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Stereoselective Synthesis of Homochiral *(E)*-Vinyl Phosphonates Derived from (-)-Ephedrine

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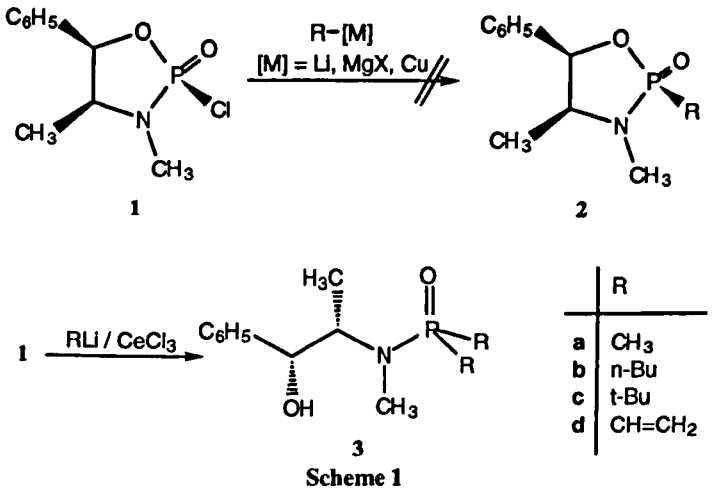
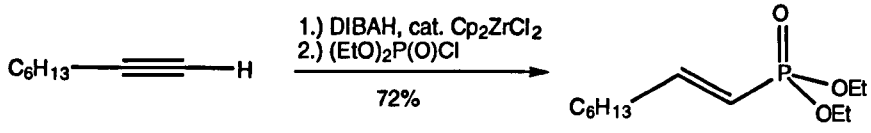
Abstract: A new synthesis of homochiral vinyl phosphonates starting from 1-alkynes is described. The title compounds were obtained in good yields by the reaction of chiral 2-chloro-1,3,2-oxazaphospholidin-2-one (1) with the "ate"-complexes of vinyl alanes. The latter were prepared by zirconocene dichloride catalyzed hydroalumination of 1-alkynes with diisobutyl aluminum hydride (DIBAH).

Despite the enormous amount of work done in the field of chiral vinyl sulfoxides[1], vinyl phosphonates containing a chiral phosphorus atom have gained little attention yet[2]. This may be due to the difficulties in the stereoselective synthesis of this type of compounds. In the present communication we wish to report the results of our investigations towards the synthesis of phosphoruschiral vinyl phosphonates derived from (-)-ephedrine. These compounds represent promising substrates for the study of stereoselective transformations such as cycloaddition reactions[2] and conjugate additions. The ability to remove the chiral auxiliary in a later olefination step[3] should be advantageous when compared to analogous reactions with vinyl sulfoxides.
Because the cyclisation of organophosphonic acid dichlorides with (-)-ephedrine remains troublesome with regard to the stereochemistry at the newly formed chiral phosphorus atom[4], we began our synthesis with enantiomerically pure *(2S,4S,5R)*-2-chloro-1,3,2-oxazaphospholidin-2-one (**1**) which can easily be obtained by means of cyclisation of (-)-ephedrine with $POCl_3$ as described by Inch et al.[5]. First attempts to react compound **1** with suitable vinylic organometallic reagents did not lead to the envisioned products. Thus, treatment of **1** with vinyl lithium or vinyl magnesium chloride at -78°C in THF or ether resulted in decomposition of the starting material, presumably by means of an endocyclic P-N or P-O bond cleavage of the formed intermediate. The chloride **1** did not react with either $(vinyl)_2CuLi$[6a] or $(vinyl)_2Cu(CN)Li_2$[6b], nor with (vinyl)Cu in the presence of $BF_3{\cdot}Et_2O$[6c]. In all cases the starting chloride **1** could be partially recovered. On the other hand, reaction of **1** with 3 eq. of alkyl lithium reagent in the presence of 1 eq. of anhydrous $CeCl_3$[7] yielded the phosphinates **3a-b** in 81% and 62% yield respectively. Attempts to perform this reaction with vinyllithium did not lead to the phospinate **3d** nor - by decreasing the amount of organolithium reagent - to the desired phosphonates **2**. Only when 1 eq. of *t*-butyllithium in the presence of 1 eq. of $CeCl_3$ was used, could the desired organophosphonate **2c** be isolated in 25% yield. In this case, the steric demand of the bulky *t*-butyl group prevents attack of a second equivalent of the organolithium species, the addition of which would lead to the phosphinate **3c**.



