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METHOD FOR PREPARATION OF METHYL 3-(2,2-DIMETHYL-4-TETRAHYDROPYRANYL)-3-OXOPROPIONATE

R. S. Vartanyan, Zh. V. Kazaryan, A. P. Engoyan, and S. A. Vartanyan

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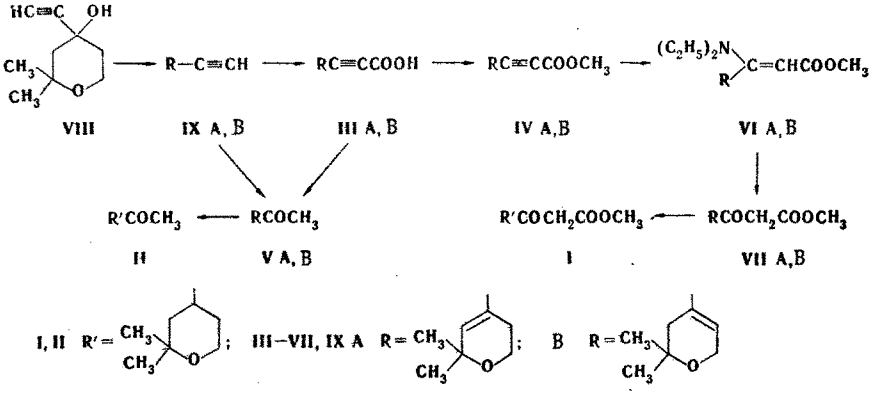
A method is proposed for the synthesis of methyl 3-(2,2-dimethyl-4-tetrahydropyranyl)-3-oxopropionate on the basis of 2,2-dimethyl-4-ethynyltetrahydro-4-pyranol.

β-Keto esters are practically universal starting compounds for the most diverse synthesis in all fields of organic chemistry and particularly in the chemistry of synthetic medicinal substances. In the present communication we propose a method for the synthesis of methyl 3-(2,2-dimethyl-4-tetrahydropyranyl)-3-oxopropionate (I). Attempts to synthesize keto ester I from 2,2-dimethyl-4-cyanotetrahydropyran and zincobromacetic ester [1, 2] by carbalkoxylation [3, 4] of 2,2-dimethyl-4-acetyltetrahydropyran (I) with diethyl carbonate in the presence of a number of basic agents, by acylation [5] of acetoacetic ester with 2,2-dimethyltetrahydropyran-4-carboxylic chloride, and by carboxylation [6] of ketone II with methoxymagnesium methylcarbonate were unsuccessful. An attempt to directly hydrate acetylenecarboxylic acids III and their esters IV in the presence of mercury catalysts, concentrated sulfuric acid, and alkali was also unsuccessful [7]. Ketones V were obtained in this case under acidic conditions. Indirect hydration IV → VII [7], on the basis of which the synthesis of keto ester I was also developed, proved to be extremely effective:



The dehydration of alcohol VIII [8] to a mixture of isomeric ethynyldihydropyrans IX was accomplished by a known method [9]. In the course of the entire synthesis the work was carried out with a mixture of isomers A and B, the ratio of which was determined both by gas–liquid chromatography (GLC) and PMR spectroscopy (Table 1).

A. L. Mndzhoyan Institute of Fine Organic Chemistry, Academy of Sciences of the Armenian SSR, Erevan 375014. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 466-469, April, 1979. Original article submitted July 31, 1978.

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TABLE 1. Parameters of the PMR Spectra of III-VII and IX*

Compound	Isomer A: δ, ppm (J, Hz)				Isomer B: δ, ppm (J, Hz)			
	C=CH	5-CH_2	6-CH_2	2-CH_3	3-CH_2	C=CH	6-CH_2	2-CH_3
III	6,20 t (1,60)	2,15 td (5,6; 1,6)	3,75 t (5,6)	1,27 s	2,15 m	6,33 tt (2,80; 1,6)	4,20 m	1,23 s
IV	6,21 t (1,80)	2,15 td (5,6; 1,8)	3,72 t (5,6)	1,25 s	2,15 m	6,35 tt (3,0; 1,8)	4,17 m	1,20 s
VI	5,35 t (1,6)	2,10 td (5,4; 1,6)	3,87 t (5,4)	1,27 s	2,15 m	5,55 tt (2,8; 1,6)	4,15 m	1,15 s
V	6,63 t (1,6)	2,15 td (5,6; 1,6)	3,65 t (5,6)	1,27 s	2,15 m	6,78 tt (2,8; 1,6)	4,20 m	1,15 s
VII	6,65 t (1,6)	2,25 td (5,6; 1,6)	3,77 t (5,6)	1,35 s	2,2 m	6,83 tt (2,8; 1,6)	4,3 m	1,20 s
IX	5,93 t (1,7)	2,10 td (5,6; 1,7)	3,67 t (5,6)	1,20 s	2,1 m	6,05 tt (2,8; 1,7)	4,10 m	1,15 s

