UDC 547.455

α-SUBSTITUTED α-AMINO ACIDS

COMMUNICATION 9. BROMINATION OF 4-METHYL-2-(TRIFLUOROMETHYL)-2-OXAZOLIN-5-ONE

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Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 1,
pp. 99-103, January, 1964
Original article submitted September 5, 1962

In 1955 a method was developed for the preparation of α-substituted α-(acylamino) acids which consisted in the bromination of azlactones of benzamido acids with subsequent treatment of the bromooxazolinones with nucleophilic reagents [1]. In further publications [2-8] the syntheses were described of a large number of α-substituted α-benzamido acids and some peptides containing residues of these acids. All these compounds had an N-protective group, which was difficult to remove without breakdown of the molecule.

It was of interest to attempt the syntheses of α-substituted α-(acylamino) acids with an N-protective group that could be removed under fairly mild conditions, which would permit an approach to the synthesis of peptides containing C-end residues of α-substituted α-amino acids. As such a protective group we selected the trifluoroacetyl group, which can be removed by mild alkaline or acid hydrolysis [9].

For the synthesis of α-substituted α-(trifluoroacetamido) acids we studied the bromination of 4-methyl-2-(trifluoromethyl)-2-oxazolin-5-one (I) under conditions developed earlier for 2-phenyloxazolinones. The original oxazolinone (I) was synthesized by Weygand's method [10] from DL-alanine and trifluoroacetic anhydride. This oxazolinone was brominated in dry dichloroethane solution at 3-5°, and about one molecular proportion of bromine was consumed. It should be noted that when the oxazolinone is completely freed from traces of CF_3COOH by distillation with quinoline the bromination does not go. Treatment of the dichloroethane solution obtained with water with vigorous stirring did not lead to the expected 2-hydroxy-N-(trifluoroacetyl)alanine. We were able to establish qualitatively only the presence of an α-keto acid (reaction with o-phenylenediamine in 10% trichloroacetic acid solution). This prompted us to make a more detailed investigation both of the bromination product and of the original oxazolinone (I). It was found that in the reaction of 5% HBr with 4-methyl-2-(trifluoromethyl)-z-oxazolin-5-one (I) we were unable to isolate (trifluoroacetyl)alanine, but could detect only pyruvic acid. When the oxazolinone (I) was treated with 2,4-dinitrophenylhydrazine in methanolic HCl, the 2,4-dinitrophenylhydrazone of methyl pyruvate (IV) was formed*.

We isolated the product of the bromination of (I) in the pure state by repeated fractional distillation of the residue obtained after the evaporation of the dichloroethane solution. The yield of the pure bromination product did not exceed 30-35%. Study of this substance showed unexpectedly that it was 4-bromo-4-(bromomethyl)-2-(trifluoromethyl)-2-oxazolin-5-one (VI), which was confirmed by its elementary analysis, infrared spectrum, and some cleavage reactions. Thus, when the oxazolinone (VI) was boiled with 20% hydrochloric acid (2 h, 100°) and the hydrolyzate was treated with 2,4-dinitrophenylhydrazine, we obtained the osazone of hydroxypyruvic acid (VII). The same osazone was prepared by independent synthesis from bromopyruvic acid.

By the action of an aqueous phosphate buffer solution (pH 8.5) on the dibromo oxazolinone (VI) we obtained 3-bromo-2-(2,2,2-trifluoroacetamido)acrylic acid (V). The acid (V) eliminates a bromine atom only with great difficulty (only 15% is eliminated in 2 h at pH 12.5). It rapidly decolorizes an alkaline potassium permanganate solution, and according to the NMR spectrum it does not contain a methyl group. When the acid (V) is hydrolyzed with 20% HCl and the product is treated with 2,4-dinitrophenylhydrazine the osazone of hydroxypyruvic acid (VII) is formed. Treamtnet of the dibromo oxazolinone (VI) with aniline readily leads to 3-anilino-2-(2,2,2-trifluoroacetamido-

