SYNTHESIS OF α-MYRCENOL ACETATE AND PROPIONATE FROM ISOBUTENYLCARBINOL

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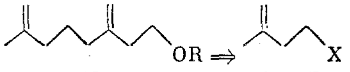
A synthesis of α-myrcenol acetate and propionate was carried out by a controled combination of suitable isobutenylcarbinol derivatives according to the Wurtz reaction.

The sexual pheromone of the dangerous pest of agricultural cultures, such as the scale insect San-Jose Quadraspidiotus perniciosus, contains in its composition the α-myrcenol (I) in the form of a propionate (II) [1]. Several syntheses of this compound are known [1-4], of which the method based on the addition of an organocopper derivative of isohexenyl bromide to the corresponding monosubstituted acetylene [2] may be of a practical interest. In the present article, an approach which is new in principle for the preparation of α-myrcenyl esters (II) and (III) is discussed, which starts from the industrially available isobutenylcarbinol (IV) and its simple derivatives (V)-(VII), the last of which was prepared by a standard method [5] from alcohol (IV).

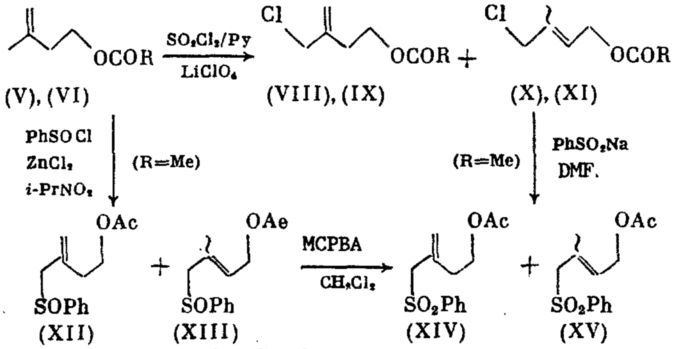


(I)—(III) (IV)—(VII)

R = H (I), COEt (II), Ac (III); X = OH (IV), OCOEt (V), OAc (VI), Br (VII).

In accordance with the accepted method, consisting of a "head-to-tail" type combination of two molecules of the precursor (IV), it was necessary to carry out a previously virtually uninvestigated functionalization of the isopropenyl fragment, enabling such a combination according to a new variant of the Wurtz reaction. To accomplish this, esters (V) and (VI) were chlorinated using SO_2Cl_2 in a CH_2Cl_2 medium, in the presence of pyridine according to a method previously developed by us in [6], the effectiveness of which could be substantially increased in the present case by the addition of ~0.2 mole·equiv. of $LiClO_4$.

However, as a result, a mixture of chlorides (VIII), (IX)/(X), (XI) ≃ 2:1 was obtained in a high overall yield with the same ratio of stereoisomers (E/Z ≃ 1:1) of the trisubstituted olefins (X), (XI). The composition of these mixtures which could not be separated chromatographically can be seen from a comparison in the PMR spectra (250 mHz) of distilled samples of these compounds of integral intensities of singlet signals, belonging to allyl chlorides (VIII) and (IX), of the $H_2C{=}C$ group protons at $\delta \simeq 5.0$ and 5.2 ppm and also of triplet signals, corresponding to E-(X), E-(XI) and Z-(X), Z-(XI) of olefinic protons with $\delta \simeq 5.5$ and 5.6 ppm, respectively. According to these data, the established ratio of the regio-(VIII) and stereoisomers (X) is retained under mild conversion conditions by the action of $PhSO_2Na$ in DMF to give the corresponding acetoxysulfones (XIV) and E/Z-(XV) (the latter were described previously in [7, 8]).



(V), (VI) (VIII), (IX) (X), (XI)

(XII) (XIII) (XIV) (XV)

R = Me (VI), (VIII), (X); Et (V), (IX), (XI).

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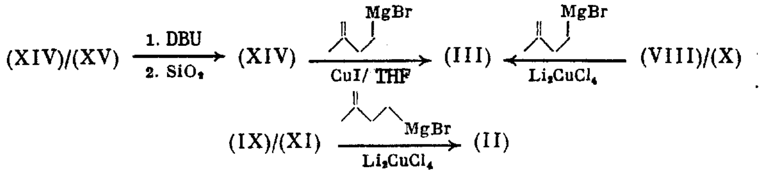
Another approach to the functionalization of the molecule of isobutenylcarbinol (IV) is illustrated by the use of an enic type reaction with PhSOCl catalyzed by Lewis acids, for example $ZnCl_2$, that we have disclosed in the series of trisubstituted isoprenoid oligo-olefins [9]. It was found as a result, with respect to acetate (VI), that carrying out this reaction under the conditions of [9] readily results in the formation of a mixture of very unstable acetoxysulfoxides (XII)/(XIII) $\approx$ 2:3, at a ratio of the stereoisomers of (XIII) E/Z $\approx$ 2:1, from which the Z-isomer could be isolated chromatographically in a pure state. These data follow from analysis of the PMR spectrum (250 MHz) of the mixture obtained together with data from the literature on related compounds [7, 8, 10], including the Z-(XIII) [8] and the hydroxysulfoxide corresponding to E-(XIII) [10] and are confirmed by data from analysis of the PMR spectrum of a similar mixture of sulfones (XIV)/(XV), formed by oxidation of a mixture of sulfoxides (XII)/(XIII) by m-chloroperbenzoic acid (MCPBA).