*Spectra of III-VII were recorded in $CDCl_3$, while that of IX was recorded in CCl_4. Abbreviations: s is singlet, t is triplet, m is multiplet, td is triplet of doublets, and tt is triplet of triplets.

Two signals — a multiplet and a more intense triplet (J = 1.6-1.8 Hz) — are observed in the PMR spectra of III-VII and IX in the region of the resonance of the olefin protons. The latter signal should be assigned to isomer A, since the 3-H proton in this form couples only with the protons of the 5-methylene group. Two spin–spin coupling constants (SSCC) of 3 and 1.6-1.8 Hz, which are evidently due to spin–spin couplings of the olefin proton of isomer B, respectively, with the 6-CH_2 and 3-CH_2 groups, are obtained from an analysis of the less intense multiplet. Structure A in the PMR spectra is also characterized by two triplet signals (J = 5.6 Hz) of the methylene groups of the 5 and 6 positions of the heteroring; in the latter case doublet splitting up of the components of the triplet due to coupling with the 3-H proton also is displayed. The multiplets of 4.1-4.2 and 2.1-2.2 ppm are related to the 6-CH_2 and 3-CH_2 groups of isomer B. A difference in the chemical shifts of the singlet signals of the 2-methyl groups of the two isomeric forms is also observed in the PMR spectra. Thus III-VII and IX are a mixture of two isomeric forms A and B with appreciable predominance of the former (70:30).

In addition to the signals already examined, a singlet at 5.05 ppm, a triplet of 6.48 ppm (J = 1.6 Hz), and a broad signal at 12.0 ppm are observed in the PMR spectrum of VII. The appearance of these signals is evidently due to the presence in solution of a keto–enol equilibrium. The triplet signal at 6.48 ppm is related to the olefinic proton of the enol form of isomer VIIA, while the two others correspond to the protons of the double bond (5.05 ppm) and the OH group (12.0 ppm) of the enol form of the same isomer. The tautomeric equilibrium constant K = ketone/enol is five in chloroform solution. On passing to alcohol solutions (CD_3OD) the amount of enol increases (K = 3), but a decrease in the intensity of the signals of the protons attached to the exocyclic double bond of this form and of the CH_2 group of the ether fragment of the keto form is observed as time passes. Consequently, these changes are not due to a shift in the equilibrium but rather to deuterium exchange of the labile protons of the OH and CH_2 groups in deuteromethanol.

Isomer B is also found in a mixture of the two tautomeric forms. However, considering the magnitude of the tautomeric equilibrium constant of isomer A, the amount of the enol form of isomer B in the overall mixture should be insignificant. The absence of signals of the enol of this isomer in the PMR spectra can evidently be explained precisely by this circumstance.

Final keto ester I was obtained by hydrogenation of VII. Its tautomeric equilibrium constant in chloroform solution is five.

EXPERIMENTAL

Analysis by GLC was carried out with filled glass columns with 5% XE-60 silicone on Chromaton N-AW-HMDS as the liquid phase. The IR spectra were recorded with a UR-20 spectrometer. The PMR spectra were recorded with a Varian T-60 spectrometer with tetramethylsilane as the internal standard.

(2,2-Dimethyl-4-dihydropyranyl)propiolic Acids (III). A 36.5-g (0.268 mole) sample of a mixture of dimethyldihydropyrans IX in an equal volume of ether was added at 10-15°C to a Grignard reagent obtained from 42.2 g (0.386 mole) of ethyl bromide, and 7.8 g (0.325 mole) of magnesium in 200 ml of ether. The next day, the mixture was cooled to −10 to −15°C, and a strong stream of dry CO_2 was passed through it until the resulting exothermic reaction ended. Hydrochloric acid solution (8-10%) was added to the mixture of hydrolyze it, and the reaction product was extracted thoroughly with ether. The ether extract was washed with water and dried with magnesium sulfate, and the solvent was removed by distillation to give a mixture of acids III with mp 148-149°C. The yield was 67%. IR spectrum: 1720 (C=O), 1660 (C=C), and 2230 cm^{-1} (C=C). Found: C 66.7; H 6.8%. $C_{10}H_{12}O_3$. Calculated: C 66.6; H 6.7%.

