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ENANTIOPURE ATROPISOMERIC PHOSPHOROTHIOATES AND PHOSPHOROTHIOAMIDATES

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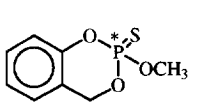
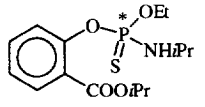
Abstract: The straightforward preparation and resolution of phosphorothioates and phosphorothioamidates from 1,1'-biphenyl-2,2'-diol **1** and 1,1'-binaphthalene-2,2'-diol **2** are described. Basic alcoholysis of phosphorothioamidate of 1,1'-binaphthalene-2,2'-diol **6b** and **6c** is highly stereoselective and gives only one diastereomer.

Phosphorothioates and phosphorothioamidates have a large applicability as agrochemicals[1]. They exhibit acetylcholinesterase (AChE) inhibition and they can be effectively used for controlling insects[2-5]. Although a variety of synthetic procedures has been investigated with the aim of obtaining organophosphorus compounds, few examples concern the preparation of chiral non racemic phosphorothioates and phosphorothioamidates[6-9]. Moreover, very little has been reported on the preparation of chiral, non racemic, O-aryl phosphorothioate and their anologues[3,10]. The high activity of salathion[2] and isofenphos[3] , two chiral insecticides, encourages the synthesis of analogous derivatives since each enantiomer exhibits different insecticidal activities.



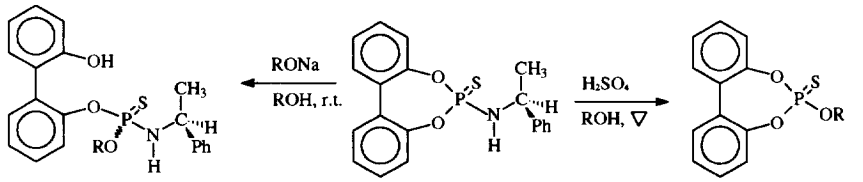
salathion



isofenphos

We have investigated the reactivity of enantiopure phosphorothioamidates of 2,2'-biphenol **1** and enantiopure phophorothioates and phosphorothioamidates of 1,1'-binaphthalene-2,2'-diol **2** towards acid and basic alcoholysis. We determined the transfer of chirality at the phosphorus atom since its chirality can have a significant effect on the biological activity[8].

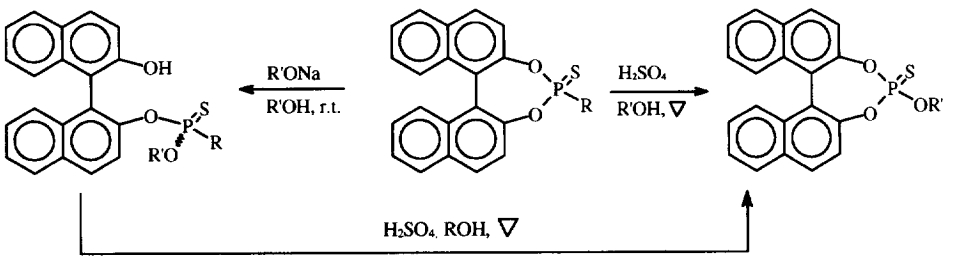
Reaction of the diol **1** with equimolar quantities of thiophosphoryl chloride and (S)-(-)-α-methylbenzylamine in pyridine gives, in virtually quantitative yield, the enantiopure phosphorothioamidate **3**.



5a R = CH_3 **3** **4a** R = CH_3
5b R = C_2H_5 **4b** R = C_2H_5

When phosphorothioamidate **3** was subjected to methanolysis or ethanolysis in the presence of refluxing 4M H_2SO_4, alkylarylphosphorothioates **4a** and **4b** have been obtained in quantitative yield. Esters **4** lose the chirality and although the structure is cyclic and twisted there is not a sufficient energy barrier of rotation to avoid racemization at room temperature. (This interconversion has been checked on compound **3** until -50 °C *via* NMR spectroscopy). Basic alcoholysis of compound **3** led to P-O bond cleavage and contemporary ring opening. For example acyclic phosphorothioamidates **5a** and **5b** have been obtained in satisfactory yield by treatment of cyclic derivative **3** with one equivalent of sodium alkoxide in alcohol at room temperature. Since the cleavage leads to a stereogenic phosphorus atom, this allows two possible diastereomers to be obtained. Indeed, P-O cleavage of phosphorothioamidate **3** gave the two diastereomers in nearly 1:1 ratio which has been measured by NMR spectroscopy. All diastereomers produced are solid, sufficiently stable and easly separated and purified by flash-chromatography.

