SYNTHESIS OF ETHYL β-(2,2-DIMETHYLTETRAHYDRO-4-PYRANYL)-β-OXOPROPIONATE

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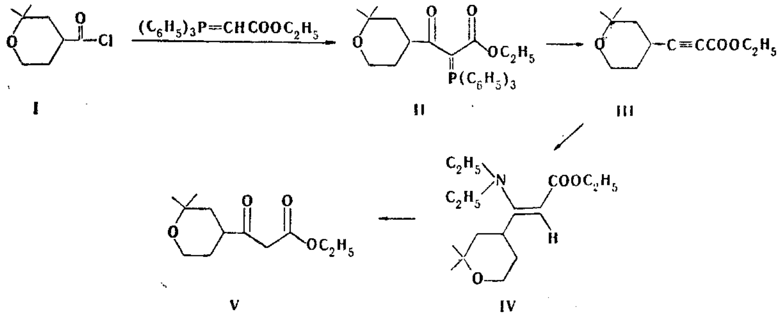
UDC 547.811'812.7.07

The acylation of carbethoxymethylenetriphenylphosphorane with 2,2-dimethyltetrahydropyran-4-carboxylic acid chloride and subsequent pyrolysis of the resulting ylid lead to the formation of ethyl 2,2-dimethyltetrahydro-4-pyranylpropiolate, the hydration of which gives the corresponding β-keto ester.

β-Keto esters are widely used in organic synthesis, but the preparative methods for their synthesis are extremely limited. In the present communication we propose a method for the synthesis of ethyl β-(2,2-dimethyltetrahydro-4-pyranyl)-β-oxopropionate from 2,2-dimethyltetrahydropyran-4-carboxylic acid chloride [1] via the following scheme:



The pyrolysis of ylid II takes place under mild conditions and gives propiolic acid ester III in good yield; the latter is easily converted to β-keto ester V.

EXPERIMENTAL

Analysis by gas–liquid chromatography (GLC) was carried out with a Khrom-4 chromatograph with tamped glass columns and 5% XE-60 silicone on silanized (with hexamethyldisiloxane) Chromaton N-AW. The IR spectra of the compounds were recorded with a UR-20 spectrometer. The mass spectra were recorded with an MKh-1303 spectrometer with direct introduction of the samples into the ionization region.

2,2-Dimethyltetrahydropyran-4-carboxylic Acid Chloride (I) [1]. This compound had bp 67-68 deg C (4 mm) and n_D^{20} 1.4642.

2,2-Dimethyltetrahydro-4-pyranoylcarbethoxymethylenetriphenylphosphorane (II). A solution of 14.4 g (0.08 mole) of I in 250 ml of dry benzene was added at room temperature to a solution of 58.6 g (0.16 mole) of carbethoxymethylenetriphenylphosphorane in 250 ml of dry benzene, and the mixture was stirred for 12 h. The liberated triphenylphosphonium salt was removed by filtration and washed with benzene. The filtrate was evaporated in vacuo, and the residue was dissolved in the minimum amount of ethanol. Water was added to the ethanol solution until the turbidity vanished, and the solution was allowed to stand overnight. The precipitated crystals were removed by filtration and dried in a desiccator over calcium chloride to give 31 g (78%) of II with mp 132-133 deg C. IR spectrum: 1565 (ketone C = O) and 1665 cm^{-1} ($COOC_2H_5$). Found: C 75.0; H 7.0; P 6.5%. $C_{30}H_{33}O_4P$. Calculated: C 74.9; H 6.9; P 6.4%. M^+ 488.

A. L. Mndzhoyan Institute of Fine Organic Chemistry, Academy of Sciences of the Armenian SSR, Yerevan 375014. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 309-310, March, 1979. Original article submitted May 29, 1978; revision submitted July 17, 1978.

