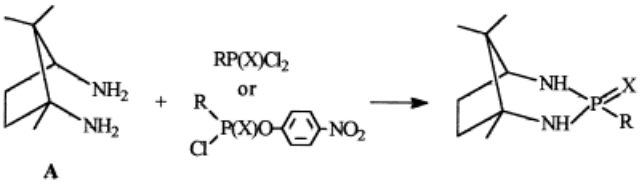
INTRODUCTION

With the purposes of pursuing new auxiliaries or ligand catalysts for asymmetric synthesis and developing some effective methods for preparation of chiral phosphorus agents, we have recently been exploring the asymmetric cyclizations of various phosphoryl chlorides and their thio-analogs with chiral diamines or amino alcohols. These chiral substrates are, in general, derived from natural products. For example, optically pure cyclopentanediamine **A,** derived from D-camphor via oxidation and amination, cyclizes with thiophosphoryl dichloride or *O*-(4-nitrophenyl) thiophosphoryl chloride to affording the expected cyclic thiophosphorodiamidates consisting of unequal amounts of diastereomeric pairs (Scheme 1) [1]. In some cases, the diastereomeric excess percentage (de%) of the major cyclization product is more than 60%, even up to 100%. The influences on such cyclization stereochemical outcome (evaluated in terms of de%) of reaction conditions and various phosphorus reagents have also been investigated.

More recently, we have described the asymmetric cyclization of L-(+)-prolinol, derived from L-proline, with phosphoryl dichlorides and their thio-analog [2]. Under appropriate conditions, L-prolinol **B** cyclizes with some selected phosphorus agents to afford products **C** with more than 80% de values (Scheme 2). In most cases, cyclization products in



A

SCHEME 1

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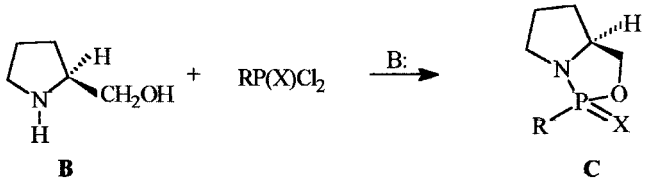


SCHEME 2

the form of unequal amounts of diastereomeric pairs can be separated readily by column chromatography or recrystallization. This provides consequently a possibility for direct preparation of chiral phosphorus reagents from diastereomerically pure **C** by stereospecific nucleophilic attack at the P–N or P–O bond.

As a continuation of our investigations, we present here some new results obtained from the asymmetric cyclizations of various phosphoryl dichlorides using L-serinoates and *N*-benzyl L-serinoate as chiral amino alcohol substrates. Products **3–8** were obtained with diastereomeric preference (Scheme 3). Their de% values were determined on the basis of ^{31}P NMR data. By the column chromatographic method, products **6–8** were successfully isolated as diastereomerically pure isomers, and their configurational assignments, were established on the basis of their spectra and specific rotations.

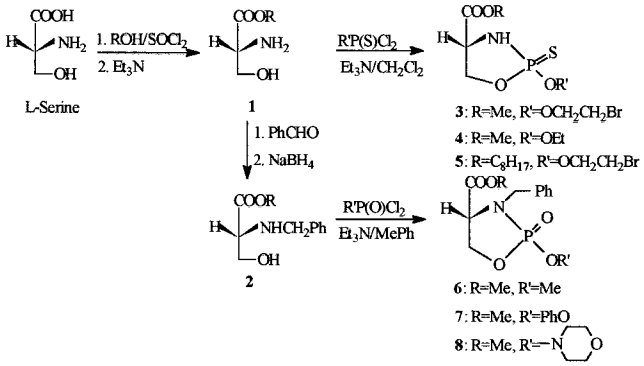
EXPERIMENTAL

^{1}H and ^{31}P NMR spectra were recorded in $CDCl_3$ as solvent on FX-90Q and AC-P200 instruments using TMS as an internal standard for ^{1}H NMR, and 85% H_3PO_4 as an external standard for ^{31}P NMR. IR-spectra were measured on a Nicolet 5DX IR-spectrometer. Elemental analyses were conducted on an MF-3 automatic analyzer. Melting points were determined on an MP-500 melting point apparatus. Optical rotations were measured on a Perkin-Elmer 241MC polarimeter. All temperatures and pressures are uncorrected. The following L-serinoates were prepared as described in the literature.