Phosphorothioamidate **6c**[11] showed low reactivity toward the above acid-catalyzed alcoholysis and compounds **7a** and **7b** have been produced in very poor yield. Higher concentration of acid and longer reaction time did not change the product composition. It should be noticed the poor solubility of compound **6c** in H_2SO_4/MeOH solution.



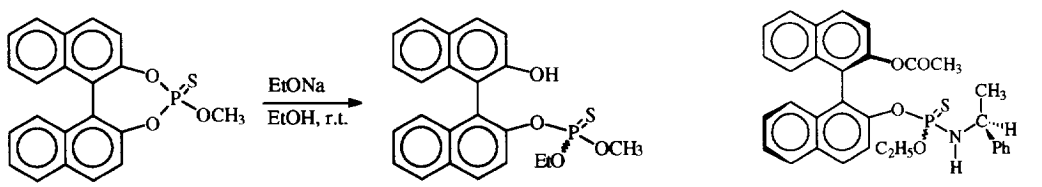
8 R = -N(C_2H_5)$_2$ R' = -CH_3
9 R = -NHCH_2Ph R' = -C_2H_5
10a R = (S)-NHCH(CH_3)Ph R' = -CH_3
10b R = (S)-NHCH(CH_3)Ph R' = -C_2H_5

6a R = -N(C_2H_5)$_2$
6b R = -NHCH_2Ph
6c R = (S)-NHCH(CH_3)Ph

7a R' = -CH_3
7b R' = -C_2H_5

Following the same procedure described above, phosphorothioamidates **6a** and **6b** was prepared starting from racemic diol **2** and using diethylamine and benzylamine as amine, respectively. Basic alcoholysis of phosphorothioamidates **6** induced P-O cleavage and ring opening. In the presence of one equivalent of sodium methoxide in alcohol at room temperature, compound **6a** gave a 6:4 mixture of diastereomers **8** whereas the reaction is highly stereoselective for diastereopure compound **6c.** Only one diastereomer **10a** and **10b** has been obtained in the presence of sodium methoxide and sodium ethoxide in alcohol, respectively.

The same stereoselectivity has been observed when a mixture 1:1 of diastereomers **6c** (starting from a mixture 1:1 of (R)-(+) and (S)-(+) diol **2**) have been treated either with sodium methoxide in methanol or sodium ethoxide in ethanol at room temperature. Only two of the four diastereomers, **10a** (**10b**) have been obtained in 1:1 ratio and in virtually quantitative yield. Satisfactory yield but low stereoselectivity have been observed for racemic phosphorothioate **7a** under basic alcoholysis conditions. Acyclic phosphorothioamidate **11** has been obtained in 6:4 ratio.



7a **11** **12**

In order to understand better the chiral contributions of both the binaphthyl and the amine skeletons we treated phosphorothioamidate **6b** with sodium ethoxide in ethanol at room temperature. As for phosphorothioamidate **6a** the chirality is restricted to the binaphthyl structure but, in this case, compound **6b** has a secondary nitrogen. Only one diastereomer **9** has been obtained from racemic **6b** showing that the presence of the hydrogen atom bonded to the nitrogen may play a role in determing the stereochemistry of the product.

The hydroxyl group of acyclic phosphorothioamidates can be readily acylated in the presence of refluxing acetyl chloride using triethylamine as solvent. Diastereomers **12** have be produced in virtually quantitative yield starting from diastereomers **10b**. Enantiopure cyclic phosphorothioates **7a** and **7b** have been prepared in quantitative yield by treatment of each diastereopure **10a** and **10b** with H_2SO_4 in refluxing methanol and ethanol, respectively. α-Methylbenzylamine has been recovered without lose of enantiomeric purity.

No thiono-thiol transposition was found at any reaction step or if so, it was not there in any significant amount.

