ETHYL α -FLUOROACRYLATE IN CYCLOADDITION AND DIENE SYNTHESIS REACTIONS

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The reactions of α -fluoroacrylic acid and its derivatives have received little study up to now. At the same time, there is every reason to believe that these compounds exhibit a quite high reactivity and can be widely used for the synthesis of other classes of organofluorine compounds, including (and in particular) difficultly accessible monofluorides. The preparation of γ -fluoroglutamic acid [1] can serve as an example of this.

In the present paper we studied some diene synthesis and cycloaddition reactions involving the ethyl ester of α -fluoroacrylic acid (I). The synthesis of 1-fluoro-substituted cyclohexene- and cyclohexanecarboxylic acids is also interesting for the reason that the cyclohexene- and cyclohexanecarboxylic acids and their derivatives manifest a definite physiological activity [2], while the introduction of fluorine, as is known, can lead to a substantial change in these properties. The heating of (I) with 1,3-butadiene (140°, 10 h) leads to the formation of the ethyl ester of 1-fluoro- Δ^3 -cyclohexenecarboxylic acid, the saponification of which gives the free acid, while its hydrogenation over Pd-black gives the ethyl ester of 1-fluoro-cyclohexanecarboxylic acid



(I) adds to piperylene under these same conditions, giving the ethyl ester of 1-fluoro-2-methyl- Δ^3 cyclohexenecarboxylic acid, which represents, based on the NMR data, a mixture of geometric isomers in a cis:trans ratio of approximately 2.5:1; hydrogenation leads to a mixture of the corresponding isomers of the ethyl ester of 1-fluoro-2-methylcyclohexanecarboxylic acid



The ortho-structure of the adduct was adopted by analogy with other diene synthesis reactions involving piperylene (see [3]). The condensation of (I) with isoprene under the same conditions gave an adduct, which, also on the basis of known analogies, must be assigned the structure of the ethyl ester of 1fluoro-4-methyl- Δ^3 -cyclohexenecarboxylic acid



Institute of Heteroorganic Compounds, Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 2, pp. 358-362, February, 1971. Original article submitted June 23, 1969.

● 1971 Consultants Bureau, a division of Plenum Publishing Corporation, 227 West 17th Street, New York, N. Y. 10011. All rights reserved. This article cannot be reproduced for any purpose whatsoever without permission of the publisher. A copy of this article is available from the publisher for \$15.00. The reaction of (I) with cyclopentadiene (80°, 6 h) leads to a mixture of the endo- and exo-isomers (when based on the carbethoxyl group) of the ethyl ester of 1-fluoro-2,5-endomethylene- Δ^3 -cyclohexanecarboxylic acid in a 2:1 ratio. The configuration of the adducts was proved in conventional manner – by conversion to the sodium salts and subsequent treatment with iodine and potassium iodide in aqueous solution; here the salt of the endo-form forms the iodolactone, while the salt of the exo-form remains unchanged. The exo-isomer of adduct (I) and cyclopentadiene was obtained again after esterification



The heating of (I) with tetrafluoroethylene and trifluorochloroethylene in heptane (170-175°, 14 h) gave the corresponding cycloadducts in moderate yields

 $\begin{array}{ccc} CH_2 = CF - COOC_2H_5 & CH_2 - CF - COOC_2H_5 & CH_2 - CF - COOC_2H_5 \\ + & & \\ CF_2 = CFX & & CF_2 - CFX & or & & \\ & & & \\$

The F^{19} NMR spectra of the synthesized compounds were obtained on a Hitachi H-60 spectrometer (operating frequency 56.4 MHz), using CF₃COOH as the external standard. Their complete interpretation requires additional measurements and analysis; here we will limit ourselves only to a brief description of the spectra of some of the compounds.

