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Diastereoselective Synthesis of Phosphite Triesters Through a New Bicyclic Intermediate

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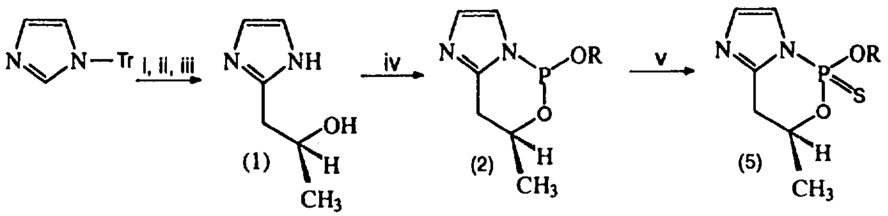
Abstract: The diastereoselective synthesis of phosphite triesters and their corresponding thiophosphate triesters is described. The new bicyclic imidazo-oxazaphosphorine, synthesized as a single diastereomer, is used as an intermediate that undergoes a diastereoselective displacement when reacted with an alcohol. This process eliminates the use of an acid catalyst.

As part of our interest in the use of chiral and cyclic phosphoramidite derivatives as precursors in the diastereoselective synthesis of DNA phosphorothioates, we were looking for a precursor that would allow us to reach this goal with no acid-catalyzed coupling step. We recently proved that diastereoselectivity can be achieved in this synthesis,[1a,2] by the use of chiral cyclic phosphoramidite as substrates and bulky acidic imidazoles instead of tetrazole as catalysts. However, the use of tetrazole or other acidic catalyst turns out to be a source of epimerization at the phosphorus center.[1a,3a,b] We therefore tried to replace the amine moiety on these amidite derivatives by an azole, usually used as a catalyst for the phosphoramidite reaction. The imidazole moiety appeared to be a good candidate. Its condensation on tervalent phosphorus has already been reported,[4a,b] as well as its high reactivity when submitted to nucleophilic displacement.

We chose (S)-1-(imidazol-2-yl)-propan-2-ol **1** as a chiral auxiliary for the synthesis of various phosphite triesters and their corresponding thiophosphate triesters. It was synthesized according to the method described by Kirk[5,1b] in 75% overall yield (Scheme 1).

This chiral auxiliary was then subjected to condensation with methyl- or ethyl dichlorophosphite in methylene chloride or deuteriochloroform, in order to yield the corresponding imidazo-oxazaphosphorines **2a** and **2b**. The formation of this new class of compounds was followed by ^{31}P NMR, which initially showed the formation of two compounds, characterized by a minor and a major peak at 120.6 and 118.8 ppm respectively for **2a**, and at 120.4 and 118.3 ppm for **2b**, presumably due to the two possible diastereomers. Equilibration to a single diastereomer occurred after about 20 minutes upon standing at R.T., as evidenced by a single signal at 118.8 ppm for **2a** and at 118.3 ppm for **2b**. As a result of the desired high reactivity of these compounds, they could not be isolated or purified. For instance, a simple concentration of the solution was enough to decompose them.



2a: R = CH_3
2b: R = C_2H_5
one diastereomer

5a: R = CH_3
5b: R = C_2H_5
one diastereomer

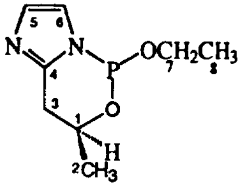
i: BuLi, THF, -78°C to RT; ii: (S)-propylene oxide, -78°C to -10°C;
iii: 5%AcOH in MeOH; iv: $ROPCl_2$, Et_3N, CH_2Cl_2, 0°C; v: S_8

Scheme 1

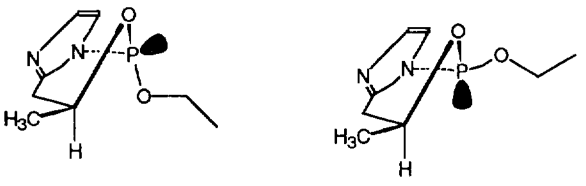
Imidazo-oxazaphosphorines **2** were characterized by means of ^{13}C NMR spectroscopy on the crude mixture. Peak assignments were done based on APT experiments, and the coupling constants were calculated in order to obtain some structural information on this new bicyclic structure. Table 1 summarizes the ^{13}C NMR data of compound **2b**. Unfortunately, ^{1}H NMR data could not be obtained due to the presence of triethylamine, which masked the desired signals.