Despite their chemical and biological importance, the stereochemical course of acid-catalyzed P-N bond cleavage of phosphoramidates has not been studied systematically in the literature and A-2 mechanism with inversion of configuration at phosphorus has been accempted without any stereochemical evidence[12-20]. In our case both of compounds **7a** and **7b** do not have a chiral phosphorus atom since a C_2 symmetry axis goes through it. Although racemic esters **7** have been already prepared starting from diol **2** *via* binaphthylthiophosphoric chloride[21], our method allows to obtain enantiopure **7** starting from racemic **2** *via* phosphorothioamidate **6c**.

Here we have described a simple and effective method to prepare new enantiopure phosphorothioates and phosphorothioamidates[22] that can be tested as agrochemicals. The procedure can be scaled up easily.

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22. *selected data of compounds*:
3: ^{1}H-NMR δ(ppm): 1.56 (dd, *J* = 0.6, 6.9 Hz, 3H); 4.80 (m, 1H), 4.78 (m, 1H); 6.92 (m, Ar, 1H); 7.14 (m, Ar, 1H); 7.30-7.40 (series of m, Ar, 9H); 7.50-7.55 (series of m, Ar, 2H); ^{31}P-NMR δ(ppm): 79.82; $[\alpha]_D^{25}$ -17.2 (*c* 1.0, $CHCl_3$). **4a**: ^{1}H-NMR δ(ppm): 3.95 (d, *J* = 14.1 Hz, 3H); 7.20 (m, Ar, 2H); 7.30 (m, Ar, 2H); 7.39 (m, Ar, 2H); 7.48 (d, *J* = 7.5 Hz, Ar, 1H); 7.49 (d, J = 7.5 Hz, Ar, 1H); ^{31}P-NMR δ(ppm): 76.06. **4b**: ^{1}H-NMR δ(ppm): 1.40 (t, *J* = 7.2 Hz, 3H), 4.39 (m, 2H); 7.20 (d, *J* = 7.8 Hz, Ar, 2H); 7.29 (d, *J* = 7.8 Hz, Ar, 2H); 7.36 (d, *J* = 8.2 Hz, Ar, 1H); 7.39 (d, *J* = 8.2 Hz, Ar, 1H); 7.44 (d, *J* = 8.1 Hz, Ar, 1H); 7.48 (d, *J* = 8.1 Hz, Ar, 1H); ^{31}P-NMR δ(ppm): 76.00. **5a** major (52%): ^{1}H-NMR δ(ppm): 1.29 (d, *J* = 6.9 Hz, 3H), 3.27 (d, *J* = 13.8 Hz, 3H), 3.49 (m, 1H), 4.10 (m 1H), 5.31 (bs, 1H), 6.98 (dd, *J* = 1.2, 7.2 Hz), Ar, 1H), 7.04 (dd, *J* = 0.9, 6.9 Hz, 1H), 7.10-7.44 (series of m, Ar, 10H), 7.65 (d, *J* = 8.1 Hz, Ar, 1H); ^{31}P-NMR δ(ppm): 68.56; $[\alpha]_D^{25}$ -60.7 (*c* 1.0, $CHCl_3$). **5a** minor (48%):