Scheme 1

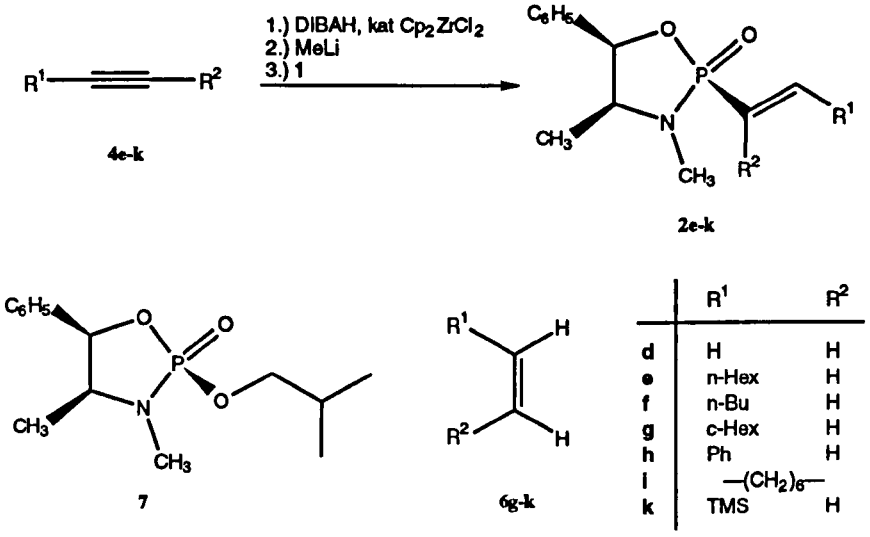
We found that the vinyl alane formed by reaction of 1-octyne with diisobutyl aluminum hydride (DIBAH) in the presence of 5% of zirconocene dichloride[8] for 24h reacted smoothly at 0°C with diethyl chlorophosphate, leading to the *(E)*-configured vinyl phosphonate **5** in 72% yield (see Scheme 2).



Scheme 2

In order to synthesize enantiomerically pure compounds, the 2-chloro-1,3,2-oxazaphospho-lidin-2-one **1** was treated with the vinyl alanes formed by hydroalumination of 1-octyne and 1-hexyne. After aqueous work-up the vinyl phosphonates **2e** and **2f** were isolated in 56% and 45% yield respectively. The reaction with the chloride took place within 2 hours leading stereospecifically to the *(E)-(2R)*-configured phosphonates with retention of configuration at the phosphorus atom. The stereochemistry at the chiral phosphorus atom was assigned by NOE experiments. A 3% NOE could be observed for the signal of the aromatic protons at the phenyl group at C5 upon irradiation of the olefinic signal at 5.57 ppm. The *(E)*-configuration of the double bonds in **2e** and **2f** were assigned by the vicinal coupling constants of the olefinic signals which were 16Hz each.

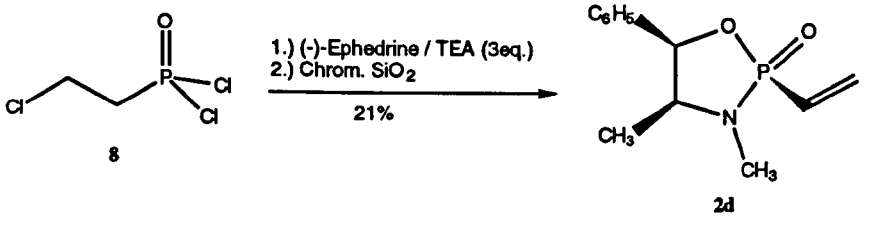
In order to increase the isolated yields of the vinyl phosphonates **2e** and **2f**, the intermediate vinyl alanes were transformed into the corresponding "ate"-complexes by addition of 1 eq. of methyl lithium at 0°C. Subsequent treatment with the chloride **1** lead to the homochiral vinyl phosphonates **2e** and **2f** in enhanced yields of 78% and 75% respectively[9].



Scheme 3

Starting from alkynes **4g-k** we could not isolate the desired products from the reaction of their corresponding vinyl alanates with the chloride **1** but obtained only the reduced alkenes **6g-k** and 2-isobutoxy-1,3,2-oxazaphospholidin-2-one **7** in yields between 30% and 50%. The formation of compound **7** could be explained by hydride transfer from the isobutyl group of the vinyl alanate to the 2-chloro-1,3,2-oxazaphospholidine-2-one and consecutive addition to the formed isobutene catalysed by the present alane.

