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Reaction of 5-Allyl-2,3,5-trichloro-4,4-dimethoxycyclopent-2-en-1-one with Amino Acids

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Abstract—5-Allyl-2,3,5-trichloro-4,4-dimethoxycyclopent-2-en-1-one reacts with L-proline and L-methionine methyl esters to give diastereoisomeric mixtures of the corresponding chlorine replacement products at C^3.

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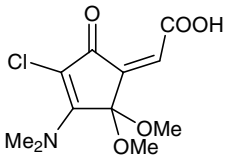
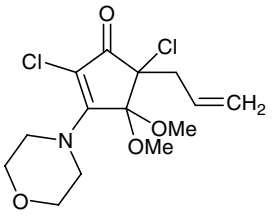
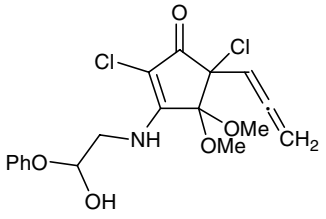
Taking into account increasing propagation of various viral infections, studies in the field of synthesis of effective antiviral agents have become especially important in the recent years [1, 2]. Among a series of trichlorocyclopentenones [3] synthesized in our laboratory, compounds **I**–**III** showed a high activity against tobacco mosaic virus [4, 5].



I



II



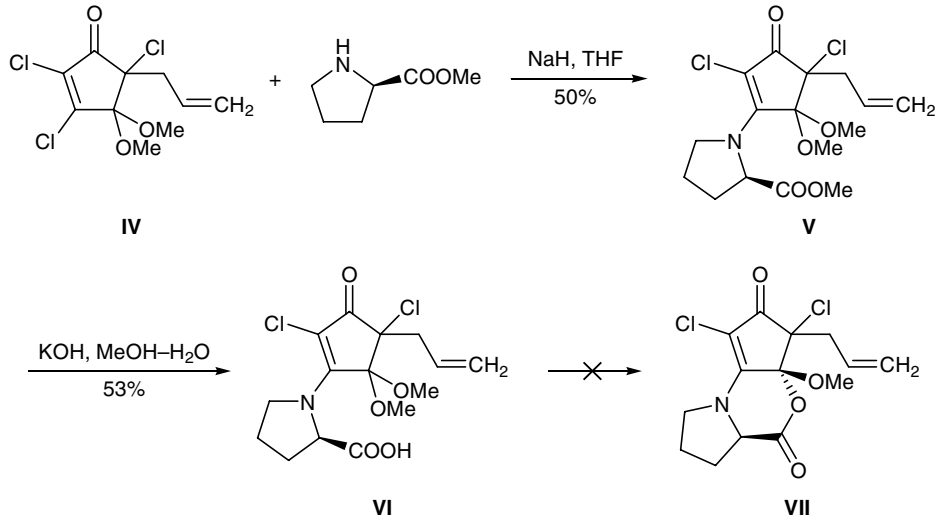
III

In the present work we examined reactions of 5-allyl-2,3,5-trichloro-4,4-dimethoxycyclopent-2-en-1-one (**IV**) [3] with some amino acids, in particular with L-proline and L-methionine. When the reaction of **IV** with L-proline was performed under standard conditions for the synthesis of 3-amino-5-allyl-2,5-dichloro-4,4-dimethoxycyclopent-2-en-1-ones [3] (2.5–3 equiv of a primary or secondary amine, MeOH or benzene, 20°C), an intractable mixture of products was slowly formed. We modified the conditions and used the corresponding amino acid methyl ester, NaH as base, and THF as solvent. In this case, the expected 3-substituted derivative **V** was obtained in 54% yield (Scheme 1). Compound **V** was purified by column chromatography on silica gel and was subjected to alkaline hydrolysis (KOH in aqueous methanol) to obtain acid **VI**.

