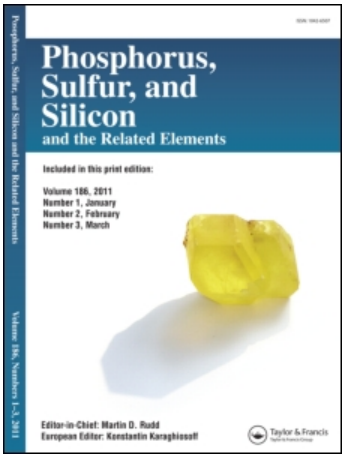

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Unexpected Rearrangement of Diethyl (±)(S,S)-1,2-epoxy-2-Phenylpentylphosphonate by NH 3(aqu.) : An Easy Entry to Ethyl 1-Formyl-1-Phenylbutylphosphonate

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UNEXPECTED REARRANGEMENT OF DIETHYL (±)(S,S)-1,2-EPOXY-2-PHENYLPENTYLPHOSPHONATE BY $NH_{3(aqu.)}$: AN EASY ENTRY TO ETHYL 1-FORMYL-1-PHENYLBUTYLPHOSPHONATE

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A simple reaction of diethyl (±)(S,S)-1,2-epoxy-2-phenylpentylphosphonate with 28% $NH_{3(aqu.)}$ in MeOH led to the ethyl 1-formyl-1-phenylbutylphosphonate in excellent yield. The procedure consists simply in stirring the substrate and 28% $NH_{3(aqu.)}$ in MeOH, at 40°C.

Keywords: 1-formylmethylphosphonate; 1,2-epoxy phosphonic ester; rearrangement

Epoxides rank among the most versatile synthetic intermediates, constituting convenient building blocks for the synthesis of many products of biological interest. Among them phosphonic acids with heteroatoms in the α and/or β positions have recently attracted considerable interests because of their inhibitory activity in some important biological processes.[1–3]

Our recent studies on the total synthesis of 2-amino-1-hydroxy-2-arylethylphosphonic esters led us to the discovery, that opening of *trans* 1,2-epoxy-2-arylethylphosphonic esters with 28% $NH_{3(aqu.)}$ in methanol is the convenient method for the synthesis of these compounds.[4]

The use of β-disubstituted 1,2-epoxyphosphonic esters gave a completely unexpected result. The opening of diethyl (±)(S,S)-1,2-epoxy-2-phenylpentylphosphonate with ammonia (28% $NH_{3(aqu.)}$) in MeOH

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resulted in ethyl 1-formyl-1-phenylbutylphosphonate, instead of the expected and desired 2-amino-1-hydroxy-2-arylethylphosphonate. This compound may be considered as a useful synthon for the preparation of functionalized alkanephosphonic acids.

This finding suggests, that under the applied conditions the formation of the aldehyde from β-disubstituted 1,2-epoxyphosphonic ester proceeds by cleavage of the (P—)C—O bond and is favored over the expected S_N2 opening of oxirane by NH_3.

Thus, our procedure started from standard Michael addition of arylmagnesium bromide in the presence of cuprous chloride on appropriate alkynylphosphonate **1**, at 30°C in ether, which gave after hydrolysis the corresponding 2, $\sqrt{H}$2-disubstituted alkenylphosphonates **2** with high stereoselectivity and good yields.[5]

Diethyl (E)-2-phenyl-pent-1-enylphosphonate **2** was converted into the corresponding 1,2-epoxyphosphonic ester **3** by epoxydation with dioxirane in a two-phase system according to a previously developed procedure.[6]

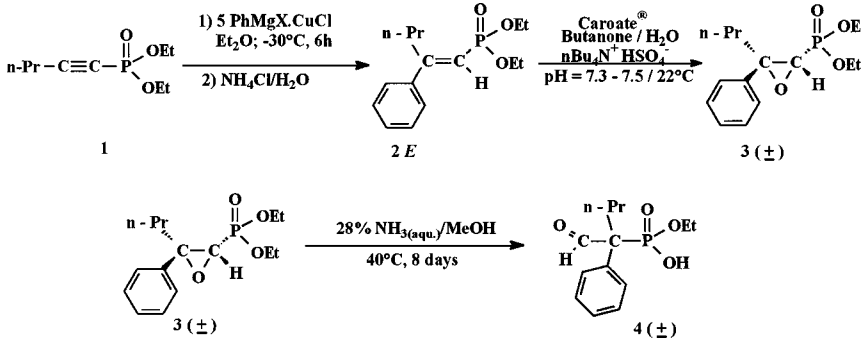
Reaction of diethyl (±)-(S,S)-1,2-epoxy-2-phenylpentylphosphonate **3** with a 84-fold of ammonia (28% $NH_{3(aqu.)}$) in MeOH gave ethyl 1-formyl-1-phenylbutylphosphonate in excellent (96%) yield.* The compound was satisfactorily identified by ^{31}P-NMR, ^{1}H-NMR and ^{13}C-NMR (and additionally compared with simulated values of chemical shifts by ACD-CNMR program), IR and MS FAB$^+$.**

