

## Synthesis of Asymmetric 4H-1, 3, 2-Benzodioxaphosphorin 2-Sulfides from Intramolecular Cyclization Reaction

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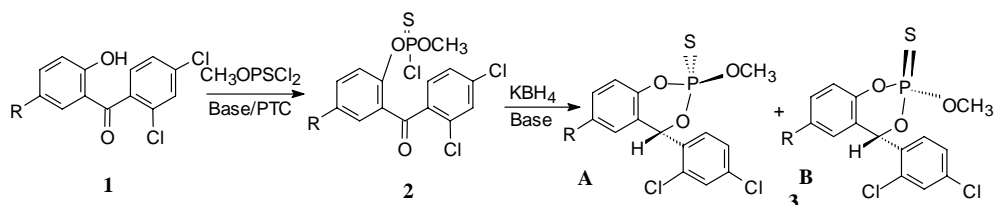
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**Abstract:** Asymmetric 6-substituted-2-methoxy-4-(2,4-dichlorophenyl)-4H-1,3,2-benzodioxaphosphorin 2-sulfides were prepared from intramolecular cyclization. The diastereomers were separated by column chromatography and fractional crystallization. Their structures were characterized on the basis of  $^1\text{H}$  NMR,  $^{31}\text{P}$  NMR and x-ray diffraction analysis.

**Keywords:** 4H-1,3,2-benzodioxaphosphorin, diastereomer, intramolecular cyclization reaction.

A variety of biological activities of some 4H-1,3,2-benzodioxaphosphorin 2-sulfides have been reported, for example the insecticide Salithion<sup>1</sup>. The cyclic phosphonothionates have been prepared by intermolecular condensation of phosphorodichloridithioates with salicylalcohol or its derivatives in the presence of a base<sup>2</sup>, and by intramolecular cyclization reaction of the salicylal as the starting material<sup>3</sup>. However, the intramolecular cyclization reaction of the 2-hydroxybenzophenones and stereochemical studies have not been reported. We now describe a new synthesis of 6-substituted-2-methoxy-4-(2,4-dichlorophenyl)-4H-1,3,2-benzodioxaphosphorin 2-sulfides **3** as a mixture of diastereomers from 5-substituted-2-hydroxybenzophenones **1** (Scheme 1). The intermediates **2** were not purified. These products were obtained with satisfactory yields and simple procedure. Three couples diastereomers of the compounds **3** were separated by column chromatography on silica gel and fractional crystallization. The A- and B-isomer of the cyclicphosphonothionates were assigned by  $^1\text{H}$  NMR and  $^{31}\text{P}$  NMR (Table 1). A comparison of the spectra of A and B showed clearly a regularity in chemical shift of two kinds of isomers. These mixtures of **3** diastereomers are A:B=2:3, which were judged from  $^1\text{H}$  NMR and  $^{31}\text{P}$  NMR. The x-ray diffraction analysis indicated that S and 2, 4-dichlorophenyl of **3a-A** were *cis* oriented and its relative configuration was (2R, 4S; 2S, 4R)<sup>4</sup>, from which the relative configuration of the B-isomer can be deduced to be (2R, 4R; 2S, 4S).

Scheme 1



**Table 1** Physical properties and data of  $^1\text{H}$  NMR and  $^{31}\text{P}$  NMR of the compounds 3

Comp.	R	Yield	Isomer	$R_f^*$	m.p. ( $^{\circ}\text{C}$ )	$^1\text{H}$ NMR	$^{31}\text{P}$ NMR
3a	CH <sub>3</sub>	69.3%	A	0.49	98~100	6.36 (s, 4-H), 3.90 (d, -OCH <sub>3</sub> )	59.44
			B	0.44	83~84	6.41 (s, 4-H), 3.79 (d, -OCH <sub>3</sub> )	60.99
3b	Cl	55.6%	A	0.49	109~110	6.55 (d, 4-H), 3.92 (d, -OCH <sub>3</sub> )	58.87
			B	0.45	80~82	6.60 (d, 4-H), 3.82 (d, -OCH <sub>3</sub> )	60.66
3c	H	53.8%	A	0.47	94~95	6.59 (d, 4-H), 3.92 (d, -OCH <sub>3</sub> )	59.35
			B	0.43	73~74	6.63 (d, 4-H), 3.80 (d, -OCH <sub>3</sub> )	60.92

\* petroleum ether : ethyl acetate=10:1

All these isomers were being tested for biological activities. The preliminary bioassays indicated that the insecticide activity of A-isomer was higher than B-isomer.

#### General procedure:

A solution of potassium hydroxide (5%, 5.3mmol) containing PTC ( $\text{Bu}_4\text{NBr}$ , 30mg) was added dropwise to a mixture of 5-substituted-2-hydroxybenzophenone **1** (5mmol) and O-methyl phosphorodichloridothioate (5.5mmol) in toluene at  $0\sim 2^{\circ}\text{C}$ . After stirring for 6 h. at r.t., the organic layer was separated, washed with water, and a solution of **2** was obtained. A solution of  $\text{KBH}_4$  (7mmol) dissolved in 0.1mol/L KOH (15ml) was added dropwise to the solution of **2** with stirring for 8 h. at r.t.. The organic phase was washed with water, then dried. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel to get a mixture of **3** as A- and B-isomer.

The separation of the diastereomers was accomplished by fractional crystallization (petroleum ether : ethyl acetate =10:1)

#### Acknowledgment:

This project was supported by the Natural Science Foundation of Tianjin (983602711).

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4. The figure of the stereo structure of **3a-A** molecule have been deposited in the editorial office of CCL

Received 20 January 1999