Table 1: ^{13}C NMR data for compound **2b** (with respect to the residual signal of $CDCl_3$ at 77.0 ppm)

Carbon assignment	Chemical shift (ppm)	Coupling constant (Hz)
C_1	65.94	$^2J_{C\text{-}P}=6.3$
C_2	20.38	$^3J_{C\text{-}P}=4.1$
C_3	32.74	$^3J_{C\text{-}P}<0.3$
C_5	127.57	$^3J_{C\text{-}P}=5.2$
C_6	115.07	$^2J_{C\text{-}P}=18.1$
C_7	60.23	$^2J_{C\text{-}P}=19.4$
C_8	15.53	$^3J_{C\text{-}P}=5.0$



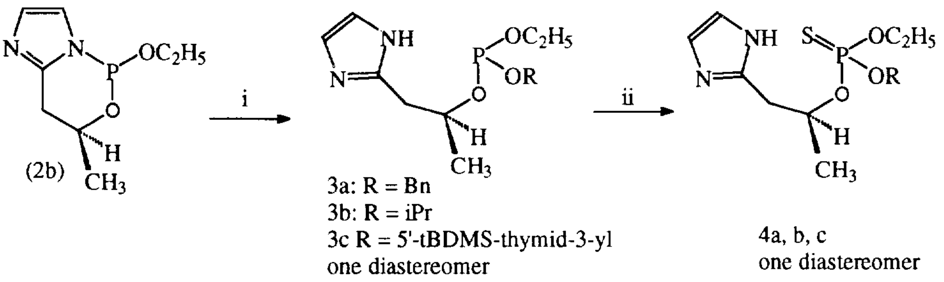
Assuming that the exocyclic methyl group is in a pseudo-equatorial orientation, the large coupling constant observed for the exocyclic methylene group on the phosphorus substituent suggests that this group is in the pseudo-axial orientation with respect to the tervalent phosphorus center. As already described in the literature,[6,7] the coupling constants between phosphorus and carbon are extremely sensitive to substituent orientation of the carbon atom with respect to the phosphorus lone pair. The large coupling constant exhibited by C_6 on the imidazole ring suggests that this carbon has a small dihedral angle with respect to the phosphorus lone pair. Therefore, the structure of imidazo-oxazaphosphorine **2b** would be better represented as depicted in **A** rather than **B** (Figure 1).



A B

Figure 1

The sulfuration of **2a** and **2b** using elemental sulfur or Beaucage's reagent[8] allowed us to obtain the corresponding thio adducts **5a** and **5b**, which were stable enough to be chromatographed and isolated. Their ^{1}H, ^{13}C, ^{31}P and mass spectra were in agreement with the proposed structure. Compound **2b** was subjected to nucleophilic opening by various alcohols in absence of any external acid catalyst, by direct injection of the alcohol solution into the reaction mixture. The result was an opening of the oxazaphosphorine ring to yield a single diastereomer of the corresponding triesters **3a,b,c** (Scheme 2).



i: ROH in solution in CH_2Cl_2; ii: S_8 or Beaucage's reagent

Scheme 2

The displacement took between 2 and 30 minutes depending on the alcohol. Subsequent sulfuration yielded the thiophosphate triesters **4a,b,c** as single diastereomers, as evidenced by ^{31}P NMR. As a control, the displacement was performed on a 1: 8 mixture of the two diastereomers of **2b**, before the equilibration to a single diastereomer had occurred. The result was a mixture of two compounds in a ratio of 1:8, as evidenced by their ^{31}P NMR signals at 141.1 and 140.6 ppm. Table 2 gives the relative reaction time and ^{31}P NMR data for compounds **3** and **4**. As expected, reaction with benzyl alcohol was faster than with isopropanol than with 5'-TBDMS-thymidine.

Table 2: Chemical shifts and reaction time for the formation of phosphite triesters **3a,b,c**

Alcohol	Phosphite triester **3** (ppm)[a]	Thiophosphate triester **4** (ppm)	Reaction time[b] (min.)
a: BnOH	139.8	66.3	2
b: iPrOH	140.6	64.8	20
c: 5'-TBDMS-thymidine	141.2	66.3	30

[a]: chemical shifts are given downfield from 85% phosphoric acid

[b]: as evaluated by ^{31}P NMR

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