The pair of acetoxysulfones (XIV)/(XV) obtained by two different methods could not be separated chromatographically and the main component, the previously unknown sulfone (XIV), was isolated in the pure state only after further treatment of this pair by 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) and flash-chromatography on SiO_2 of the reaction products which may be formed by the decomposition of extremely labile sulfonyl derivatives of isoprene, see [11].



The CuI-catalyzed condensation of (XIV) with a Grignard reagent prepared from bromide (VII) led smoothly to α-myrcenyl acetate (III). The latter was also obtained in a >40% yield by a Li_2CuCl_4-catalyzed combination of the same Grignard reagent with a mixture of C_5-chloroacetates (VIII)/(X) after flash chromatography on SiO_2 of the mixture of compounds formed, among which condensation products involving chloroacetates (X) were not detected. In a similar manner, starting from a mixture of (IX)/(XI), α-myrcenyl propionate (II) was obtained in ~40% yield. Its physicochemical characteristics, like those of acetate (III), matched those published for these esters [2, 3].

EXPERIMENTAL

The IR spectra of the solutions in $CHCl_3$ were run on a UR-20 spectrophotometer. The PMR spectra (in $CDCl_3$) were measured on a "Bruker WM-250" spectrometer. The mass spectra were obtained on a "Varian MAT CH-6" mass spectrometer at 70 eV. The R_f values are given for a brand Silufol stationary SiO_2 layer.

Acetates of 3-Methyleno-4-chlorobutan-1-ol (VIII) and 3-Methyl-4-chlorobut-2E/Z-en-1-ol (X). A solution of 14.13 g (104.7 mmoles) of SO_2Cl_2 in 7 ml of CH_2Cl_2 was added in the course of 5 min to a vigorously stirred (Ar. at −60°C) suspension of 10.3 g (80.4 mmoles) of (VI), 8.28 g (104.7 mmoles) of pyridine and 1.71 g (16.1 mmoles) of $LiClO_4$ in 60 ml of CH_2Cl_2. The reaction mixture was allowed to stand for 20 min at −60°C and was then treated with ether and neutralized with a saturated solution of $NaHCO_3$. The organic layer was separated, washed with water, dried over $MgSO_4$, evaporated under vacuum, and distilled. Yield 9.36 g (72%) of a (VIII):E-(X):Z-(X) $\approx$ 4:1:1 mixture (PMR data) in the form of a colorless liquid, bp 64-66°C (3 mm), n_D^{20} 1.4591. IR spectrum (ν, cm^{-1}): 925, 990, 1050, 1210-1270, 1375, 1390, 1450, 1660, 1740, 2980, 3030. Mass spectrum (m/z): 162 (M^+), 127 ($-Cl^{35}$), 102, 89, 71, 67; for $C_7H_{11}ClO_2$, mol. wt. 162.6.

PMR spectrum for (VIII) (δ, ppm, J, Hz): 2.01 s (3H, CH_3), 2.46 br.t (2H, HC^2, J = 7). 4.04 br.s (2H, CH_2Cl), 4.18 t (2H, CH_2O, J = 7), 4.99 and 5.18 br.s (2H, $H_2C{=}C$).

PMR spectrum for E-(X) (δ, ppm, J, Hz): 1.85 br.s (3H, CH_3), 2.01 s (3H, CH_3CO), 3.99 br.s (2H, CH_2Cl), 4.59 br.d (2H, CH_2O, J = 7), 5.51 br.t (1H, $HC{=}C$, J = 7).

PMR spectrum for Z-(X) (δ, ppm, J, Hz): 1.78 br.s (3H, CH_3), 2.01 s (3H, CH_3CO), 4.08 br.s (2H, CH_2Cl), 4.59 br.d (2H, CH_2O, J = 7), 5.64 br.t (1H, $HC{=}C$, J = 7).