^{1}H-NMR δ(ppm): 1.32 (d, *J* = 6.6 Hz, 3H), 3.34(m, 1H), 3.46 (d, *J* = 14.1 Hz, 3H), 4.37 (m, 1H), 5.27 (bs, 1H), 6.95-7.04 (series of m, Ar, 2H), 7.16-7.40 (series of m, Ar, 11H); ^{31}P-NMR δ(ppm): 69.52; $[\alpha]_D^{25}$ -22.6 (*c* 1.6, $CHCl_3$). **5b** major (56 %): ^{1}H-NMR δ(ppm): 0.91 (t, *J* = 7.2 Hz, 3H); 1.29 (d, *J* = 6.9 Hz, 3H); 3.52 (m, 1H), 3.54 (m, 1H); 3.78 (m, 1H); 4.16 (m, 1H); 5.27 (bs, 1H); 6.90 (dd, *J* = 1.2, 7.8 Hz, Ar, 1H); 7.00 (d, *J* = 7.8 Hz, Ar, 1H); 7.11 (dd, *J* = 1.8, 8.1 Hz, Ar, 1H); 7.18-7.42 (series of m, Ar, 9H); 7.63 (d, *J* = 8.1 Hz, Ar, 1H); ^{31}P-NMR δ(ppm): 66.30; $[\alpha]_D^{25}$ -57.4 (*c* 1.2, $CHCl_3$). **5b** minor (44 %): ^{1}H-NMR δ(ppm): 1.12 (t, *J* = 7.2 Hz, 3H); 1.34 (d, *J* = 6.6 Hz, 3H); 3.32 (m, 1H); 3.77 (m, 1H); 3.83 (m, 1H); 4.39 (m, 1H); 5.20 (bs, 1H); 6.82-7.20 (series of m, Ar, 13H); ^{31}P-NMR δ(ppm): 67.48; $[\alpha]_D^{25}$ -20.7 (*c* 2.0, $CHCl_3$). **6a**: ^{1}H-NMR δ(ppm): 1.09 (t, *J* = 6.9 Hz, 6H); 2.95 (m, 2H); 3.21 (m, 2H); 7.20-7.99 (series of m, 12H); ^{31}P-NMR δ(ppm): 70.09. **6b**: ^{1}H-NMR δ(ppm): 3.55 (m, 1H); 4.20 (m, 2H); 7.18-7.46 (series of m, Ar, 12H); 7.58 (dd, *J* = 1.2, 8.4 Hz, Ar, 1H); 7.82-7.94 (series of m, Ar, 3H); 8.00 (d, *J* = 9.0 Hz, Ar, 1H); ^{31}P-NMR δ(ppm): 82.04. *(R)*-**7a**: $[\alpha]_D^{25}$ -363.6 (*c* 1.1, $CHCl_3$). *(R)*-**7b**: $[\alpha]_D^{25}$ -380.8 (*c* 0.9, $CHCl_3$). **8** major (60 %): ^{1}H-NMR δ(ppm): 0.68 (t, *J* = 6.9 Hz, 6H); 2.80 (m, 4H); 3.40 (d, *J* = 13.8 Hz, 3H); 5.20 (bs, 1H); 7.10-8.15 (series of m, Ar, 12H); ^{31}P-NMR δ(ppm): 74.91. **8** minor (40 %): ^{1}H-NMR δ(ppm): 0.87 (t, *J* = 7.2 Hz, 6H); 2.97 (m, 4H); 3.19 (d, *J* = 13.8 Hz, 3H); 7.10-8.15 (series of m, Ar, 12H); ^{31}P-NMR δ(ppm): 74.08. **9**: ^{1}H-NMR δ(ppm): 0.93 (t, *J* = 7.2 Hz, 3H); 3.29 (m, 1H); 3.43 (m, 1H); 3.67 (m, 1H); 3.72 (m, 2H); 5.25 (bs, 1H); 7.06-7.52 (series of m, Ar, 12H); 7.82 (d, *J* = 8.7 Hz, Ar, 1H); 7.84 (d, *J* = 9.0 Hz, Ar, 1H); 7.88 (d, *J* = 9.0 Hz, Ar, 1H); 7.95 (d, *J* = 8.7 Hz, Ar, 1H); 8.03 (d, *J* = 9.0 Hz, Ar, 1H); ^{31}P-NMR δ(ppm): 67.54. **10a** (from *(R)*-(+) **2**): ^{1}H-NMR δ(ppm): 1.25 (d, *J* = 6.6 Hz, 3H); 3.19 (d, *J* = 14.1 Hz, 3H); 3.31 (m, 1H); 4.00 (m, 1H); 4.85 (bs, 1H), 6.98 (d, *J* = 7.2 Hz, Ar, 2H); 7.06 (d, *J* = 8.1 Hz, Ar, 1H), 7.20-7.38 (series of m, Ar, 8H), 7.46 (m, Ar, 1H), 7.55 (d, *J* = 8.7 Hz, Ar, 1H), 7.82 (d, *J* = 7.8 Hz, Ar, 1H), 7.89 (t, *J* = 8.7 Hz, 3H); ^{31}P-NMR δ(ppm): 67.51; $[\alpha]_D^{25}$ 