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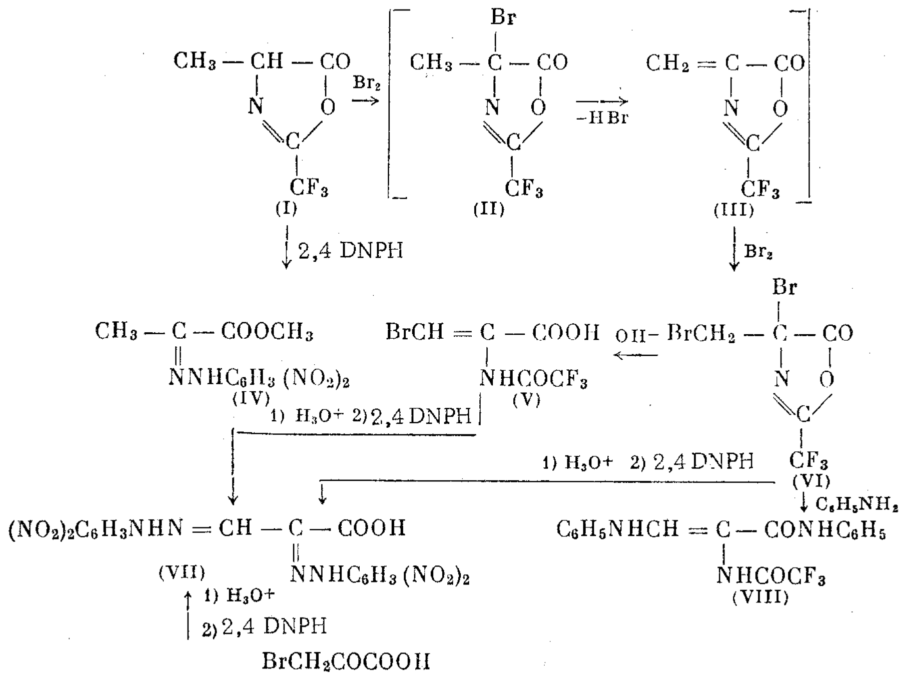
*When this part of the work had been completed there appeared a paper by Weygand [11] which confirmed our observations.



acrylanilide (VIII). In this case both bromine atoms are replaced, which is evidently due to the higher mobility of the β-bromine in the intermediately formed anilide of the acid (V) than in the acid itself (cf. [12]). The structure of the anilide (VIII) was confirmed by qualitative reactions, analytical data, and also the NMR and infrared spectra.

Hence, unlike 4-methyl-2-phenyl-2-oxazolin-5-one, 4-methyl-2-(trifluoromethyl)-2-oxazolin-5-one is brominated both in the 4-position and in the methyl group. This result may probably be explained by the ready dehydrobromination of the first formed 4-bromo-4-methyl-2-(trifluoromethyl)-2-oxazolin-5-one (II) to the 4-methyleneoxazolinone (III), which then combines with two atoms of bromine at the double bond. The relatively low yield of the dibromo oxazolinone (VI) is probably due to the binding of the hydrogen bromide liberated by the original oxazolinone (I) with formation of a hydrobromide that is incapable of bromination.

Attempts to hold back the reaction at the stage of the formation of the monobromo oxazolinone (II) by change in the bromination conditions were unsuccessful.

EXPERIMENTAL

4-Methyl-2-(trifluoromethyl)-2-oxazolin-5-one (I). This was prepared by Weygand's method [10]; yield 64-66%; b.p. 52-53° (22 mm); $n_D^{18.5}$ 1.3688; $d_4^{18.5}$ 1.479. Characteristic frequencies in the infrared spectrum (cm^{-1}): 1816 (C=O); 1663 (C=N); 1203 (C–O); 1160 (C–F).

(Trifluoroacetyl)alanine Anilide. 0.335 g of the oxazolinone (I) was mixed with 0.186 g of aniline, and the mixture was heated for 30 min at 80°. The mixture was then poured into 15 ml of 2 N HCl, and the precipitate formed was filtered off, washed with water, dried, and crystallized from benzene; yield 0.35 g (72%); m.p. 169-170°. Characteristic frequencies in infrared spectrum (cm^{-1}): 3286, 3110 (N–H), 1719 (C=O in CF_3CONH); 1665 (C=O in $CONHC_6H_5$); 1565 (amide band II); 1188 (C–F).

Reaction of the Oxazolinone (I) with 2,4-Dinitrophenylhydrazine. 0.167 g of the oxazolinone (I) was mixed with a solution of 0.003 mole of 2,4-dinitrophenylhydrazine in methanol saturated with HCl. The mixture was kept for 30 minutes at 20°, and the precipitate was filtered off. The methyl pyruvate 2,4-dinitrophenylhydrazone obtained, m.p. 186-187° (from a mixture of methanol and dioxane), melted without depression in admixture with a sample prepared from methyl pyruvate.

Bromination of 4-Methyl-2-(trifluoromethyl-2-oxazolin-5-one. 8.35 g of the oxazolinone (I) was dissolved in 40 ml of dry dichloroethane, and a solution of 8 g of bromine in 40 ml of dichloroethane was added to the solution dropwise with stirring. The first two or three drops were added at 20°, and reaction set in after 5-20 min and was then vacuum-evaporated at not above 30°. The residue was vacuum-fractionated, and we obtained a fraction of b.p. 45-50° (0.1 mm) with a yield of 8.1 g (50%). Three further vacuum fractionations gave pure 4-bromo-4-(bromomethyl)-2-(trifluoromethyl)-2-oxazolin-5-one (VI), b.p. 46-47° (0.08 mm). The substance was lacrimatory.

