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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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SYNTHESIS OF CHIRAL 2-OXO- AND 2-THIO-1,3,2-OXAZAPHOSPHO - LIDINES VIA THE ASYMMETRIC CYCLIZATION OF L-SERINOATES WITH (THIO)PHOSPHORYL DICHLORIDES

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Abstract: In this paper is described the asymmetric cyclization of L-serine derivatives with phosphoro(no-)dichloridates or their thio-analogues, and investigated the asymmetric induction effect of chiral carbon centre on the forming chiral phosphorus centre. Some cyclization products have been separated as a pure diastereomer and their configuration is preliminarily discussed.

With the purposes of pursuing new auxiliaries or ligand catalysts for asymmetric synthesis and developing some effective methods for preparation of chiral phosphorus agents, recently we have been exploring the asymmetric cyclizations of various phosphoryl chlorides and their thio-analogues 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 affording the expected product cyclic

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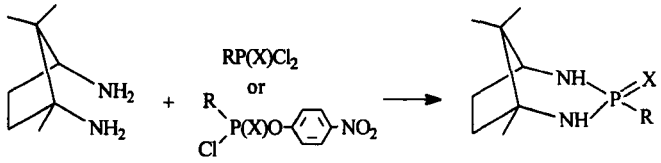
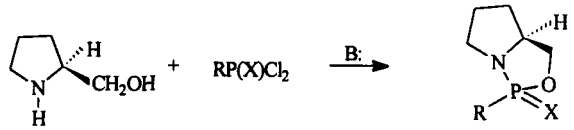
thiophosphorodiamidate consisting of unequal amounts of diastereomers[1]. In some cases, the diastereomeric excess percentage (de%) of the cyclization product is more than 60%, even up to 100%. The influences on such cyclization stereochemical outcome (evaluated in terms of de%) of reaction conditions and various phosphorus reagents have also been investigated therein.



A

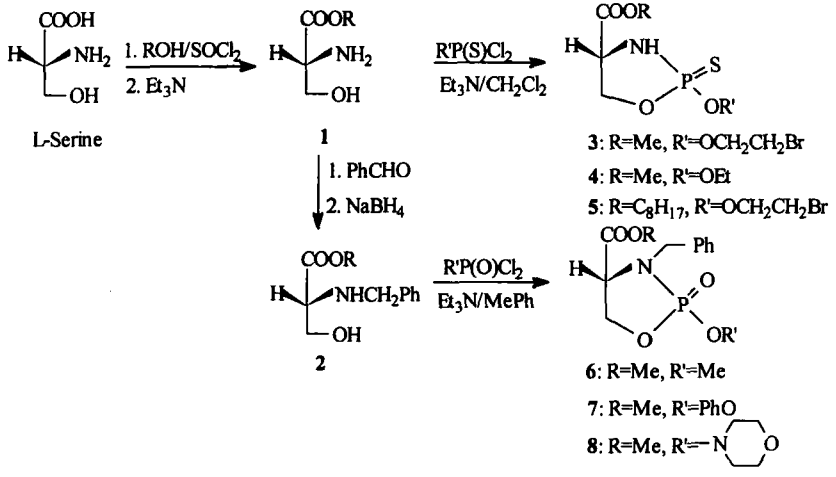
More recently we have described the asymmetric cyclization of L-(+)-prolinol, derived from L-proline, with phosphoryl dichlorides and their thio-analogues[2]. Under appropriate conditions, L-prolinol **B** cyclizes with some selected phosphorus agents to afford products **C** with more than 80% de values. In most cases, cyclization products as a pair of unequal amounts of diastereomers can be readily separated by column chromatography or recrystallization. This provides consequently a possibility for direct preparation of chiral phosphorus reagents from diastereomerically pure **C** by stereospecifically nucleophilic attack at P–N or P–O bond.



