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REGIOSELECTIVE REACTION OF ALKYL DIAZOACETATES WITH TRIMETHYLSILYLISOPROPENYLACETYLENE AND CHEMICAL CONVERSIONS OF THE RESULTING ESTERS OF TRIMETHYLSILYLETHYNYLMETHYLCYCLOPROPANECARBOXYLIC ACID

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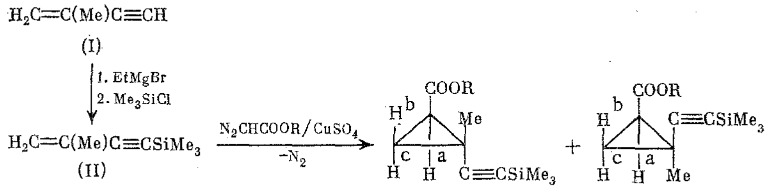
The reaction of alkyl diazoacetates (ADA) with conjugated enynes with an internal triple bond proceeds regioselectively both with respect to the triple and the double bond [1]. The reaction of ADA with enynes with a terminal triple bond such as isopropenylacetylene (I) affords only pyrazoles, the products of 1,3-dipolar addition to the C ≡ C bond [2]. It was therefore of obvious interest to develop a method of synthesis from terminal enynes of ethynylcyclopropanecarboxylate esters, which could be of value as insecticides and drugs [3].

Since the introduction of the trialkylsilyl substituent substantially reduces the reactivity of the triple bond in reactions with ADA [4], it would be expected that similar deactivation of the triple bond in conjugated enynes would direct the attack of ADA on the double bond to form the cyclopropane adduct, from which the Me_3Si group could be removed by alkaline hydrolysis of the Si–C bond [5].

It has been found that reaction of ADA in the presence of $CuSO_4$ at 100-110°C with an excess of trimethylsilylisopropenylacetylene (II), obtained in 68% yield by the silylation of (I), affords the alkyl esters of the isomeric 2-methyl-2-trimethylsilylethynylcyclopropanecarboxylic acid (III) in yields up to 80%. Products of the addition of alkoxycarbonylcarbenes to the triple bond, or diadducts of the carbenes to the double and triple bonds, were not found, enabling a threefold excess of the enyne (II) to be employed.



trans-(III) cis-(III)

R = Me(a), Et(b).

Thus, the introduction of the Me_3Si group reduces the reactivity of the triple bond in the enyne to such an extent as to enable the ADA to react selectively under the usual conditions with enynes exclusively at the double bond.

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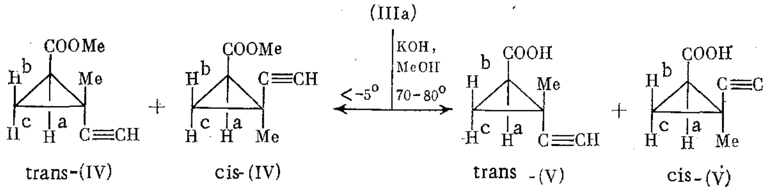
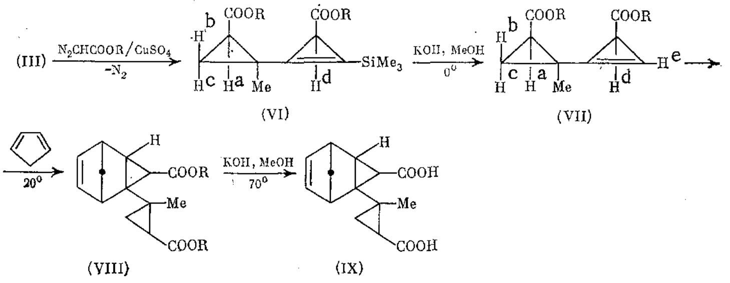
Hydrolysis of the esters (III) with aqueous-alcoholic KOH is highly temperature-dependent. At −5° and below, only the Me_3Si group is removed to give an overall yield of 72% of a mixture of the methyl esters of trans- and cis-2-methyl-2-ethynylcyclopropanecarboxylic acids (IV), which were separated by TLC and identified by their IR, PMR, and mass spectra. At 70-80°, fission of the Me_3Si group is accompanied by hydrolysis of the ester group, affording a mixture of isomeric acids (V) in an overall yield of 62%.



Thus, this method enables the acids (V) to be obtained from the enyne (I) in an overall yield of 35-40%, and can obviously be regarded as a general method for the synthesis of ethynylcyclopropanecarboxylic acids from enynes possessing a terminal triple bond.