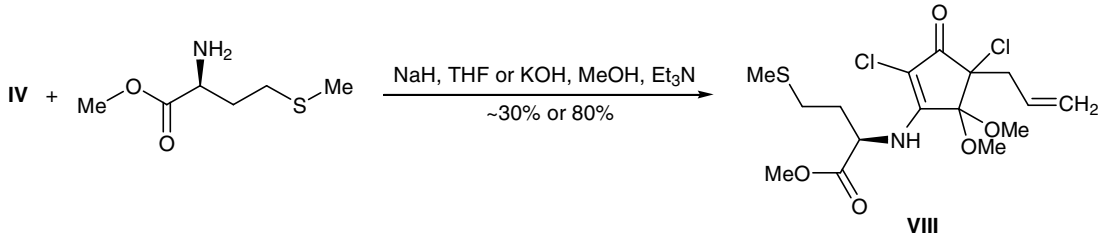
According to the ^{1}H and ^{13}C NMR data, product **V** was a ~1:1 mixture of diastereoisomers (the diastereoisomer ratio was determined from the intensities of the ester methoxy proton signals). The ^{13}C NMR spectrum of **V** contained doublets from the NCH_2 group at δ_C 44.69 and 43.34 ppm and from the NCH carbon atom at δ_C 62.39 and 61.60 ppm; signals from $C^{1'}$, $C^{3'}$, and $C^{4'}$ were also doubled. Protons of the methoxycarbonyl group resonated in the ^{1}H NMR spectrum of **V** as two almost merged singlets at δ 3.67 and 3.68 ppm. Methoxy groups on C^4 give rise to three singlets at δ 3.50, 3.20, and 3.10 ppm with an intensity ratio of about 6:3:3. In the ^{1}H NMR spectrum of acid **VI** methoxy groups in different diastereoisomers are not diastereotopic, and the corresponding singlets with equal intensities appear at δ 3.22 and 3.52 ppm. We failed to effect cyclization of compound **VI** into lactone **VII** by heating in boiling toluene in the presence of *p*-toluenesulfonic acid, and the initial acid was recovered from the reaction mixture.

Under analogous conditions, in the reaction of L-methionine methyl ester with trichlorocyclopentenone **IV** we obtained 3-amino derivative **VIII** in 30% yield (Scheme 2). We succeeded in raising the yield of **VIII** to 80% by carrying out the reaction in methanol

Scheme 1.



Scheme 2.



in the presence of KOH. Like compound **V**, ester **VIII** was isolated as a mixture of two diastereoisomers. In the ^{1}H NMR spectrum of **VIII** we observed three signals from methoxy groups on $C^{5'}$ as singlets at δ 3.35, 3.48, and 3.52 ppm with an intensity ratio of 6:3:3 (in the spectrum of **V**, the upfield signals had lower intensity), and methoxy protons of the ester fragment resonated as two singlets at δ 3.81 and 3.82 ppm. Compound **VIII** showed in the ^{13}C NMR spectra doubled signals from carbon atoms at the allyl double bond, $C^{1'}$, and SMe and MeO groups.

EXPERIMENTAL

The IR spectra were recorded on UR-20 and Specord M-80 spectrometers from samples prepared as thin films (neat) or dispersed in mineral oil. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker AM-300 instrument at 300.13 and 75.47 MHz, respectively, using tetramethylsilane as internal reference. Thin-layer chromatography was performed on Silufol plates; spots were visualized by calcination or treatment with an alkaline solution of potassium permanganate. The optical rotations were measured on a Perkin–Elmer 341 polarimeter.

Methyl 1-(4-allyl-2,4-dichloro-5,5-dimethoxy-3-oxocyclopent-1-en-1-yl)pyrrolidine-2-carboxylate (V). Sodium hydride, 0.3 g (6.14 mmol; a 55% suspension in mineral oil was preliminarily washed with anhydrous hexane) was dispersed in 5 ml of anhydrous benzene, a solution of 0.34 g (2.63 mmol) of proline methyl ester in 6 ml of benzene was added dropwise under argon, the mixture was stirred for 30 min, and a solution of 0.5 g (1.78 mmol) of compound **IV** in 3 ml of benzene was added dropwise. The mixture was stirred at room temperature until initial compound **IV** disappeared (TLC), and 5 ml of a saturated solution of ammonium chloride was added. The organic layer was separated, the aqueous layer was extracted with chloroform (3×10 ml), and the extracts were combined with the organic phase, washed with a saturated solution of sodium chloride, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel using petroleum ether–ethyl acetate (4:1) as eluent. Yield 0.3 g (~50%), oily substance, $[\alpha]_D^{20}$ = +1.0° (c = 0.28, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.96–2.03 m (8H, CH_2, proline), 2.64 m (4H, CH_2, allyl), 3.10 s and 3.20 s (3H each, OCH_3), 3.50 s (6H, OCH_3), 3.67 s and 3.68 s (3H each, CO_2Me), 3.35 m and 3.80 m (2H each, NCH_2), 4.96–5.03 m

(4H, $=CH_2$), 5.25 m (2H, NCH), 5.80 m (2H, =CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 22.52 (CH_2, proline); 30.12 (29.93) (CH_2, allyl); 44.69 (43.34) (CH_2N); 51.25, 52.66, and 53.11 (OCH_3); 51.83 ($CO_2\mathbf{C}H_3$); 62.39 (61.60) (CH); 74.29 ($C^{4'}$); 102.72 (103.10) ($C^{5'}$); 104.45 (103.6) ($C^{2'}$); 118.48 ($=CH_2$); 132.39 (132.01) (=CH); 156.77 ($C^{1'}$); 172.12 ($\mathbf{C}O_2Me$); 186.78 (186.89) ($C^{3'}$). Found, %: C 50.64; H 6.00; Cl 19.12; N 3.50. $C_{16}H_{21}Cl_2NO_5$. Calculated, %: C 50.81; H 5.60; Cl 18.75; N 3.70.

