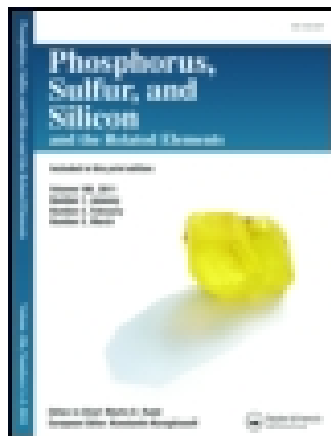


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STUDIES ON CHIRAL THIOPHOSPHORIC ACIDS AND THEIR DERIVATIVES 14. THE ASYMMETRIC CYCLIZATION OF (+)-CIS-1,2,2-TRIMETHYL-1,3-DIAMINOCYCLOPENTANE WITH THIOPHOSPHORODICHLORIDATES AND O-(4-NITROPHENYL)THIOPHOSPHOROCHLORIDATE

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STUDIES ON CHIRAL THIOPHOSPHORIC ACIDS AND THEIR DERIVATIVES 14. THE ASYMMETRIC CYCLIZATION OF (+)-CIS-1,2,2-TRIMETHYL-1,3- DIAMINOCYCLOPENTANE WITH THIOPHOSPHORODICHLORIDATES AND O-(4- NITROPHENYL)THIOPHOSPHOROCHLORIDATES

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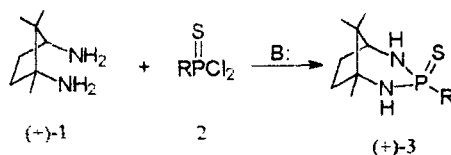
(Received January 10, 1996; in final form March 11, 1996)

The cyclization of (+)-cis-1,2,2-trimethyl-1,3-diaminocyclopentane **1** with thiophosphorodichloridates **2** or O-(4-nitrophenyl)thiophosphorochloridates **4** forms (+)-2,4,5-diazaphosphabicyclo[3.2.1]octane **3** and **3'**, respectively, but the stereoselectivity arising from the condensation of (+)-**1** with **4** is less than that of (+)-**1** with **2**. The distinction between the two product distributions might be due to the significance of different mechanistic routes. In the light of a trigonal bipyramid (TBP) intermediate and Berry pseudorotation (BPR) concept their mechanism are discussed.

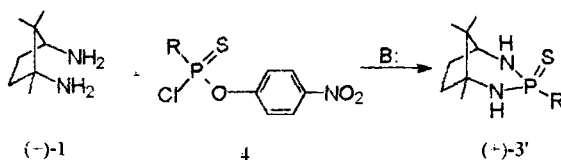
Key words: Asymmetric cyclization, diastereoisomer, diaminocyclopentane, thiophosphorodichloridate, thiophosphorochloridate, diazaphosphabicyclooctane.

1. INTRODUCTION

It was reported previously that (+)-cis-1,2,2-trimethyl-1,3-diaminocyclopentane **1** derived from D-camphor reacts with thiophosphorodichloridates **2** to form a diastereoisomeric mixture of (+)-2,4,5-diazaphosphabicyclo[3.2.1] octane **3**.¹



Recently, we found that the cyclization of (+)-**1** with O-(4-nitrophenyl)thiophosphorochloridates **4** can also take place and give a different distribution of the same diastereoisomers **3'**.

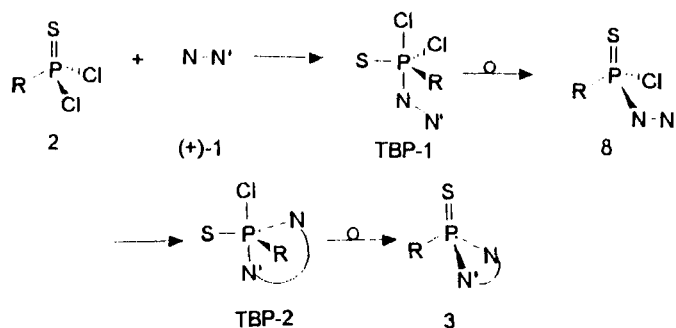


In this paper, the difference in stereochemical outcome between the rationalization of cyclization of (+)-1 with phosphorus agent 2 and that of (+)-1 with phosphorus agent 4 has been attempted.

2. RESULTS AND DISCUSSION

The cyclizations of (+)-1 with 2 or 4 were performed in the presence of triethylamine at 55–60°C for 8 h in chloroform solvent. The crude products 3 or 3' were purified by vacuum liquid chromatography (VLC) on silica gel followed by recrystallization. The diastereomeric ratios of 3 and 3' were determined by ³¹P NMR, then the %de were calculated from the intensities of the ³¹P NMR resonances (Table I). In addition, a pair of diastereoisomers of 3_a' were successfully isolated by VLC and gravity column chromatography on silica gel. The distinction between the two reactions might be caused by the different mechanisms involved. It is discussed in the light of a trigonal bipyramid (TBP) intermediate and the Berry pseudorotation (BPR) concept.²⁻⁴

In compound 2 two leaving groups are chlorine atoms, which have not only very good leaving activity, but also very good apicophilicity. When (+)-1 reacts with 2, nucleophilic attack of nitrogen atom (N) in (+)-1 always occurs at phosphorus opposite a chlorine atom to form the TBP-1 intermediate resulting in N and Cl each occupying an apical position. When the Cl atom departs from the apical position the TBP-1, breaks down giving product 8 with inversion of configuration. In 8 an intramolecular attack of another nitrogen atom (N') at phosphorus leads to the formation of the TBP-2, and then another Cl departs from the apical position to give the product 3 with inversion of configuration. The total stereochemical process of two-step reactions should be retention of configuration at phosphorus.