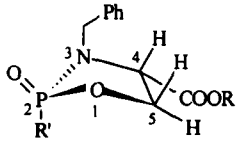
B **C**

As the 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 some certain diastereomeric preference. Their de% values were determined on the basis of diastereomeric mixture ^{31}P NMR data. By column chromatographic method, products **6** – **8**

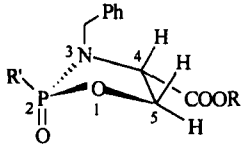
were successfully isolated as diastereomerically pure isomers, and their configurational assignment is conducted depending on their spectra and specific rotations.



From the result, it can be found that there is some degree's asymmetric induction effect of chiral carbon center on the forming chiral phosphorus center, but the de% value is not very perfect. At the same time, according to the literature method based on the data of ^{31}PNMR[8]、IR[8,9] and optical rotation[10],compounds **6a~8a** and **6b~8b** should be cis and trans form respectively. Thus, the phosphorus conformation in these compounds can be preliminarily established. Their related data are shown in Table 1 and 2.



cis- **6a**
7a
8a



trans- **6b**
7b
8b

Experimental

^{1}H and ^{31}P NMR were recorded in $CDCl_3$ as solvent on FX-90Q and AC-P200 instruments

Table 1.The data of Compds. **3~8**

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

Table 2. The relationship of Configuration to the Spectro and Specific Rotation data of **6~8**

Compd.	^{31}PNMR δ (ppm)	IR(P=O) (ν , cm^{-1})	$[\alpha]^{20}_D$	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

using TMS as internal standard for ^{1}H NMR, and 85% H_3PO_4 as external standard for ^{31}P NMR. IR-spectra were measured on Nicolet 5DX IR-spectrometer. Elemental analyses were conducted on MF-3 automatic analyzer. Melting points were determined on MP-500 melting point apparatus. Optical rotations were measured on a Perkin-Elmer 241MC polarimeter. All temperatures and pressures were uncorrected.

1. The following L-serinoates were prepared as described in literatures.

n-Octyl L-serinoate hydrochloride[3]: obtained from the reaction of L-serine with excess n-octyl alcohol and thionyl chloride in 88.7% yield, m.p. 72–74 °C.

Methyl L-serinoate hydrochloride[3]: prepared from 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 solvent with triethylamine, then reacted with benzaldehyde, followed by reduction with sodium borohydride to give the desired product in 71.8% yield, m.p. 31–33 °C.

2. Preparations of phosphoryl dichlorides used in the present study

O-ethyl thiophosphorodichloridate: according to an ordinary method, obtained from 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^{25}_D 1,5030.

O-(2-bromoethyl) thiophosphorodichloridate: according to a general procedure, prepared from the reaction of equivalent 2-bromo ethanol, thiophosphoryl chloride and triethylamine in benzene at 15 – 40 °C in 62.8% yield, b.p. 66–68 °C / 26.7 Pa , n^{25}_D 1.5539.

Methylphosphonodichloride[5]: prepared from the reaction of O,O-dimethyl methylphosphonate with excess thionyl chloride catalyzed by anhydrous calcium fluoride under reflux for 20 h in 92.8% yield, b.p. 36 – 38 °C / 267 Pa, m.p. 29–30 °C.

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

Morpholinophosphoryl dichloride[7]: prepared from 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^{25}_D 1.4958.

3. 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 stirred at room temperature for 1 h. Then a solution of O-(2-bromoethyl) thiophosphorodichloridate (2.58 g, 10 mmol) in 5 mL of methylene chloride was slowly dropwise added at 20 °C. After addition, the reaction mixture was stirred at room temperature for additional 2–3 h, 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 test was taken from the reaction mixture to determine de% value. After removal of solvent, the crude product was purified by vacuum column chromatography on silica gel eluted with 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 from the reactions of methyl or n-octyl L-serinoate with the corresponding thiophosphorodichloridates as diastereomeric mixtures, respectively. Their related data are listed in Table 1 and Table 2.

4. 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 was stirred at room temperature overnight. After removal of by-product triethylamine hydrochloride by filtration, a sample for ^{31}P NMR test was taken from the reaction mixture to calculate de% value. Evaporation of the filtrate under reduced pressure gave the crude product **6**, which was purified and resolved 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 related data are shown in Table 1 and Table 2.

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