Ethyl 2,2-Dimethyltetrahydro-4-pyranylpropiolate (III). A 31-g (0.06 mole) sample of phosphorane II was placed in a Claisen flask, and the flask was evacuated to 1-3 mm and heated gradually with a bath to 200-250 deg C. The product that distilled was collected in a receiver cooled with a mixture of dry ice and acetone. The fraction that boiled up to 200 deg C (1-3 mm) was collected. The reaction product contained admixed triphenylphosphine oxide. Redistillation gave 10 g (75.2%) of acid III with bp 126 deg°C (3 mm), n_D^{20} 1.4770, and d_4^{20} 1.0492. IR spectrum: 2250 ($C\equiv C$) and 1720 ($C=O$) cm^{-1}. Found: C 68.6; H 8.6%; MR_D 56.627. $C_{12}H_{18}O_3$. Calculated: C 68.5; H 8.6%; MR_D 56.711.

Ethyl β-Diethylamino-β-(2,2-dimethyltetrahydro-4-pyranyl)acrylate (IV). A 3-g (0.04 mole) sample of diethylamine was added in the cold to 6 g (0.03 mole) of III in 50 ml of absolute ethanol, after which the mixture was refluxed for 1 h. The ethanol was removed by distillation, and the product was vacuum fractionated to give 4.2 g (50%) of IV with bp 140-141 deg C (2 mm), n_D^{20} 1.4880, and d_4^{20} 1.0130. IR spectrum: 1580 ($C=C$) and 1690 cm^{-1} ($C=O$). Found: C 67.8; H 10.3; N 4.9%; MR_D 80.601. $C_{16}H_{29}NO_3$. Calculated: C 67.8; H 10.3; N 4.9%; MR_D 80.658.

Ethyl β-(2,2-Dimethyltetrahydro-4-pyranyl)-β-oxopropionate (V). A 3.5-g (0.013 mole) sample of IV was dissolved in a small amount of ether, and a saturated solution of 3 g of oxalic acid in ethanol–ether (1:10) containing traces of water was added with vigorous stirring. The mixture was then stirred for 12 h, after which the precipitated amine salt was removed by filtration, and the filtrate was evaporated to half its original volume and washed twice with water. The ether solution was dried with magnesium sulfate, and the solvent was removed by vacuum distillation to give 2 g (71.7%) of acid V with bp 130-131 deg C (2 mm), n_D^{20} 1.4710, and d_4^{20} 1.0868. IR spectrum: 1720 (ketone $C=O$), 1750 ($C=O$ in $COOC_2H_5$), 1660 (enol $C=C$), and 3400 cm^{-1} (enol OH). Found: C 63.1; H 8.8%; MR_D 58.712. $C_{12}H_{20}O_4$. Found: C 63.1; H 8.8%; MR_D 58.724.

LITERATURE CITED

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THREE-DIMENSIONAL STRUCTURES OF 2-ALKYL-4-FORMYLTETRAHYDROPYRANS

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UDC 541.63:547.811:543.422.25

The three-dimensional structures of a number of diastereomeric 2-alkyl-4-formyltetrahydropyrans were studied by means of ^1H and ^{13}C NMR spectroscopy. It is shown that the 2,2-dialkyl derivatives are mixtures of two configurational isomers in which the formyl group is equatorially oriented. 2-Monoalkyl-4-formyltetrahydropyrans exist in the form of mixtures of two diastereomeric forms that have different orientations (axial and equatorial) of the formyl group; the alkyl group in both isomers is equatorially oriented.

2-Alkyl-4-formyltetrahydropyans are the starting compounds in the synthesis of new biologically active substances that have a coronary-dilating effect. Since the physiological activity of organic compounds depends to a considerable extent on the geometry of the molecules, the isolation of each isomer and the determination of its activity are of great interest. In this case it is more convenient to separate the isomers of the starting compounds and subsequently synthesize biologically active compounds with a definite configuration. For this reason, in the present research we undertook a study of the three-dimensional structures of 2-alkyl-4-formyltetrahydropyrans and of the corresponding carboxylic acids and their methyl esters by means of ^1H and ^{13}C NMR spectroscopy.

A. L. Mndzhoyan Institute of Fine Organic Chemistry, Academy of Sciences of the Armenian SSR, Yerevan 375014. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 311-314, March, 1979. Original article submitted April 27, 1978.

0009-3122/79/1503-0254$07.50