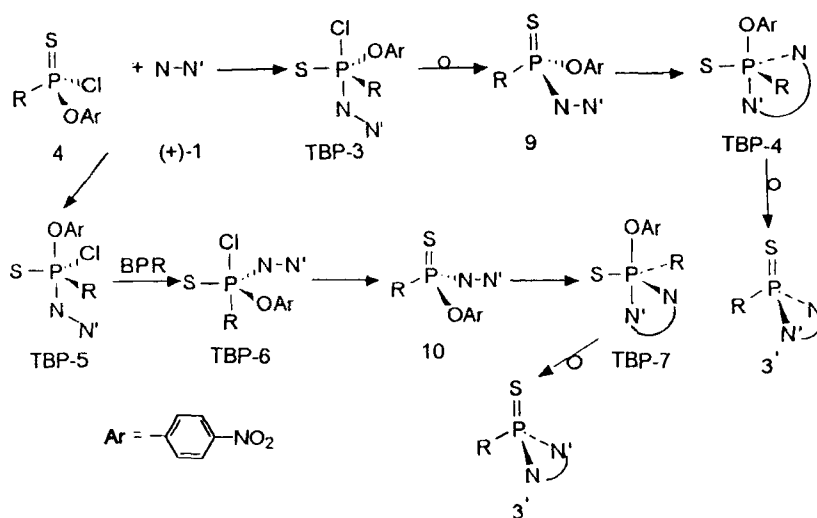


In compounds 4 there are also two leaving groups, chlorine atom and ArO group. Generally, chlorine has very close apicophilicity with ArO,⁵ but it is a better leaving group than ArO. For making a comparison between leaving activity of Cl and ArO, we tested the reaction of (+)-1 with O-ethyl O,O-di(4-nitrophenyl)thiophosphate 4_a, but no reaction took place. Since the reactions of (+)-1 with 2 or 4_{a-c} can proceed smoothly due to Cl or Cl and ArO as leaving groups, while the reaction of (+)-1 with 4_a can not. This fact indicates that this ArO is a less readily leaving group than Cl. Thus, when the reaction of (+)-1 with 4, there are two possible tendencies in the attack of N at phosphorus.

TABLE I
Data of **3** and **3'** prepared

Compound	R	mp (°C)	³¹ P NMR (ppm)	Yield (%)	de (%)	IR, (cm ⁻¹)		P-O-C (P-S-C)	C %		Elem. Analy. H %		N %	
						N-H	P-N		Calc.	Found	Calc.	Found	Calc.	Found
3a	EtO	142-145	68.29 65.54	48.2	60	3209	949	1149 1038	48.37	48.50	8.52	8.45	11.28	10.99
3b	PhO	103-104	66.19	51.1	100	3228	965	1200 913	56.74	56.50	7.14	6.98	9.45	9.31
3c	PrO	125-127	67.30 64.48	54.0	80	3217	991	1049	50.36	50.86	8.84	9.09	10.68	10.47
3'a	EtO	140-143	68.29 65.44	46.9	23	3265	971	1153 1034	48.37	48.38	8.52	8.58	11.28	10.97
3'b	PhO	100-102	65.87 60.52	34.7	4	3220	971	1201 905	56.74	56.60	7.14	7.09	9.45	9.15
3'c	PrS	88-91	78.75 70.13	56.6	8	3220	969	602	47.46	47.72	8.33	8.72	10.06	9.85

Firstly, attack of N initially occurs opposite Cl to form the TBP-3 intermediate, in which N and Cl both occupy the apical positions. When Cl departs from the apical position, the product **9** with inversion of configuration at phosphorus is obtained. Then, attack of another nitrogen (N') in **9** occurs opposite ArO forming the TBP-4, which breaks down and the product **3'** with inversion of configuration is obtained. The total stereochemical process of two-step reactions should also be retention of configuration at phosphorus. This stereochemical result is the same as that of the reaction of (+)-**1** with **2**. Secondly, attack of N initially occurs opposite ArO to form the TBP-5. Since ArO is a poorer leaving group than Cl, it can not depart from the apical position in the TBP-5. Only after the TBP-6 is formed by ligand reorganization of the TBP-5 via a single BPR can Cl then possibly attain the apical position, and departs from the apical position to give product **10** with retention of configuration. Then, attack of N' in **10** takes place opposite ArO to form the TBP-7. When ArO departs from the apical position, the TBP-7 breaks down and product **3'** with inversion of configuration is obtained. The total stereochemical process of two-step reactions should be inversion of configuration.