n-Octyl L-serinoate hydrochloride [3]. obtained by the reaction of L-serine with excess *n*-octyl alcohol and thionyl chloride in 88.7% yield, m.p. 72–74°C (lit. 72~73°C).

Methyl L-serinoate hydrochloride [3]. This compound was prepared by the reaction of L-serine with excess methanol and thionyl chloride in 93.5% yield, m.p. 161–163°C.

Methyl N-benzyl L-serinoate [4]. Methyl L-serinoate hydrochloride was neutralized in methanol as the solvent with triethylamine, then reacted with benzaldehyde, followed by reduction with sodium



SCHEME 3

borohydride to give the desired product in 71.8% yield, m.p. 31–33°C.

Preparations of Phosphoryl Dichlorides

O-ethyl Thiophosphorodichloridate. According to an ordinary method, this product was obtained by the reaction of thiophosphoryl chloride with excess absolute ethanol at 5–10°C in 81.0% yield, b.p. 28–30°C/26.7 Pa, n_D^{25} 1.5030.

O-(2-bromoethyl)thiophosphorodichloridate. This compound was prepared by the reaction of an equivalent of 2-bromoethanol, thiophosphoryl chloride, and triethylamine in benzene at 15–40°C in 62.8% yield, b.p. 66–68°C/26.7 Pa, n_D^{25} 1.5539.

Methylphosphonodichloride [5]. This compound was prepared by the reaction of *O,O*-dimethyl methylphosphonate with excess thionyl chloride catalyzed by anhydrous calcium fluoride under reflux for 20 hours in 92.8% yield, b.p. 36–38°C/267 Pa, m.p. 29–30°C (lit. m.p. 35°C).

O-phenyl phosphoryl dichloride [6]. This compound was obtained by the reaction of phenol with excess phosphorus oxychloride catalyzed by anhydrous sodium chloride under reflux for 6 hours in 74.1% yield, b.p. 108–112°C/267 Pa, n_D^{25} 1.5210.

Morpholinophosphoryl dichloride [7]. This compound was prepared by the reaction of morpholine, phosphorus oxychloride, and triethylamine in benzene at about 0°C in 44.6% yield, b.p. 108–110°C/66.5 Pa, n_D^{25} 1.4958. (lit. 116~120°C/270 Pa).

Preparation of Compounds **3, 4, 5**

To a solution of methyl L-serinoate hydrochloride (1.56 g, 10 mmol) in 35 mL of methylene chloride, triethylamine (3.5 g, 35 mmol) was added and the mixture was stirred at room temperature for 1 hour. Then a solution of *O*-(2-bromoethyl) thiophosphorodichloridate (2.58 g, 10 mmol) in 5 mL of methylene chloride was slowly added dropwise at 20°C. After the addition, the reaction mixture was stirred at room temperature for an additional 2–3 hours,

then washed with water (3 × 20 mL). The aqueous phase was extracted once with 20 mL of methylene chloride, and the combined organic layer was dried over anhydrous magnesium sulfate. A sample for ^{31}P NMR examination was taken from the reaction mixture to determine the de% value. After removal of the solvent, the crude product was purified by vacuum column chromatography on silica gel with elution by petroleum ether (60–90°C)/ethyl acetate to afford 2.2 g of compound **3** as a diastereomeric mixture in 72.3% yield.

Accordingly, compounds **4** and **5** were also prepared by the reactions of methyl or *n*-octyl L-serionate with the corresponding thiophosphorodichloridates as diastereomeric mixtures, respectively. Their relevant data are listed in Table 1 and Table 2.