In order to investigate selective reactions of homochiral vinyl phosphonates we also synthesised the unsubstituted derivative **2d**. As the hydroalumination of ethyne only gives poor results we reacted 2-chloroethyl phosphonic acid dichloride **8** with (-)-ephedrine in the presence of 3 eq. of triethylamine. From the resulting complex reaction mixture we only could isolate one of the two possible diastereoisomers in enantiomerically pure form. Compound **2d** could be isolated in 21% yield and the stereochemistry was assigned by NOE as described abovefor compound **2e**.



Scheme 4

In summary, we present a new method for the synthesis of the title compounds. Unbranched terminal alkynes can be converted in good yields to chiral vinyl phosphonates with retention of the configuration at both the phosphorus atom of the chiral chlorophosphate and at the double bond. In addition the cerium chloride promoted reaction of organolithium reagents with chlorophosphates yielding phosphinates **3** has been described. Further investigations on the reactivity of the synthesised compounds are currently being performed in our laboratories.

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9. *Synthesis of (E)-(2R,4S,5R)-2-(1-octenyl)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one* (**2 e**) *typical experimental procedure:* To a solution of 10 mmol (1.42 g) DIBAH and 0.5 mmol (146 mg) Cp_2ZrCl_2 in 10 ml of CH_2Cl_2, 10 mmol (1.10 g) 1-octyne were added at room temperature and the mixture was refluxed for 24h. It was cooled down to 0°C and 6.7 ml of a 1.5 *M* solution of MeLi in diethyl ether were slowly added. After 30 min a solution of 10 mmol (2.45 g) of the chloride **1** in 20 ml of CH_2Cl_2 were added at the same temperature. The mixture was stirred for 2 h allowing to warm up to room temperature. Then the solution was concentrated by evaporation to 5-10 ml and partitionated between 150 ml methyl *t*-butyl ether (MTBE) and 50 ml of ice cold 10% H_2SO_4. The aqueous layer was extracted twice with 30 ml MTBE each and the combined organic layers were washed with each 50 ml of cold 2 *M* HCl, water and sat. $NaHCO_3$ solution. After drying over $MgSO_4$ and evaporation of the solvents the residue was purified by silica gel chromatography with MTBE / methanol (25:1) yielding 2.50 g (7.77 mmol, 78%) of a colourless solid with R_f = 0.29 and m.p. 40-42°C. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 0.77 (d, J = 6.5 Hz, 3H, C4-C$\underline{H}_3$), 0.89 (t, J = 7 Hz, 3H, C8´-$\underline{H}$), 1.25-1.39 (m, 6H, C5´-$\underline{H}$-C7´-$\underline{H}$), 1.43 (tt, J = 7,7 Hz, 2H, C4´-$\underline{H}$), 2.27 (ttdd, J = 7, 6.5, 2, 1.5 Hz, 2H, C3´-$\underline{H}$), 2.71 (d, J_{PH} = 9.5 Hz, 3H, N-C$\underline{H}_3$), 3.72 (ddq, J = 12, 6, 6.5 Hz, 1H, C4-$\underline{H}$), 5.57 (ddt, J = 22. 16. 1.5 Hz, 1H, C1´-$\underline{H}$), 5.75 (d, J = 6 Hz, 1H, C5-$\underline{H}$), 6.94, (ddt, J = 22, 16, 6.5 Hz, 1H, C2´-$\underline{H}$), 7.25-7.39 (m, 5H, Ar-$\underline{H}$); **^{13}C-NMR** (100.6 MHz, $CDCl_3$): δ = 13.9, 14.0 (q, C4-$\underline{C}H_3$ and C8´), 22.5, 27.8, 28.7, 31.5 (t, C4´-C7´), 28.9 (dq, $^2J_{CP}$ = 7 Hz, N-$\underline{C}H_3$), 34.2 (dt, $^3J_{CP}$ = 20 Hz, C3´), 60.2 (dd, $^2J_{CP}$ = 9 Hz, C4), 80.2 (d, C5), 118.6 (dd, $^1J_{CP}$ = 172 Hz, C1´), 125.7 (d, Ar-$\underline{C}$(m)), 127.9 (d, Ar-$\underline{C}$(p)), 128.3 (d, Ar-$\underline{C}$(o)), 136.3 (d, $^3J_{CP}$ = 9 Hz, Ar-$\underline{C}$), 155.9 (d, C2´); **IR** (CCl_4): ν = 3020, 3000-2860, 1630, 1460, 1260, 990, 710 cm^{-1}; $[\alpha]_D^{20}$ = -33.1 (c = 0.5, $CDCl_3$); **Anal.:** calc. C = 67.27, H = 8.78, N = 4.36, found C = 66.98, H = 8.99, N = 4.45%.

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