Propionates of 3-Methyleno-4-chlorobutan-1-ol (IX) and 3-Methyl-4-chlorobut-3E/Z-en-1-ol (XI). As described above, from 2.0 g (14.1 mmoles) of (V), 1.45 g (18.3 mmoles) of pyridine, 0.3 g (2.8 mmoles) of $LiClO_4$ and 2.47 g (18.3 mmoles) of SO_2Cl_2 in 20 ml CH_2Cl_2, 1.45 g (58%) of a (IX):E-(XI):Z-(XI) $\approx$ 4:1:1 mixture was obtained (PMR data) in the form of a colorless liquid, bp 63-64°C (1.5 mm), n_D^{20} 1.4608. IR spectrum (ν, cm^{-1}: 915, 1020, 1085, 1180, 1275, 1350, 1380, 1415, 1640, 1735, 2940, 2990, 3030. Mass spectrum (m/z): 176 (M^+), 141 ($-Cl^{35}$) 102, 89. 71, 67; for $C_8H_{13}ClO_2$, mol. wt. 176.6.

PMR spectrum for (IX) (δ, ppm, J, Hz): 1.12 t (3H, CH_3, J = 10.5), 2.30 q (2H, CH_2CO, J = 10.5), 2.51 br.t (2H, HC^2, J = 8), 4.07 br.s (2H, CH_2Cl), 4.22 t (2H, CH_2O, J = 8), 5.01 and 5.20 br.s (2H, $H_2C{=}C$).

PMR spectrum for E-(XI) (δ, ppm, J, Hz): 1.14 t (3H, CH_3, J = 10.5), 1.88 br.s (3H, CH_3), 2.32 q (2H, CH_2CO, J = 10.5), 4.01 br.s (2H, CH_2Cl), 4.62 br.d (2H, CH_2O, J = 8), 5.54 br.t (1H, $H_2C{=}C$, J = 8).

PMR spectrum for Z-(XI) (δ, ppm, J, Hz): 1.14 t (3H, CH_3, J = 10.5), 1.82 br.s (3H, CH_3), 2.32 q (2H, CH_2CO, J = 10.5), 4.09 s (2H, CH_2Cl), 4.62 br.d (2H, CH_2O, J = 8), 5.67 br.t (1H, $H_2C{=}C$, J = 8).

3-Methyleno-4-benzenesulfinylbutan-1-ol Acetate (XII) and Acetoxysulfoxides E/Z-(XIII). A solution of 3.72 g (23.2 mmoles) of PhSOCl in 3 ml of i-$PrNO_2$ was added in the course of 5 min to a stirred (Ar, at −40°C) suspension of 2.26 g (17.6 mmoles) of (VI) and 3.2 g (23.5 mmoles) of $ZnCl_2$ in 25 ml of i-$PrNO_2$. The temperature of the reaction mixture was raised in the course of 30 min to −10°C and it was allowed to stand at this temperature for 40 min. It was then diluted by ether and decomposed by a saturated solution of $NaHCO_3$. The aqueous layer was separated and extracted with ether. The usual treatment of the combined organic layer gave ~3 g of a compound which was chromatographed on 100 g of SiO_2. Gradient elution from hexane to ether gave 0.43 g (~10%) of Z-(XIII) [8] in the form of a colorless oil, R_f 0.32 (ether–hexane, 4:1) and 1.58 g (36%) of a (XII)/E-(XIII) $\approx$ 1:1 mixture (PMR data) in the form of colorless crystals, mp 62-65°C (ether–hexane).

PMR spectrum for (XII) (δ, ppm, J, Hz): 1.93 s (3H, CH_3), 2.35 br.t (2H, HC^2, J = 7), 3.38 br.s (2H, CH_2S), 4.08 t (2H, CH_2O, J = 7), 4.82 and 4.95 br.s (2H, $H_2C{=}C$), 7.4 m (5H, C_6H_5).

PMR spectrum for E-(XIII) (δ, ppm, J, Hz): 1.75 s (3H, CH_3), 1.93 s (3H, CH_3CO), 3.30 br.s (2H, CH_2S), 4.47 br.d (2H, CH_2O, J = 7), 5.25 br.t (1H, $HC{=}C$, J = 7), 7.4 m (5H, C_6H_5), see [10].

3-Methyleno-4-benzenesulfonylbutan-1-ol Acetate (XIV) and Acetoxysulfones E/Z (XV). A solution of 4.97 g (30.6 mmoles) of the above-described (VIII)/(X) mixture and 7.53 g (45.9 mmoles) of $PhSO_2Na$ in 30 ml of DMF was stirred (Ar) at 70°C for 3 h and treated with ether and water. The aqueous layer was separated and extracted by ether. The usual treatment of the combined organic layer gave ~7 g of a product which was chromatographed on 150 g of SiO_2. Gradient elution from hexane to ether gave 1.05 g (12%) of Z-(XV) in the form of a colorless oil with R_f 0.30 (ether–hexane, 2:1) [8] and 5.26 g (64%) of a (XIV)/E-(XV) $\approx$ 4:1 mixture (PMR data), see [7], in the form of colorless crystals mp 52-54°C (ether–hexane).