Preparation of Compounds **6, 7** *and* **8**

To a solution of methyl *N*-benzyl L-serinoate (1.10 g, 5.0 mmol) in 30 mL of toluene, a solution of methylphosphonodichloride (0.70 g, 5.0 mmol) in 30 mL of toluene was added at room temperature, followed by triethylamine (1.10 g, 10.0 mmol). The reaction mixture was stirred at room temperature overnight. After removal of triethylamine hydrochloride by filtration, a sample for ^{31}P NMR examination was taken from the reaction mixture to calculate the de% value. Evaporation of the filtrate under reduced pressure gave the crude product **6,** which was purified and separated by column chromatography (petroleum ether:ethyl acetate as eluent) to afford two individual diastereomers: **6a,** 0.50 g; **6b,** 0.40 g, total yield 85.5%.

Similarly, compounds **7** and **8** were prepared from the corresponding phosphoryl dichlorides as a pair of individual diastereomers. Their relevant data are shown in Table 1 and Table 2.

RESULTS AND DISCUSSION

Synthesis

Thompson et al. [4] have described the cyclization of methyl *N*-benzyl L-serinoate **2** with phosphorus oxychloride to provide diastereomeric 2-chloro-1,3,2-oxazaphospholidin-2-ones, which were isolated in crude form, followed by reaction with the appropriate alcohol or phenol to give the chiral cyclic phosphoramidates in a near 1:1 diastereomeric ratio. In such cyclization reactions no asymmetric induction effect had previously been observed. In our study, L-serinoate **2** does cyclize directly with an appropriate phosphoryl dichloride with some degree of diastereomeric preference to afford the corresponding chiral cyclization products **6–8,** which can be readily separated in the form of individual diastereomers by column chromatography on silica gel. In the cyclization, the de% value of the product depends on the difference in the R′ group of the phosphoyl dichloride. However, all of the de% values are, in general, poor, and the best is only 54.7% (R′ = Me). We also attempted the cyclization of L-serinoate **1** with various phosphoryl dichlorides. Firstly, we

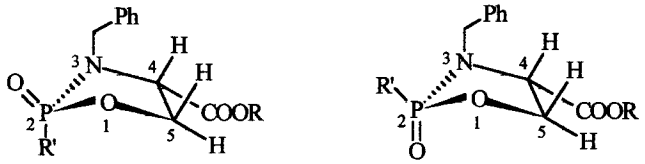
TABLE 1 Data of Compounds 3–8

						Elementary Analysis		
Compound	*m.p.* (°*C*)	$[\alpha]_D^{20}$ (*c, g/100 mL*)	^{31}*PNMR* δ (*ppm*)	*de %*	*Yield* (*%*)	*C% Calc.* (*Found*)	*H% Calc.* (*Found*)	*N% Calc.* (*Found*)
3	thick	+17.9(0.67)	85.94	21.6	72.3	23.68	3.62	4.61
	liq.		84.56			(23.88)	(3.68)	(4.46)
4	thick	−15.7(1.07)	86.03	32.6	68.7	32.00	5.33	6.22
	liq.		84.87			(31.96)	(5.05)	(6.23)
5	thick	+12.8(0.4)	84.81	62.9	61.7	38.81	6.22	3.48
	liq.		86.15			(38.60)	(6.21)	(3.70)
6a	thick	−43.6(2.35)	45.46	54.7	85.5	53.53	5.95	5.20
	liq.					(53.40)	(5.95)	(5.46)
6b	86~88	−93.8(0.80)	44.28	54.7	85.5	53.53	5.95	5.20
						(53.34)	(5.55)	(5.23)
7a	97~99	−36.2(0.76)	16.14	19.2	71.5	58.79	5.19	4.03
						(58.92)	(4.98)	(3.86)
7b	85~87	−94.0(0.70)	14.76	19.2	71.5	58.79	5.19	4.03
						(58.41)	(4.96)	(3.91)
8a	thick	−22.4(0.70)	25.83	5.6	69.4	52.94	6.18	8.24
	liq.					(52.78)	(6.12)	(7.88)
8b	85~87	−79.4(0.50)	23.64	5.6	69.4	52.94	6.18	8.24
						(52.93)	(6.36)	(8.47)