44.5 (*c* 1.0, $CHCl_3$). **10a** (from *(S)*-(-) **2**): ^{1}H-NMR δ(ppm): 0.85 (d, *J* = 6.6Hz, 3H); 3.10 (d, *J* = 14.1 Hz, 3H); 3.35 (m, 1H); 3.50 (m, 1H), 5.16 (bs, 1H), 7.04 (dd, *J* = 0.9, 6.6 Hz, Ar, 2H), 7.15 (d, *J* = 8.4 Hz, Ar, 1H), 7.20-7.41 (series of m, Ar, 8H), 7.49 (m, Ar, 1H), 7.75 (d, *J* = 8.1 Hz, Ar, 1H), 7.91-8.0.6 (series of m, Ar, 4H); ^{31}P-NMR δ(ppm): 68.26; $[\alpha]_D^{25}$ -185.5 (*c* 1.0, $CHCl_3$). **10b** (from *(R)*-(+) **2**): ^{1}H-NMR δ(ppm): 0.87 (t, *J* = 7.2 Hz, 3H); 1.30 (d, *J* = 7.2 Hz, 3H); 3.24 (m, 1H); 3.35 (m, 1H); 3.64 (m, 1H); 4.10 (m, 1H); 5.20 (bs, 1H); 7.01-7.10 (series of m, Ar, 3H); 7.20-7.36 (series of m, Ar, 8H), 7.45 (dt, *J* = 1.5, 8.1 Hz, 1H); 7.56 (dd, *J* = 0.9, 9.0 Hz, 1H); 7.82 (d, *J* = 7.2 Hz, 1H); 7.87 (d, *J* = 9.0 Hz, 1H); 7.90 (d, *J* = 8.1 Hz, 2H); ^{31}P-NMR δ(ppm): 66.42; $[\alpha]_D^{25}$ 21.8 (*c* 0.6, $CHCl_3$). **10b** (from *(S)*-(-) **2**): ^{1}H-NMR δ(ppm): 0.80 (t, *J* = 6.9 Hz, 3H); 0.91 (d, *J* = 6.9 Hz, 3H); 3.25-3.52 (series of m, 3H); 3.70 (m, 1H); 5.21 (bs, 1H); 7.08 (dd, *J* = 1.8, 8.1 Hz, Ar, 2H); 7.15-7.53 (series of m, Ar, 10H); 7.88 (dd, *J* = 1.8, 8.7 Hz, Ar, 1H); 7.94-8.05 (series of m, Ar, 4H); ^{31}P-NMR δ(ppm): 65.52; $[\alpha]_D^{25}$ -220.7 (*c* 1.0, $CHCl_3$). **11** major (60 %): ^{1}H-NMR δ(ppm): 1.20 (t, *J* = 7.2 Hz, 3H); 3.25 (dd, *J* = 1.2, 13.8 Hz, 3H); 3.92 (m, 2H); 5.40 (bs, 1H); 7.19 (d, *J* = 8.4 Hz, Ar, 1H); 7.25-7.54 (series of m, Ar, 6H); 7.69 (d, *J* = 9.0 Hz, Ar, 1H); 7.90 (d, *J* = 7.8 Hz; Ar, 1H); 7.96 (m, Ar, 2H); 8.05 (d, *J* = 7.8 Hz, Ar, 1H); ^{31}P-NMR δ(ppm): 65.53. **11** minor(40 %): ^{1}H-NMR δ(ppm): 0.95 (t, *J* = 7.2 Hz, 3H); 3.48 (m, 1H); 3.53 (dd, *J* = 1.2, 13.5 Hz, 3H); 3.77 (m, 1H); 5.40 (bs, 1H); 7.19 (d, *J* = 8.4 Hz, Ar, 1H); 7.25-7.54 (series of m, Ar, 6H); 7.65 (d, *J* = 9.0 Hz, 1H); 7.90 (d, *J* = 7.8 Hz, Ar, 1H); 7.96 (m, Ar, 2H); 8.05 (d, *J* = 7.8 Hz, Ar, 1H); ^{31}P-NMR δ(ppm): 65.48. **12** (two diastereomers): ^{1}H-NMR δ(ppm): 0.82 (d, *J* = 6.6 Hz, 3H, one diast.); 0.92 (dt, *J* = 0.9, 7.2 Hz, 3H, one diast.); 1.00 (d, *J* = 6.9 Hz, 3H, one diast.); 1.04 (dt, *J* = 0.9, 7.2 Hz, one diast.); 1.80 (s, 3H, one diast.); 1.86 (s, 3H, one diast.); 3.34 (bs, 1H, two diast.); 3.54-3.89 (series of m, 3H, two diast.); 6.99-7.03 (m, Ar, 2H, two diast.); 7.17-7.54 (m, Ar, 10H, two diast.); 7.81-8.10 (m, Ar, 5H, two diast.); ^{31}P-NMR δ(ppm): 64.39 (one diast.); 66.20 (one diast.).

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