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GRIGNARD REACTION OF 2-PHENYL-TETRAHYDROPYRROLO-1,3,2-OXAZAPHOSPHOLES, OBSERVATION OF THE STEREOSPECIFIC INVERSION OF CONFIGURATION

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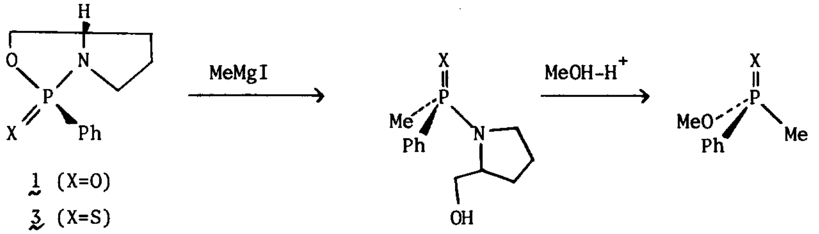
Summary: Grignard reaction of bicyclic oxazaphospholes proceeded with inversion of configuration to provide chiral phosphinic esters of known absolute configurations.

The reaction of carbanions such as Grignard reagents with phosphorus esters has been well established to cause the phosphorus-carbon bond formation with inversion of configuration.[1)] Recently, Inch et al.[2)] reported that the reaction of 1,3,2-oxazaphosphole-2-sulfide with phenyl lithium proceeded with complete retention of configuration. Here we describe a contrasting result which reveals that Grignard reaction of bicyclic oxazaphospholes proceeds with inversion of configuration. In a preceding paper[3)] we have described the preparation and the absolute configurations of the diastereomeric bicyclic oxazaphospholes **1**~**4**. When **1** was treated with MeMgI (2 equiv) in THF at room temperature for 3 h, the corresponding amidate, P-O fission product, was obtained almost quantitatively. The compound without further purification was subjected to protic acid-catalyzed methanolysis (0.1 M H_2SO_4-MeOH, reflux for 1 h) to afford (+)-$(R)_P$ methyl methylphenylphosphinate, bp 90-95°/0.04 Torr, $[\alpha]_D^{28}$ +45.2° (c 3.7, MeOH),[4)] ee 92 %, in 56 % overall yield.



1 (X=O)
3 (X=S)

The diastereomer **2** also yielded (-)-$(S)_P$ methyl methylphenylphosphinate, bp 90-95°/0.04 Torr, $[\alpha]_D^{17}$ -36.0° (c 1.1, MeOH), ee 73 %, in 32 % overall yield. Similarly the diastereoisomeric oxazaphosphole-2-sulfide **3** and **4** afforded after methanolysis (0.2 M H_2SO_4-MeOH, reflux for 2 h) (+)-$(S)_P$ methyl methylphenylthiophosphinate, bp 90-95°/0.04 Torr, $[\alpha]_D^{24}$ +34.2° (c 1.8), ee ~99 %, and (-)-$(R)_P$ methyl methylphenylthiophosphinate, bp 90-95°/0.04 Torr, $[\alpha]_D^{24}$ -27.7° (c 1.8), ee >84 %, in 78 % and 71 % yields respectively.[5)] Since the protic acid-catalyzed methanolysis was established to proceed with inversion of configuration,[6)] the stereochemistry of the Grignard reaction should be concluded to be the stereospecific inversion of configuration which is a good contrast to that of monocyclic oxazaphospholes.[2] It is quite interesting that the reaction of bicyclic oxazaphospholes is different from that of the monocycles in two respects, position of the bond fission (base-catalyzed solvolysis in the preceding paper) and the stereochemical course (Grignard reaction). To elucidate whether the difference could be attributed to the intrinsic nature of the bicyclic oxazaphospholes in general or the special characteristics of the 5/5 fused ring system itself, further stereochemical investigations using various oxazaphospholes are required.

As it had been found that the reaction with MeMgI proceeded in high degree of stereospecificity, we then carried out the reaction of **1** and **2** with sevaral Grignard reagents. The results after the acid-catalyzed methanolysis are summarized in Table. The optical purities of these phosphinates may be comparable[7] with that of methyl methylphenylphosphinate considering the stereospecificity of the above reactions. Thus, the Grignard reaction of the bicyclic oxazaphospholes would provide a convenient route for the preparation of chiral phosphinates of known absolute configurations.

Table Grignard Reactions of the Bicyclic Oxazaphosphole-2-oxides

Starting oxazaphospholes	Grignard reagent (RMgX)	Phenylphosphinate Ph-P(O)(R)(OMe)		
		Yield (%)	$[\alpha]_D$	(c, temp)
1	EtMgBr	63	+41.8°	(1.7, 19°)
2	EtMgBr	41	-40.1°	(1.7, 18°)
1	$CH_2=CHCH_2MgBr$	60	+13.5°	(1.2, 16°)
2	$CH_2=CHCH_2MgBr$	49	-15.8°	(1.2, 18°)
1	o-MeO-PhMgBr	44	+4.6°	(0.9, 14°)
2	o-MeO-PhMgBr	43	-8.3°	(0.9, 15°)

References and Notes

1) a) O. Korpiun, R. A. Lewis, J. Chikos, and K. Mislow, *J. Amer. Chem. Soc.*, **90**, 4842(1968).
   b) R. A. Lewis, and K. Mislow, *Ibid.*, **91**, 7009(1969).
2) C. R. Hall, T. D. Inch, and I. W. Lawston, *Tetrahedron Lett.*, **1979**, 2729.
3) T. Koizumi, R. Yanada, H. Takagi, H. Hirai, and E. Yoshii, Preceding paper.
4) All compounds isolated were purified by the microdistillation (bath temperature is described) and gave satisfactory elemental analyses and spectral data. Optical rotations were measured in CCl_4 unless otherwise noted.
5) The reaction of **3** with methyl lithium followed by the acid-catalyzed methanolysis also afforded (+) methyl methylphenylthiophosphinate, $[\alpha]_D^{21}$ +30.9°(c 1.8) in 61.4 % yield.
6) a) T. Koizumi, Y. Kobayashi, and E. Yoshii, *Chem. Pharm. Bull.*, **24**, 834(1976).
   b) T. Koizumi, Y. Kobayashi, and E. Yoshii, *Heterocycles*, **9**, 1723(1978).
7) The specific rotations of these compounds are unknown and the chiral shift reagent method was not effective.

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