We have also examined the reaction of ADA with the esters (III). It is known that despite the reduced reactivity of the triple bond consequent upon substitution with Me_3Si, silylated acetylenes react with ADA to form esters of silylcyclopropene-3-carboxylic acids, which are readily desilylated with alkalis [4]. We have also succeeded in alkoxycarbonylmethylenating the triple bond in (III) by reaction with a threefold excess of ADA in the presence of $CuSO_4$ at 110-120° to give the diesters (VI) in yields of up to 30% and 70-80% conversion of the esters (III).



R = Me(a), Et(b).

Treatment of the silylated diesters (VI) with aqueous-alcoholic KOH at 0° resulted, as would be expected [4], in removal of the Me_3Si group to form the unstable diesters (VII), which polymerize under the reaction conditions. Reliable spectral proof of the formation of the diesters (VII) is the presence of a signal in the PMR spectra of chloroform extracts of the reaction mixture with δ 6.3 ppm which disappears on keeping the sample, due to the H^e atom on the multiple bond of the cyclopropene ring.

Separation of the labile diesters (VII) was effected as the adducts with cyclopentadiene (CPD). Treatment with an excess of CPD of a toluene solution of (VIIa), obtained by extraction of the hydrolysis products of (VIa), gave the methyl ester of 2-(1-methyl-2-methoxycarbonylcyclopropyl)-tricyclo[3.2.1.$0^{2,4}$]oct-6-ene-3-carboxylic acid (VIIIa) in a yield of 70% calculated on ester (VIa). The diester (VIIIb) was similarly obtained in 60% yield. Hydrolysis of the diester (VIIIa) with aqueous-alcoholic KOH gave the acid (IX) in 52% yield.

The silylated diester (VIb) did not react with CPD even on prolonged boiling in xylene, in agreement with the previously observed behavior of similar esters in this reaction [6].

EXPERIMENTAL

GLC analyses were carried out on an LKhM-8MD instrument with a katharometer, on 2 m × 2 mm columns with 15% Reoplex on Chromaton N-AW-DMCS, carrier gas helium, 30 ml/min. The PMR spectra of solutions in $CHCl_3$ and CCl_4 were obtained on a Tesla BS-497 instrument (100 MHz, internal standard TMS). The IR spectra were obtained on a UR-10 instrument, and mass spectra on a Varian MAT CH-6 instrument. Separation of pure compounds was achieved by preparative TLC (PTLC) on silica gel, eluent hexane—benzene—ether in a volume ratio of 4:2:1.

The alkyl diazoacetates (ADA) were obtained as described in [7]. Isopropenylacetylene was prepared by the dehydration of dimethylethynylcarbinol according to [8].

Trimethylsilylisopropenylacetylene (II). To a solution of EtMgBr (from 1 g-atom of Mg and 1 mole of EtBr) in 0.7 liter of absolute ether was added 0.6 mole of (I); the mixture boiled for 3 h, 1 mole of Me_3SiCl added over 1 h, and boiling continued for 6 h. The mixture was decomposed with a saturated solution of NH_4Cl, and extracted with ether. The extracts were washed with water, 5% $NaHCO_3$, and a saturated solution of NaCl, dried over anhydrous Na_2SO_4, and evaporated to give 56.6 g (68%) of (II), bp 61° (58 mm), n_D^{20} 1.4440. IR spectrum (ν, cm^{-1}): 2150 ($C \equiv C$). PMR spectrum (in $CHCl_3$, δ, ppm): 0.39 s (9H), 2.08 s (3H), 5.5 dd (2H).

Methyl and Ethyl Esters of 2-Methyl-2-trimethylsilylethynylcyclopropanecarboxylic Acid (IIIa and b). To a suspension of 0.01 g of anhydrous $CuSO_4$ in 40 g of (II) heated to 105° was added over 7 h a mixture of 11 g (0.11 mole) of methyl diazoacetate (MDA) and 9 g of (II) [total amount of (II) 49 g (0.36 mole)]. Heating was continued for 0.5 h, until evolution of N_2 had ceased, unreacted (II) was distilled off, and the residue distilled to give 18.3 g (80%) of a mixture of isomeric (IIIa), bp 91° (7 mm), n_D^{20} 1.4615, d_4^{20} 0.9344. IR spectrum (ν, cm^{-1}): 1735 ($C=O$), 2170 ($C \equiv C$). PMR spectrum (in $CHCl_3$, δ, ppm): 3.64 s (OCH_3), 1.97 dd (H^a of the trans isomer), 1.5-1.7 (H^a and H^b of the cis isomer), 1.3 s (CH_3), 1.07-1.3 (H^b and H^c of the trans isomer), 0.95 m (H^c of the cis isomer), 0.05 s [$Si(CH_3)_3$]. Mol. wt. 210 (mass spectrometric). The trans-cis isomer ratio was 1.15:1 (GLC, 160°).