1-(4-Allyl-2,4-dichloro-5,5-dimethoxy-3-oxocyclopent-1-en-1-yl)pyrrolidine-2-carboxylic acid (VI). Compound **V**, 0.2 g (5.29 mmol), was dissolved in 10 ml of methanol, 0.5 ml of a solution of KOH (prepared from 0.38 mol of KOH and 2 ml of water) was added under stirring, and the mixture was stirred for ~2 h (TLC). Methanol was distilled off, and the aqueous phase was acidified with 1 N hydrochloric acid to pH 4 and extracted with diethyl ether (4×10 ml). The extracts were combined, washed with a solution of NaCl, dried over $MgSO_4$, and evaporated to obtain 0.102 g (53%) of acid **VI** as an oily substance. The product was treated with petroleum ether–ethyl acetate (10:1) to isolate a colorless powder with mp 118–120°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.79–2.17 m (4H, CH_2, proline), 2.68 m (2H, CH_2, allyl), 3.49 m and 3.90 m (1H each, NCH_2), 3.22 s (3H, OCH_3), 3.52 s (3H, OCH_3), 5.02 m (2H, $=CH_2$), 5.25 m (1H, NCH), 5.84 m (1H, =CH), 9.15 br.s (1H, COOH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 22.36 and 23.31 (CH_2, proline); 30.02 (29.17) (CH_2, allyl); 44.68 (43.14) (CH_2N); 51.92, 52.59, 53.15 (OCH_3); 62.16 (61.48) (CH); 74.20 ($C^{4'}$); 102.50 (103.17) ($C^{5'}$); 104.30 (103.48) ($C^{2'}$); 118.74 (118.58) ($=CH_2$); 132.23 (131.79) (=CH); 157.49 ($C^{1'}$); 174.5 (CO_2H); 187.62 ($C^{3'}$).

Methyl 2-(4-allyl-2,4-dichloro-5,5-dimethoxy-3-oxocyclopent-1-en-1-ylamino)-4-(methylsulfanyl)-butanoate (VIII). Compound **IV**, 0.2 g (0.7 mmol), was dissolved in 10 ml of methanol, 0.2 g (1.2 mmol) of L-methionine methyl ester, 0.04 g (0.7 mmol) of KOH, and 0.1 ml (0.7 mmol) of triethylamine were added under stirring, and the mixture was stirred until the initial compound disappeared (TLC). Methanol was distilled off, and the residue was acidified with 1 N hydrochloric acid to pH 4 and extracted with chloroform (4×10 ml). The extracts were combined, washed with a solution of sodium chloride, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography on silica gel using petroleum ether–ethyl acetate (10:1) as eluent. Yield 0.24 g (80%), colorless crystals, mp 74–76°C, $[\alpha]_D^{20}$ = +23.5° (*c* = 1.71, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.10 s (6H, SMe), 2.17–2.29 m (4H, CH_2), 2.56 m (4H, CH_2, allyl), 2.73 m (4H, SCH_2), 3.40 s (6H, OMe), 3.48 s and 3.52 s (3H each, OMe), 3.81 s and 3.82 s (3H each, CO_2Me), 5.00–5.20 m (6H, $=CH_2$, CH), 5.71–6.00 m (2H, =CH), 6.24 br.s (2H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.28 (15.33) (SMe); 29.17 (29.37) and 32.0 (32.19) (CH_2); 51.75, 51.98, and 52.17 (OMe); 52.92 ($CO_2\mathbf{C}H_3$); 54.74 (54.49) (CH); 75.03 (74.09) ($C^{4'}$); 101.49 ($C^{2'}$); 102.04 ($C^{5'}$); 118.91 (118.67) ($=CH_2$); 131.82 (132.39) (=CH); 158.99 (158.50) ($C^{1'}$); 171.30 ($\mathbf{C}O_2Me$); 187.17 ($C^{3'}$). Found, %: C 47.02; H 5.80; Cl 17.24; N 3.52; S 7.17. $C_{16}H_{23}Cl_2NO_5S$. Calculated, %: C 46.61; H 5.62; Cl 17.20; N 3.40; S 7.78.

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