Where necessary, the acid was purified by the usual method.

Methyl (2,2-Dimethyl-4-dihydropyranyl)propiolates (IV). An ether solution of 0.2 mole of diazomethane (where necessary, the diazomethane was added until N_2 evolution ceased) was added with stirring to a solution of 28 g (0.15 mole) of a mixture of acids III in 200 ml of absolute ether, and the mixture was stirred for another 30 min, after which the solvent was removed by distillation. Vacuum distillation of the residue gave 22 g (70%) of a mixture of esters IV with bp 134°C (7 mm), n_D^{20} 1.4952, and d_4^{20} 1.0590. IR spectrum: 1720 (C=O), 1635 (C=C), and 2230 cm^{-1} (C=C). Found: C 68.1; 7.3%; MR_D 53.50. $C_{11}H_{14}O_3$. Calculated: C 68.0; H 7.2%; MR_D 51.63.

Methyl 3-(2,2-Dimethyl-4-dihydropyranyl)-3-diethylaminoacrylates (VI). A 2.5-g (0.03 mole) sample of diethylamine was added in the cold to the solution of 4.6 g (0.023 mole) of a mixture of esters IV in 30 ml of absolute ethanol, and the mixture was refluxed for 30 min. It was then distilled to give 5.5 g (75%) of a mixture of amino esters VI with bp 153-155°C (5 mm), n_D^{20} 1.5029, and d_4^{20} 1.0322. IR spectrum: 1715 (C=O) and 1570 cm^{-1} (C=C). Found: 67.4; H 9.5; N 5.3%; MR_D 76.56. $C_{15}H_{25}NO_3$. Calculated: C 67.3; H 9.4; N 5.2%; MR_D 75.57.

Methyl 3-(2,2-Dimethyl-4-dihydropyranyl)-3-oxopropionates (VII). A saturated solution of 6.3 g (0.048 mole) of oxalic acid in a mixture of ethanol and ether (1:10) containing a few drops of water was added to a stirred solution of 10.7 g (0.04 mole) of a mixture of amine esters VI in 50 ml of ether, and the mixture was stirred for 12 h, after which it was filtered, and the filtrate was evaporated to half its original volume. The residue was washed with water and dried with magnesium sulfate. The solvent was removed by distillation, and the hydrolysis product was vacuum distilled to give 6.2 g (73%) of a mixture of keto esters VII with bp 134-135°C (3 mm), n_D^{20} 1.4787 and d_4^{20} 1.1144. IR spectrum: 1765 (ester C=O), 1690 (C=O), 1620 (C=C), and 1650 cm^{-1} (enol C=C). Found: C 62.7; H 7.6%; MR_D 53.98. $C_{11}H_{16}O_4$. Calculated: C 62.2; H 7.7%; MR_D 53.64.

Methyl 3-(2,2-Dimethyl-4-tetrahydropyranyl)-3-oxopropionate (I). A 3.1-g (0.015 mole) sample of a mixture of keto esters VII in 50 ml of absolute ethanol was hydrogenated in the presence of 0.1 g of platinum dioxide (the Adams catalyst) until the calculated amount of hydrogen had been absorbed. Workup gave 2.8 g (90%) of I with bp 122-123°C (2 mm), n_D^{20} 1.4660,and d_4^{20} 1.0989. IR spectrum: 1765 (ester C=O), 1730 (C=O), and 1650 cm^{-1} (enol C=C). Found: C 61.7; H 8.5%; MR_D 54.00. $C_{11}H_{18}O_4$. Calculated: C 61.6; H 8.4%; MR_D 54.21.