Yield 5.4 g (33%); n_D^{20} 1.4560; d_4^{20} 1.9477. Characteristic frequencies in infrared spectrum (cm^{-1}): 1815 (C=O), 1663 (C=N); 1200 (C−O); 1165 (C−F). Found: C 19.03; H 0.61; Br 49.99; N 4.47%. $C_5H_2O_2NBr_2F_3$. Calculated: C 18.47; H 0.62; Br 49.19; N 4.31%.

3-Bromo-2-(2,2,2-trifluoroacetamido)acrylic Acid (V). 0.975 g of the dibromo oxazolinone (VI) was dissolved in 40 ml of dioxane, the solution was cooled to 8-10°, and a solution of 0.005 mole of K_2HPO_4 and 0.0006 mole of KH_2PO_4 in 10 ml of water was added. The mixture was shaken vigorously, and was then set aside at 20° for two days with periodic shaking. It was then vacuum-evaporated to dryness at not above 35°, and the residue was treated with dry ethyl acetate and filtered; the filtrate was again evaporated to dryness. The residue was chromatographed on a column (30 x 1.5) containing ASM silica gel in the solvent system benzene-ether (3 : 1). From the first fractions of the eluate we obtained 0.21 g (27%) of crystalline substance. After two crystallizations from a mixture of benzene and ether it had m.p. 150-151°. Characteristic frequencies in infrared spectrum (cm^{-1}): 1720 (CO in CF_3CONH); 1705 (CO in carboxyl); 1628 (C=C); 1530 (amide band II); 1215 (C−O); 1188 (C−F). Found: C 22.99; H 1.25; Br 30.25; N 5.44%. $C_5H_3O_3NBrF_3$. Calculated: C 22.92; H 1.15; Br 30.50; N 5.34%. Equivalent by titration with 0.01 N KOH (Methyl Red): found 280, 278; calculated 262.

Osazone of Hydroxypyruvic Acid (VII). a) 0.325 g of the dibromo oxazolinone (VI) was boiled for 2 h with 10 ml of 20% hydrochloric acid. A solution of 0.6 g of 2,4-dinitrophenylhydrazine in concentrated hydrochloric acid was added to the solution obtained. After 2-3 min at the boil an orange-red precipitate separated and was purified by boiling it four times with glacial acetic acid. The osazone of hydroxypyruvic acid had m.p. 272-273°; yield 0.32 g (70%). Characteristic frequencies in the infrared spectrum (cm^{-1}): 1703 (CO); 1661 (C=N); 1612 (C=C aromatic); 1512 (NO_2). Found: C 38.83; H 2.28; N 23.75%. $C_{15}H_{10}O_{10}N_8$. Calculated: C 38.96; H 2.18; N 24.23%.

b) 0.26 g of 3-bromo-2-(2,2,2-trifluoroacetamido)acrylic acid (V) was treated as described above. The osazone melted at 270-272°; yield 75%.

c) 0.18 g of bromopyruvic acid was treated as described in paragraph (a). The product melted at 271-273°. The infrared spectra of the substances obtained in the three experiments were identical.

3-Anilino-2-(2,2,2-trifluoroacetamide)acrylanilide (VIII). 1.47 g of the dibromo oxazolinone (VI) was dissolved in 20 ml of dry methylene chloride, and with stirring a solution of 1.67 g of aniline in 20 ml of dry methylene chloride was added dropwise at −20°. The mixture was kept for 15-20 min and left for three days at 20°. The precipitate of aniline hydrobromide was then filtered off, and the filtrate was washed with 1 N HCl and with water, dried with magnesium sulfate, and evaporated to dryness. The yield of the anilide (VIII) was 0.74 g (47%). The substance was crystallized from benzene; m.p. 170-172°. Characteristic frequencies in the infrared spectrum (cm^{-1}): 3240, 3250 (NH); 1719 (CO in CF_3CONH); 1667 (CO in $CONHC_6H_5$); 1608 (C=C aromatic); 1560 (amide band II); 1188 (C−F); 1215 (C−O). Found: C 58.27; H 4.12; N 12.12%. $C_{17}H_{14}O_2N_3F_3$. Calculated: C 58.45; H 4.03; N 12.03%.

NMR spectra were determined and interpreted in M. V. Vol'kenshtein's laboratory (Institute of Macromolecular Compounds of the Academy of Sciences of the USSR), and the authors express their thanks for this service.

SUMMARY

In the bromination of 4-methyl-2-(trifluoromethyl)-2-oxazolin-5-one, 4-bromo-4-(bromomethyl)-2-(trifluoromethyl)-2-oxazolin-5-one is formed. The reactions of this oxazolinone with water, aniline, and 2,4-dinitrophenylhydrazine were studied.

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