There was obtained similarly a mixture of the trans and cis isomers of (IIIb) in a ratio of 1.15:1 (GLC, 160°), yield 75%, bp 97-100° (6 mm), n_D^{20}1.4600. IR spectrum (ν, cm^{-1}): 1735 ($C=O$), 2170 ($C \equiv C$). PMR spectrum (in $CHCl_3$, δ, ppm): 4.1 q (OCH_2), 1.95 dd (H^a of the trans isomer), 1.5-1.7 (H^a and H^b of the cis isomer), 1.3 s (CH_3), 1.20 (CH_3CH_2O), 1.07-1.3 (H^b and H^c of the trans isomer), 0.95 m (H^c of the cis isomer), 0.05 s [$Si(CH_3)_3$].

Methyl Ester of 2-Methyl-2-ethynylcyclopropanecarboxylic Acid (IV). To a cooled solution (−40°) of 1 g (0.018 mole) of KOH in 24 ml of MeOH was added over 10 min 4.2 g (0.02 mole) of (IIIa). The mixture was warmed to −5°, and kept at this temperature for 5 h until the reaction was complete, the progress of the reaction being followed by GLC at 160°. The mixture was neutralized with 5% sulfuric acid, diluted with 50 ml of water, and extracted with ether following saturation of the aqueous layer with NaCl. Yield 2 g (72%) of a mixture of the trans and cis isomers of (IV), bp 70-75° (33 mm), from which the pure isomers were isolated by PTLC.

trans-(IV). IR spectrum (ν, cm^{-1}): 1730 ($C=O$), 2125 ($C \equiv C$), 3315 ($\equiv C-H$). PMR spectrum (in $CHCl_3$, δ, ppm): 3.64 s (CH_3O), 2.05 dd (H^a), 1.93 s ($C \equiv CH$), 1.39 s (CH_3), 1.1-1.3 ($H^b + H^c$). Mol. wt. 138 (mass spectrometric).

cis-(IV). IR spectrum (ν, cm^{-1}): 1730 ($C=O$), 2125 ($C \equiv C$), 3315 ($\equiv C-H$). PMR spectrum (in $CHCl_3$, δ, ppm): 3.65 s (CH_3O), 1.96 s ($C \equiv CH$), 1.70 dd (H^a), 1.53 dd (H^b), 1.33 s (CH_3), 1.01 dd (H^c). Mol. wt. 138 (mass spectrometric).

2-Methyl-2-ethynylcyclopropanecarboxylic Acid (V). To a solution of 8 g (0.14 mole) of KOH in 40 ml of methanol was added 1.21 g (0.058 mole) of (IV), boiled for 8 h, and evaporated to dryness. The residue was dissolved in water, washed with ether, acidified with 5% sulfuric acid, and extracted with ether after saturation of the aqueous layer with NaCl. Yield 4.45 g (62%) of (V), bp 100-105° (7 mm), mp 47-48°. IR spectrum (KBr, ν, cm^{-1}): 1700 ($C=O$), 2125 ($C \equiv C$), 3000 br (OH), 3290 ($\equiv C-H$). PMR spectrum (in $CHCl_3$, δ, ppm): 11.0 s (OH), 2.00 and 1.92 s ($C \equiv CH$ of the trans and cis isomers), 1.43 and 1.37 s (CH_3 of both isomers). Mol. wt. 124 (mass spectrometric).

Methyl and Ethyl Esters of 1-(1-Methyl-2-alkoxycarbonylcyclopropyl)-2-trimethylsilylcyclopropene-3-carboxylic Acids (VIa and b). To a suspension of 0.02 g (0.2 mmole) of anhyd. $CuSO_4$ in 25.4 g (0.12 mole) of (IIIa) heated to 115° was added over 18 h a solution of 25 g (0.25 mole) of MDA in 20 ml of toluene, and the mixture kept for 30 min until evolution of N_2 had ceased. The toluene was removed and the residue distilled to give 10.4 g (31%) of isomeric (VIa), bp 101-104° (2 mm), n_D^{20} 1.4772. IR spectrum (ν, cm^{-1}): 1730 ($C=O$), 1825 ($C=C$). PMR spectrum (in $CHCl_3$, δ, ppm): 3.48-3.66 group of singlets (OCH_3), 1.9 s (H^d), 1.42 and 1.36 s (CH_3, two isomers), 1.0-2.1 m (H^a, H^b, and H^c), 0.1 s [$Si(CH_3)_3$]. Mol. wt. 292 (mass spectrometric).

Similarly was obtained (VIb), yield 30%, bp 110-113° (3 mm). IR spectrum (ν, cm^{-1}): 1725 ($C=O$), 1825 ($C=C$). PMR spectrum (in $CHCl_3$, δ, ppm): 3.95 m (CH_2O on the trans and cis isomers), 1.9 s (H^d), 1.40 and 1.32 s (CH_3 of the trans and cis isomers). Mol. wt. 310 (mass spectrometric).