To sum up, in the reaction of (+)-1 with 2 there is retention of configuration only, but in the reaction of (+)-1 with 4 there are two possibilities, retention and inversion of configuration. Thus, the diastereoselectivity of the former is better than the latter.

EXPERIMENTAL

Melting points were determined with Yanaco MP-500 apparatus. ¹H and ³¹P NMR spectra were measured in CDCl₃ on a JEOL FX-90Q instrument at 90 MHz, using TMS as internal standard and 85% H₃PO₄ as external standard. IR spectra were recorded on Shimadzu IR-435 spectrophotometer as thin film or KBr tablet. Optical rotations were measured on a Perkin-Elmer 241MC polarimeter. All temperatures were uncorrected.

Preparation of (+)-cis-1,2,2-trimethyl-1,3-diaminocyclopentane 1: As described previously in the literature.⁶ D-camphor was oxidized with nitric acid to give (+)-1,2,2-trimethyl-1,3-cyclopentanedicarboxylic acid, which was then treated with sodium azide to produce (+)-1.

Preparation of thiophosphorodichloridates 2: According to general method, thiophosphoryl chloride reacted with equivalent amounts of alcohol, phenol or mercaptan in organic solvent to give 2 conveniently. Data of 2 prepared are listed in Table II below.

Preparation of O-(4-nitrophenyl) thiophosphorochloridates 4 and O-ethyl O,O-di(4-nitrophenyl)thiophosphate 4 d: Using an ordinary method, compounds 2 condensed with *p*-nitrophenol in the presence Et₃N to afford 4, which were purified by column chromatography on silica gel. Data of 4 prepared are listed in Table III below.

Cyclization of (+)-1 with 2 a (Typical procedure): To a mixture of (+)-1 (2.20 g, 15.5 mmol), Et₃N (3.00 g, 29.7 mmol) and CHCl₃ (40 mL) a solution of 2_a (1.20 g, 6.7 mmol) in CHCl₃ (10 mL) was added dropwise with stirring at 15°C. The reaction mixture was heated at 55–60°C for 8 h, then cooled to room temperature, washed with water (15 mL) and dried. After removal of solvent, the residue was preliminarily purified by VLC on silica gel (300–400 mesh, petroleum ether/EtOAc gradient elution) to give crude product 3 (2.0 g), which was then recrystallized by using a mixture solvent (10 mL of petroleum ether and 1 ml of acetone) to afford white solid product 3 with m.p. 142–145°C; yield: 0.8 g (48.2%).

Cyclization of (+)-1 with 4_a (Typical procedure): To a mixture of (+)-1 (2.0 g, 15.5 mmol), Et₃N (3.00 g, 29.7 mmol) and CHCl₃ (30 mL) a solution of 4_a (1.20 g, 4.3 mmol) in CHCl₃ (20 mL) was added dropwise with stirring at 15°C. The reaction mixture was heated at 55–60°C for 8 h. After workup and purification similar to the above experiment. White solid product 3'_a with m.p. 140–143°C was obtained; yield: 0.5 g (46.9%).

Separation of a pair of diastereoisomers in 3'_a: The reaction mixture, which obtained from the above reaction of (+)-1 with 4_a, was preliminarily purified by VLC on silica gel (300–400 mesh, petroleum ether/EtOAc gradient elution), and was further isolated by gravity column chromatography on silica gel

TABLE II

2	R	bp (°C/mm)	n _D ²⁵	Yield (%)
a	EtO	66-68/20	1.5024	87.0
b	PhO	82-84/0.5	1.5740	74.5
c	PrO	42-44/4	1.5165	82.3
d	PrS	93-96/1.5	1.5756	49.0

TABLE III

4	R	mp(°C) or n _D ²⁵	Yield (%)	¹ H NMR, δ(ppm), J _{PH} (HZ)
a	EtO	1.5582	48.5	1.52(t, 3H), 4.44(dq, 2H, J=10.8), 7.84(m, 4H)
b	PhO	50-51	24.3	7.34(m, 5H), 7.87(m, 4H)
c	PrO		28.0	1.08(t, 3H), 1.86(m, 2H), 3.22(dt, 2H, J=18.0), 7.91(m, 4H)
d	PrS	115-118	36.6	1.46(t, 3H), 4.44(dq, 2H, J=10.8), 7.92(m, 4H)

TABLE IV

No.	Weight (g)	³¹ P NMR δ(ppm)	mp(°C)	[α] _D ²⁰	Elemental Analysis					
					C%		H%		N%	
					Calc.	Found	Calc.	Found	Calc.	Found
1	0.4	67.30	142-144	+14.4 (c=1.80, CHCl ₃)	48.37	48.34	8.52	8.22	11.28	10.99
2	0.2	64.48	143-145	+21.1 (c=1.32, CHCl ₃)	48.37	48.51	8.52	8.38	11.28	10.95

(200–300 mesh, petroleum ether/EtOAc, 5:1 (V/V), as eluent) to give two fraction, No. 1 and 2. Their data are listed in Table IV.

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