TABLE 2 ^{1}H NMR and IR of Compounds **3–8**

Compound	*^{1}HNMR, δ (ppm); $J_{P\text{-}H}$(Hz) ($CDCl_3$/TMS)*	IR(cm^{-1}), *film or KBr*			
		P=O or P=S	*P-O-C*	*P=N*	*C=O*
3	3.52 (t, 2H), 3.80 (s, 3H), 4.30 (m, 1H), 4.36 (dd, 2H, J=11.5), 4.56 (dt, 2H)	712	1006, 1119	965	1740
4	1.28 (t, 3H), 3.78 (s, 3H), 4.09 (m, 1H), 4.14 (m, 2H), 4.49 (m, 2H)	704	1029, 1119	961	1743
5	0.85 (t, 3H), 1.18 (m, 10H), 1.54 (m, 2H), 3.43 (t, 2H), 3.98 (m, 1H), 4.12 (dd, 2H, J=8.3), 4.30 (dt, 2H), J=13.3)	711	1007, 1116	967	1741
6a	1.67 (ds, 3H, J=17.2), 3.69 (s, 3H), 3.84 (m, 1H), 4.16 (dd, 1H, J=16.7), 4.41 (dd, 1H, J=15.0), 4.37 (m, 2H), 7.29 ~ 7.36 (m, 5H)	1204	1027, 1123	933	1739
6b	1.59 (ds, 3H, J=16.5), 3.73 (s, 3H), 3.80 (m, 1H), 4.24 (dd, 1H, J=16.1), 4.51 (dd, 1H, J=12.9), 4.39 (m, 2H), 7.24–7.34 (m, 5H)	1226	1048, 1118	926	1740
7a	3.59 (s, 3H), 3.86 (m, 1H), 4.24 ~ 4.37 (m, 2H), 4.54 (dd, 2H, J=16.0), 7.16 ~ 7.39 (m, 10H)	1265	1045, 1154	942	1730
7b	3.71 (s, 3H), 3.85 (m, 1H), 4.28 ~ 4.36 (m, 2H), 4.56 (dd, 2H, J=17.6), 7.13 ~ 7.33 (m, 10H)	1275	1028, 1133	929	1759
8a	3.16 (dt, 4H, J=13.7), 3.56 (t, 4H), 3.65 (s, 3H), 3.87 (dt, 1H, J=11.2), 4.05 ~ 4.22 (m, 2H), 4.42 (dd, 2H, J=12.0), 7.26 ~ 7.36 (m, 5H)	1206	1037, 1134	972	1741
8b	3.14 (dt, 4H, J=15.4), 3.60 (t, 4H), 3.71 (s, 3H), 3.86 (dt, 1H, J=9.6), 4.21 ~ 4.32 (m, 2H), 4.41 (dd, 2H, J=12.0), 7.24 ~ 7.31 (m, 5H)	1206	1028, 1133	971	1738

tried to cyclize **1** with phosphorus oxychloride or thiophosphoryl chloride, but we obtained only a viscous material as the predominant product instead of the expected cyclization product. Even by use of the phosphoryl dichloride $R'P(O)Cl_2$ as the substrate, no expected cyclization was achieved. Subsequently, we employed thiophosphoryl dichlorides $R'P(S)Cl_2$ and obtained the desired cyclization products **3–** with low de% values, the best being only 62.9% (**5**, R = C_8H_{17}, R′ = OCH_2CH_2Br). Efforts to further resolve the diastereomers of 3–5 by column chromatography on silica gel were unsuccessful. The de% comparison between products **3** and **5** seemingly indicates that the asymmetric induction effect is somewhat related to the carbon chain length of the carboxylic ester moiety in the L-serinoate **1.** The former was prepared from L-serinoate methyl ester (R = Me) and its de% value was 21.6%, whereas with L-serinoate *n*-octyl ester ($R = C_8H_{17}$), the de% value was 62.9%. At this stage, we consider that the reason for this result is obscure.