4-Acetyl-2,2-dimethyldihydropyrans (V). A) A 16-g (0.1 mole) sample of a mixture of ethynyldihydropyrans IX in an equal volume of methanol was added dropwise with stirring on a boiling-water bath to a mixture of 26 ml of 7% sulfuric acid, 50 ml of methanol, and 2 g of mercuric oxide; and the mixture was refluxed for 5-6 h. The next day, it was filtered, and the methanol was removed from the filtrate by evaporation. The residue was neutralized with concentrated sodium carbonate solution and extracted with ether. The extract was dried with magnesium sulfate, the solvent was removed by distillation, and the hydration product was vacuum distilled to give 16 g (88%) of a mixture of ketones V with bp 72-74°C (3 mm), n_D^{20} 1.4722 and d_4^{20} 1.0072. IR spectrum: 1690 (C=O) and 1660 cm^{-1} (C=C). Found: C 70.1; H 9.1%; MR_D 42.89. $C_9H_{14}O_2$. Calculated: C 70.1; H 9.1%; MR_D 42.75. The 2,4-dinitrophenylhydrazone has mp 182-183°C. Found: N 16.8%. $C_{15}H_{18}N_4O_5$. Calculated: N 16.7%.

B) Under similar conditions, 14.4 g (80%) of a mixture of ketones V was obtained from 18 g (0.1 mole) of a mixture of acids III.

4-Acetyl-2,2-dimethyltetrahydropyran (II). A 10-g (0.065 mole) sample of a mixture of ketones V in 50 ml of absolute ethanol was hydrogenated in the presence of 0.1 g of platinum dioxide (Adams catalyst) until the calculated amount of hydrogen (1.5 liters) had been absorbed. Workup gave 7 g (69%) of ketone II with bp 67-68°C (3mm), n_D^{20} 1.4710 and d_4^{20} 1.0074.

IR spectrum: 1725 cm^{-1} (C=O). Found: C 69.2; H 10.3%; MR_D 43.35. $C_9H_{16}O_2$. Calculated: C 69.1; H 10.3%; MR_D 43.22. The 2,4-dinitrophenylhydrazone had mp 177-178°C. Found: N 16.7%. $C_{15}H_{20}N_4O_5$. Calculated: N 16.7%.

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1-METHOXY-3,5-DIARYL-2-OXABICYCLO[4.4.0]DEC-3-ENES FROM "SEMICYCLIC" 1,5-DIKETONES

L. V. Vlasova, T. I. Tyrina,
S. K. Klimenko, and V. G. Kharchenko

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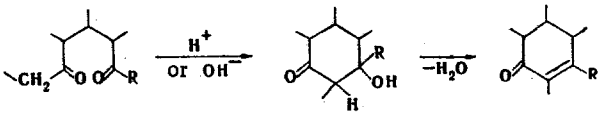
It was established that "semicyclic" 1,5-diketones are capable of reacting with methanol by the catalytic action of hydrogen chloride and are capable of forming 1-methoxy-3,5-diaryl-2-oxabicyclo[4.4.0]dec-3-enes — cyclic acetals that include an alkoxydihydropyran ring. In addition, 2,4-darylbicycle[3.3.1]non-2-en-9-ones, which are formed from 1,3-diaryl-3-(2-oxocyclohexyl)propan-1-ones by an intramolecular condensation of the erotonic type, are detected as side products. The possible mechanism of the reaction of 1,3-diaryl-3-(2-oxocyclohexyl)propan-1-ones with methanol in the presence of hydrogen chloride is discussed.

It is well known that "semicyclic" 1,5-diketones that contain a methyl or methylene group in the α position with respect to one of the carbonyls easily undergo intramolecular condensation of the aldol-crotonic type under conditions of both basic and acid catalysis [1, 2].

1,5-Diketones that contain aryl groups in the α positions are capable of undergoing conversion to pyrylium salts under the influence of acids [3, 4].



Allen and Sallans [2] have observed that under the influence of sulfuric acid 1,3-diphenyl-3-(2-oxocyclohexyl)propanone (I) reacts with methanol to give a cyclic acetal, i.e., 1-methoxy-3,5-diphenyl-2-oxabicyclo[4.4.0]dec-3-ene (VIII).

During a study of the reaction of diketone I with hydrogen sulfide in methanol under the influence of hydrogen chloride we observed that diketone I underwent reaction with methanol rather than with hydrogen sulfide to give acetal VIII, which is identical to the substance obtained by Allen and Sallans [2].

N. G. Chernyshevskii Saratov State University, Saratov 410026.

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