At this point we have to mention, that rearrangements of organophosphorus compounds are well established reactions. Several

*The synthesis of ethyl 1-formyl-1-phenylbutylphosphonate: *General Procedure*—into a Schlenk flask equipped with magnetic stirrer was introduced 2 mmol of the (±)-(*l*)-diethyl 1,2-epoxy-2-phenylpentylphosphonate, 10 ml (0.165 M) of 28% $NH_{3(aqu.)}$ and 20 ml of MeOH. The flask was tightly closed and the mixture was intensively stirred at room temperature. The progress of the reaction was monitored by ^{31}P-NMR and interrupted after 8 days. After completing of the reaction all the volatile compounds were evaporated from the mixture. The pure compound (oil), consisting of 4% of unreacted epoxyphosphonate was recovered.

**^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ at 200, 132, and 50,32 MHz respectively. ^{31}P-NMR spectra were recorded at 81.0 MHz in $CDCl_3$. ^{31}P-NMR chemical shifts are relative to 85% H_3PO_4. FT-IR spectra were recorded in $CHCl_3$ using Perkin-Elmer 377 spectrometer. Mass spectrometry [FAB$^+$] were performed using a DX300-SX102 spectrometer.

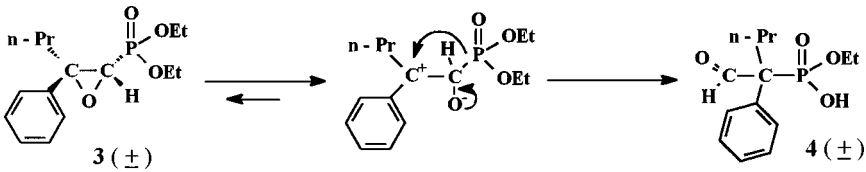
4 ethyl 1-formyl-1-phenylbutyl phosphonate: $C_{13}H_{19}O_4P$—M = 270, 263; ^{1}H-NMR: δ 0.92 (t, J = 7.0 Hz, 3H), 1,22 (t, J = 7.0 Hz, 3H), 1.31 (m, 2H), 2.3 (m, 2H), 3.96 (m, 2H), 6.47 (bs, 1H), 7.31–7.42 (m, aromat., 5H), 9.85 (d, J = 3.8 Hz, 1H); ^{13}C-NMR: δ 13.7 (s), 16.1 (d, J = 5.9 Hz), 17.7 (d, J = 9.9 Hz), 32.3 (d, J = 4.0 Hz), 61.3 (d, J = 131.4 Hz), 62.8 (d, J = 7.7 Hz), 127.6 (d, J = 2.5 Hz), 128.6 (J = 1.9 Hz), 129.0 (d, J = 6.7 Hz), 133.0 (d, J = 6.8 Hz), 197.4 (d, J = 4.2 Hz); ^{31}P-NMR = 25.1 ppm; MS FAB$^+$ = 271; IR : ν (C═O) = 1714 cm^{-1}, ν (P═O) = 1210 cm^{-1}, ν (P—O—C) = 1028 cm^{-1}.



SCHEME 1 Preparation of compounds **2**, **3**, and **4**.

papers report the use of 2,2-disubstituted-1,2-epoxyethylphosphonates as the substrates in thermic or Lewis acid—catalyzed shifts of phosphorus substituents from carbon to carbon to give diethyl 1,1-disubstituted-1-formylmethylphosphonates. The first paper concerning this topic was published in 1966 by Churi and Griffin.[7] Usually, boron trifluoride—diethyl ether complex ($BF_3{\cdot}Et_2O$) was used as catalyst for this reaction, but other Lewis acids such as $SnCl_4$, $SnBr_2$, $ZnCl_2$ or $ZnBr_2$ in C_6H_6 or CH_2Cl_2 were used in this process as well.[8–12]

In our opinion the observed reaction proceeds via an intermediate shown in Scheme 2.



SCHEME 2 Proposed mechanism of rearrangement.

This mechanism was first proposed by Kirby and Warren.[13] It views the rearrangement as being of the "carbonium ion" type and concludes that in such rearrangements the $(EtO)_2PO$ group possesses high migratory aptitude to electron—deficient center, what was already described in several papers.[8–12] In the case of compound **3**, under the conditions used (lacking of Lewis acid) the driving force for the rearrangement could be the easy formation of the carbocationic intermediate due first to the presence of the aryl group on the quaternary C_2 atom in the epoxide allowing the mesomeric stabilisation of the benzylic carbenium and secondly to the high polarity of the aqueous medium.

In summary, the present findings suggest, that β-disubstituted 1,2-epoxyphosphonic esters with $2=>\sqrt{2}$ aryl substituents show unexpected properties, which in this type of reaction could exclude them as potential substrates in the synthesis of β-amino-α-hydroxyphosphonic esters. However, the observed reaction gives an additional information about the reactivity of certain epoxyphosphonates.

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