SCHEME 4

Configuration: The configuration correlations of compounds 6–8 (see Scheme 4) prepared as diastereomerically pure isomers with some spectral data and specific rotations are shown in Table 3. Bentrude et al. [8] have found that the ^{31}P NMR chemical shift correlates with the orientation of an exocyclic group on a phosphorus atom (not P=O) in 2-oxo-1,3,2-ox-

TABLE 3 The Relationship of Configuration to the Spectral and Specific Rotation Data of **6–8**

Compound	*^{31}PNMR δ (ppm)*	*IR (P=O) (v, cm^{-1})*	*$[\alpha]_D^{20}$*	*Config. (cis/trans)*	*Config. at P atom*
6a	45.46	1204	−43.6	cis	R
6b	44.28	1226	−93.8	trans	S
7a	16.14	1265	−36.2	cis	S
7b	14.75	1275	−94.0	trans	R
8a	25.83	1206	−22.4	cis	S
8b	23.64	1208	−79.5	trans	R

azaphosphorinanes; namely, when this group resides in the axial position, the chemical shift δ is less than when it resides in the equatorial position (δ_P(axial) $< \delta_P$(equatorial)). Later, Thompson et al. [4] extended this finding to a series of 2-oxo-1,3,2-oxazaphospholidines derived from L-serine and also obtained reasonable results. In the present study, this configuration correlation with the ^{31}P NMR chemical shift is also observed (Table 3). When the R′ group on the phosphorus atom is in the axial position, that is to say, R′ is trans to the carboxy ester moiety on the ring (**6b–8b**), the ^{31}P NMR chemical shift δ is more than 1 ppm less than when R′ is cis to the carboxy ester group (**6a–8a**).

Maryanoff et al. [9] have reported that, when the phosphoryl group (P=O) occupies the axial position in 2-oxo-1,3,2-dioxaphosphorinanes, its infrared stretching frequency is lower than for that in the equatorial position. Moreover, when Bentrude *et al.* [8] investigated the infrared spectra of 2-oxo-1,3,2-oxazaphosphorinanes, they noted that the infrared stretching frequency of P=O is also influenced by whether the hydrogen on the N(3) has been substituted, as well as by the orientation of the exocyclic group on the phosphorus atom. In our compounds 6–8, the substituent at the N(3) is all benzyl. Thus, the effect of this substituent on the P=O infrared frequency may be excluded. The IR frequencies of the phosphoryl group still show a good correlation with the orientation of this group. When P=O is in the axial position (**6a–8a**), its infrared frequency is lower relative to that when in the equatorial position (**6b–8b**).

The specific rotations of compounds **6–8** listed in Table 3 show that, in all cases, the *trans* isomer (R′ group on phosphorus atom is in the axial position) has a larger absolute rotation than the corresponding *cis* isomer. This result is not only consistant with the aforementioned spectral evidence, but is also consistent with Cooper's finding [10] that the 1,3,2-oxazaphospholane isomer with an exocyclic group at the phosphorus atom in the axial position has a larger absolute rotation than its counterpart with an exocyclic group in the equatorial position. Cooper's conclusion has also been demonstrated in Thompson's work.

In summary, on the basis of ^{31}P NMR δ values, the infrared stretching frequencies of the P=O group and the specific rotations, we have preliminarily assigned the configurations of the diastereomers 6–8, prepared from the asymmetric cyclization of methyl *N*-benzyl L-serinoate with appropriate phosphoryl dichlorides, and furthermore have characterized the absolute configurations of the phosphorus atom in the aforementioned diastereomers (Table 3).

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