A solution of 0.2 g (0.75 mmoles) of the (XIV)/(XV) mixture, prepared as described in the preceding experiment and chromatographically purified without separation and 50 mg (0.33 mmole) of DBU in 3 ml of DMF was stirred (Ar) for 30 min at 0°C and then treated with ether and water. The aqueous layer was separated, neutralized with 50% H_2SO_4 and extracted with ether. The usual treatment of the combined organic layer gave ~0.2 g of a compound which was chromatographed on 10 g of SiO_2. Gradient elution from hexane to ether gave 0.12 g of (XIV) in the form of colorless crystals, mp 59-61°C (ether–hexane). IR spectrum (ν, cm^{-1}): 900, 930, 1045, 1090, 1130, 1165, 1250, 1320, 1370, 1450, 1650, 1740, 2970, 3030, 3080. PMR spectrum (δ, ppm, J, Hz): 2.04 s (3H, CH_3), 2.55 br.t (2H, HC^2, J = 6.5), 3.80 br.s (2H, CH_2S), 4.19 t (2H, CH_2O, J = 6.5), 4.92 and 5.11 br.s (2H, $H_2C{=}C$), 7.5-8.0 m (5H, C_6H_5). Found: C, 58.34; H, 6.10; S, 12.7%. $C_{13}H_{16}O_4S$. Calculated: C, 58.19; H, 6.01; S, 11.95%.

A solution of 0.36 g (1.42 mmoles) of the above-described and chromatographically purified without separation mixture of acetoxysulfoxides (XII)/(XIII) and 0.36 g (2.08 mmoles) of MCPBA in 10 ml of CH_2Cl_2 was stirred (Ar) for 1.5 h at −40°C and then 30 ml of hexane was added, the precipitate was filtered off, and washed with a cold mixture of CH_2Cl_2–hexane (1:3). The combined filtrate was evaporated under vacuum and the residue (~0.5 g) was chromatographed on 15 g of SiO_2. Gradient elution from hexane to ether (up to 50% of the latter) gave 0.36 g (94%) of a (XIV):E-(XV):Z-(XV) ≈ 2:2:1 mixture (PMR data).

Acetate (III). A 3.7 ml portion of 1.1 M of a Grignard reagent freshly prepared from (VII), in THF (4.1 mmoles) was added in the course of 5 min to a stirred (Ar, at −70°C) suspension of 0.5 g (1.86 mmoles) of (XIV) and 0.78 g (4.1 mmoles) of CuI in 5 ml of THF. The reaction mixture was heated in the course of 1 h to 25°C and then was diluted by ether and decomposed with an excess of a saturated solution of NH_4Cl. The aqueous layer was separated and extracted with ether. The usual treatment of the combined organic layer gave 0.4 g of a material which was chromatographed on 15 g of SiO_2. Gradient elution from hexane to ether (up to 10% of the latter) gave 0.23 g (63%) of (III), bp 62-63°C (2 mm), n_D^{20} 1.4545 (see [3]): bp 60°C, bath, (0.09 mm). The spectral characteristics of (III) (IR, PMR) practically coincided with those previously published [3] for this compound.

A stirred (Ar, at −70°C) solution of a Grignard reagent, freshly prepared from 8.32 g (55.8 mmoles) of (VII) and 1.8 g (74 mg-atom) of Mg in 20 ml of THF, containing 9 ml of 0.1 M solution of Li_2CuCl_4 in THF (0.9 mmole), was treated for 10 min with a solution of 6.7 g of a mixture of chlorides (VIII)/(X) containing (PMR data) ~ 4.5 g (27.7 mmoles) of (VIII) in 7 ml of THF. The reaction mixture was allowed to stand for 1 h at −70°C and, after raising the temperature in the course of 30 min to −30°C, was decomposed by a saturated solution of NH_4Cl. The aqueous layer was separated and extracted with ether. The usual treatment of the combined organic layer gave ~5 g of a material which was chromatographed on 100 g of SiO_2. Elution with a hexane–ether (9:1) mixture gave 2.4 g (44%) of (III) which was identical (GLC, PMR) with an authentic sample of this compound.

Propionate (II). In a similar way, from 2.18 g of a mixture of chlorides (IX)/(XI), containing (PMR data) ~1.45 g (8.2 mmoles) of (IX), 3 ml of 0.1 M of a solution of Li_2CuCl_4 in THF (0.3 mmole) and Grignard reagent, freshly prepared from 2.5 g (16.8 mmoles) of (VII) and 0.54 g (22.2 mg-atom) of Mg in 13 ml of THF, 0.64 g (37%) of (II), was obtained, bp 72-75°C (1 mm) (see [2], bp 70°C, bath, 1 mm). The spectral characteristics of (II) (IR, PMR) practically coincided with those previously published [2] for this compound.

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