Methyl Ester of 1-(1-Methyl-2-methoxycarbonylcyclopropyl)cyclopropene-3-carboxylic Acid (VIIa). To a cooled solution (0°) of 0.04 mole of KOH in 4 ml of methanol was added over 5 min 0.04 mole of (VIa). The mixture was kept for 2 h at 0°, neutralized at 0° with 5% sulfuric acid, and extracted with chloroform (2 × 5 ml).

The extracts were dried over $MgSO_4$ and their PMR spectra obtained (δ, ppm): 6.3 t (H^e), 2.06 t (H^d), 1.40 and 1.36 s (CH_3, trans and cis isomers); $J_{ab} \sim 2.5$ Hz.

Methyl and Ethyl Esters of 2-(1-Methyl-2-alkoxycarbonylcyclopropyl)tricyclo[3,2,1,$0^{2,4}$]oct-6-ene-3-carboxylic Acids (VIIIa and b). 0.004 mole of (VIa) was hydrolyzed as described above, and extracted with toluene (2 × 5 ml). The extracts were combined, dried over $MgSO_4$, treated with 0.4 g (0.06 mole) of freshly distilled CPD, and kept at 20° for a further 10 h, the course of the reaction being followed by TLC. Following disappearance of the spot with R_f 0.17 corresponding to the cyclopropene (VIa), the mixture was evaporated in vacuo, and the residue (1.02 g) subjected to PTLC to give 0.75 g [70% calculated on (VIa)] of (VIIIa) as a colorless, viscous oil. IR spectrum (ν, cm^{-1}): 1660 (C=C), 1730 (C=O). PMR spectrum (in $CHCl_3$, δ, ppm): 5.88 m (HC=CH), 3.4-3.7 (group of singlets, OCH_3). The mass spectrum of (VIIIa) showed the ion ($M-CH_3OH$), which is characteristic of the breakdown of the methyl esters of cyclopropanecarboxylic acids [9].

Similarly was obtained (VIIIb) in a yield of 60%, calculated on (VIb). IR spectrum (ν, cm^{-1}): 1620 (C=C), 1725 (C=O). PMR spectrum (in CCl_4, δ, ppm): 5.88 m (HC=CH), 4.05 m (OCH_2), 1.24 m ($OCH_2\underline{CH_3}$).

2-(1-Methyl-2-carboxycyclopropyl)tricyclo[3.2.1.$0^{2,4}$]oct-6-enecarboxylic Acid (IX). To a solution of 0.45 g (8 mmole) of KOH in 0.5 ml of water and 3 ml of methanol was added a solution of 0.95 g (3.4 mmole) of (VIIIa) in 1 ml of methanol. The mixture was heated for 5.5 h at 70°, evaporated to dryness, and the residue dissolved in 5 ml of water and washed with ether. The aqueous layer was acidified under a layer of ether with 5% sulfuric acid and extracted with ether following saturation of the aqueous layer with NaCl to give 0.44 g (52%) of (IX), mp 55-58°. IR spectrum (ν, cm^{-1}): 1680 (C=C), 1700 and 1730 (C=O). PMR spectrum (in CCl_4, δ, ppm): 11.93 s (OH), 5.88 m (HC=CH). The mass spectrum of (VIIIc) showed the presence of the ($M-H_2O$) ion.

CONCLUSIONS

1. Thermocatalytic reaction of alkyl diazoacetates with an excess of trimethylsilylisopropenylacetylene in the presence of $CuSO_4$ at 100-110° proceeds regioselectively at the double bond only, with the formation of esters of 2-trimethylsilylethynyl-2-methylcyclopropanecarboxylic acid, hydrolysis of which with aqueous-alcoholic KOH affords, according to the temperature, 2-methyl-2-ethynylcyclopropanecarboxylic acid (above 70°) or its esters (below − 5°) in an overall yield of up to 40%, calculated on isopropenylacetylene. This use of a silyl protecting group may be regarded as a general method for the synthesis of ethynylcyclopropanecarboxylic acids from enynes with terminal triple bonds.

2. Esters of 2-trimethylsilylethynyl-2-methylcyclopropanecarboxylic acid react in the presence of $CuSO_4$ at 110-115° with an excess of alkyl diazoacetates at the triple bond with the formation of alkyl esters of 1-(1-methyl-2-alkoxycarbonylcyclopropyl)cyclopropene-3-carboxylic acids in yields of up to 30%. These are hydrolyzed by alkali to the unstable esters of 1-(1-methyl-2-alkoxycarbonylcyclopropyl)cyclopropene-3-carboxylic acids, isolated as their adducts with cyclopentadiene.

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