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Regioselectivity in the C-alkylation of triethyl 3-methyl-4-phosphonobut-2-enoate

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The reaction of triethyl 3-methyl-4-phosphonobut-2-enoate (1) with three alkyl halides AlkX (Alk = Pr, Me_2CHCH_2CH_2, and c-C_5H_9; X = Br, I) in the system KOH(solid)—DMF—Bu_4NBr at -20 °C gives exclusively products of alkylation at C(2) with \( \Delta^2 \) and/or \( \Delta^3 \) position of the double bond. Under the same conditions, the reaction of 1 with MeI gives a mixture of products with different substitution patterns. Only the use of an ion pair extraction technique affords 2-methyl-\( \Delta^2 \)-products selectively, albeit in rather moderate yields. The Horner—Emmons olefination of PhCHO with the resulting phosphonates gives ethyl 2-alkyl-3-methyl-5-phenylpenta-2,4-dienoates in high yields.

Key words: triethyl 3-methyl-4-phosphonobut-2-enoate, alkylation; phase transfer catalysis; Horner—Emmons reaction; regioselectivity.

In a continuation of our studies on the use of the Horner—Emmons reaction for the stereocontrolled synthesis of derivatives of 3-methylalka-2,4-dienoic acids (see the review, Ref. 1) and on stereospecific transformation of the latter into Z-trisubstituted olefins with a homoallylic type of functional substitution,\(^2\) we intended to use this reaction sequence for the stereospecific construction of trisubstituted double bonds. For this purpose, we needed alkyl 4-alkyl-3-methylalka-2,4-dienoates (as substrates for stereospecific 1,4-cis-hydrogenation) and, correspondingly, alkyl 3-methyl-4-phosphonobut-2-enoates.

In this communication, we report an attempt to obtain phosphonates of the type specified above above by direct C-alkylation of the readily accessible triethyl 3-methyl-4-phosphonobut-2-enoate (1) under conditions of phase transfer catalysis. The results of this reaction demonstrate its high regioselectivity, the reaction occurring as an electrophilic attack almost exclusively at the C(2) atom of ester 1.

It is known that simple phosphonates of the type (AlkO)\(_2\)P(O)CH_2X (where X is an electron-withdrawing substituent) form C-alkylation products in both traditional variants of carbanionic reactions\(^3\) and under conditions of phase transfer catalysis (using the ion-pair...
extraction technique, which requires an equimolar amount of the phase transfer catalyst). It is also known that under both classical conditions of carbonation generation and under conditions of phase transfer catalysis, unsaturated ambient CH-acids of the type MeC(R)=CHCOR (where R = H, Alk; R 1 = OAlk, Me) undergo alkylation with electrophiles R 2X in low-polarity media preferentially at the α-position with respect to the carbonyl group to give products of the type CH 2 =C(R)−CH(R 2 )COR 1 and MeC(R)=CR 2 COR 1 , the equilibrium between which depends on a number of factors. This direction of the alkylation is in agreement with the data of quantum-chemical calculations.

The methylene moiety at position 4 in phosphonate 1 and in other allylic phosphonates of similar structure is activated both by the adjacent phosphonate group and by the vinylogous group CO 2 Et. It is known that irrespective of the ratio of the E- and Z-isomers in phosphonate 1 the action of strong bases rapidly transforms it into a delocalized carbanion (an equilibrium mixture of E- and Z-isomers), which reacts with aldehydes exclusively through the anionic pole at C(4). In the absence of quantum-chemical calculation data, it was of interest to check experimentally the possibility of C-alkylation of allylic phosphonate 1 at position 4.

In order to carry out the reaction of ester 1 with alkyl halides under conditions of phase transfer catalysis, we tested three variants of the two-phase catalytic system solid base−DMF−tetrabutylammonium bromide (TBAB) using K 2 CO 3, LiOH, and KOH as the base. Isopropyl bromide was used as the standard alkylhalide.

In the systems K 2 CO 3 (solid)−DMF−TBAB and LiOH(solid)−DMF−TBAB at −20 °C, the ester 1 virtually does not react with PrBr. However, when the system KOH(solid)−DMF is used with an equimolar ratio of the reagents and in the presence of a catalytic amount of TBAB (at −20 °C), the reaction is completed in 1 h. Judging by GLC and 1 H NMR spectroscopic data, the resulting product is a mixture of two stereoisomers in a 85:15 ratio. The type of its 1 H NMR spectrum agrees with the valence structure of a vinylic phosphonate (2a), in which the isopropyl group is located at the C(2) atom of the original substrate. The signal of the proton at the C(4) atom, which is easy to identify from the spin-coupling constants of the H and P nuclei (d 1 H, J = 16.5 Hz), is observed at δ 5.50 for the major stereoisomer and at δ 5.40 for the minor stereoisomer, whereas in the spectrum of the original ester 1 (E : Z ~ 63 : 37), the signals of the C(4) methylene group resonate at δ 2.60 (E-isomer) and 3.40 (Z-isomer) and the spin-spin coupling constant of the H and P nuclei is typical of a sp 2 -hybridized C atom (J = 23 Hz).

Whereas the signal of the olefinic proton in the spectrum of the original ester 1 is observed at δ 5.71 and has an “allylic” coupling constant (J = 2 Hz), the signal of the proton at C(2) in the spectrum of ester 2a is a doublet with δ 2.57 and a “vicinal” coupling constant ($J = 10.5$ Hz). The data obtained from 1 H NMR spectroscopy are insufficient for an unambiguous assignment of the configurations of the major and minor stereoisomers. One can assume that the signal of the allylic Me group of the major isomer (δ 1.98) is shifted downfield relative to the corresponding signal of the minor isomer (δ 1.80), since in the former case the deshielding effect of the O atom in the cis-positioned phosphoryl group is exhibited. The vinylic proton of the major isomer is not located within the zone of diamagnetic shielding exhibited by the carbonyl group, and its signal is therefore shifted downfield with respect to the similar signal of the minor isomer. Both effects are in agreement with the assumed E-configuration of the major isomer.

Under the same conditions, isopropyl iodide reacts with ester 1 to give also a binary mixture of stereoisomers of vinylic phosphonate 2a in a yield of 46%.

The reaction of phosphonate 1 with isopentyl bromide and cyclopentyl bromide in the same heterogeneous system also afforded only the products of monoalkylation at the C(2)-atom, although the qualitative composition of the products was different as compared with the binary mixture of stereoisomers 2a.

In the former case, a mixture of monoalkylated phosphonates (elemental analysis data), was obtained in 57% yield; it contained, judging by 1 H NMR spectroscopic data, conjugated [(E)-3b and (Z)-3b] and nonconjugated products of alkylation at the C(2) atom [(E,Z)-2b] in a ~87:13 ratio. The spectrum did not contain a signal around δ 5.7 typical of an olefinic proton at the α-position to the alkoxycarbonyl group, which suggests that products of alkylation at C(4) are not formed in this case, either. The ratio of integral intensities of the signals from the proton at C(4) and the methyl at C(3) (presumably, δ 3.15 and 1.88 for (Z)-3b, and 2.60 and 2.0 for (E)-3b, respectively) indicates that the conjugated Z-isomer, (2-Z)-3b, is the dominating component of the mixture. The ratio of stereoisomers in the minor component [(E,Z)-2b] is close to 1:1, as judged by the intensity of signals of the olefinic proton at C(4) (δ 5.35 and 5.45, $J_{HP} = 14$ Hz).

In the latter case, judging by GLC and 1 H NMR data, the isolated reaction product (yield 44%) is a mixture of both structural isomers (2c and 3c), in which the allylic phosphonate 3e predominates; the ratio of