Adduct of (I) and butadiene: the signal in the F^{19} NMR spectrum represents a complex multiplet with a chemical shift of 85.5 ppm. Ethyl ester of 1-fluorocyclohexane carboxylic acid: broad quintet with a chemical shift of 86.4 ppm. The distance between the lines was about 19 Hz, and the width of each line was about 17 Hz. Adduct of (I) with piperylene: two intense signals (78.5 and 105.0 ppm) and two signals of low intensity (73.5 and 84.6 ppm), caused by the presence of two geometric isomers of the o-adduct (with a predominance of the cis-isomer, the signal of which lies downfield), and containing the m-adduct as impurity, which also consists of two geometric isomers. Adduct of (I) with cyclopentadiene: signal of the fluorine atoms of the endo- and exo-isomers at 71.4 and 80.5 ppm, respectively. The signal of the exo-form represents a doublet of doublets, with weak additional splitting (J₁ 25.6, J₂ 12.8 Hz; the values of the constants agree with the literature data for analogous systems [4]). The signal of the endo-isomer is a broad triplet with additional splitting, the distance between the lines being about 22.5 Hz. The F^{19} NMR spectrum of the adduct of (I) with trifluorochloroethylene testifies to the presence of two geometric isomers. The choice between structures (IIa) and (IIb) can be made only on the basis of additional analysis of the spectra.

EXPERIMENTAL

The preparation of (I) is given in [5].

Condensation of (I) with Butadiene. A mixture of 9.0 g of (i) and 4.12 g of butadiene was heated in the presence of hydroquinone in a 50-ml stainless steel autoclave at 140° for 10 h. Distillation of the reaction mass in vacuo gave 8.5 g (65.4%) of the ethyl ester of 1-fluoro- Δ^3 -cyclohexenecarboxylic acid with bp 78-80° (10 mm); n_D^{20} 1.4447; d_4^{20} 1.0872. Found: C 62.51; 62.44; H 7.68; 7.52; F 10.72; 10.57%. C₉H₁₃FO₂. Calculated C 62.77; H 7.61; F 11.03%. Infrared spectrum: ν_{max} 1660 (w) (C = C), 1745, 1760 (C = O) cm⁻¹.

Ethyl Ester of 1-Fluorocyclohexanecarboxylic Acid. A solution of 4.2 g of the ethyl ester of 1-fluoro- Δ^3 -cyclohexenecarboxylic acid in 15 ml of ethanol was hydrogenated at room temperature over a catalytic amount of Pd-black. The theoretical amount of H₂ was absorbed in 2 h. The alcohol was distilled off, and

the residue was vacuum-distilled. We obtained 4.0 g of the ethyl ester of 1-fluorocyclohexanecarboxylic acid with bp 78° (10 mm); n_D^{20} 1.4398; d_4^{20} 1.0532. Found: C 61.38; 61.15; H 8.65; 8.59; F 10.18; 10.32%. C₃H₁₅FO₂. Calculated: C 62.04; H 8.68; F 10.91%. Infrared spectrum: ν_{max} 1745, 1760 (C = O) cm⁻¹.

<u>1-Fluoro- Δ^3 -cyclohexenecarboxylic Acid.</u> A stirred mixture of 3 g of the ethyl ester of 1-fluoro- Δ^3 cyclohexenecarboxylic acid and 10 ml of 10% aqueous KOH solution was heated on the water bath for 1 h, followed by extraction of the neutral impurities with ether, while the aqueous layer was acidified with hydrochloric acid solution (1:1) and extracted with ether. The ether extract was dried over MgSO₄, and the ether was distilled off. We obtained 1.75 g of 1-fluoro- Δ^3 -cyclohexenecarboxylic acid with mp 51-52° (from heptane). Found: C 58.06; 58.31; H 6.06; 6.04; F 13.09; 13.18%. C₇H₉FO₂. Calculated: C 58.31; H 6.29; F 13.19%. Infrared spectrum: ν_{max} 1660 (w) (C = C), about 1730 (C = O) cm⁻¹.

Condensation of (I) with Piperylene. In a 50-ml stainless steel autoclave was heated a mixture of 3.0 g of piperylene and 4.9 g of (I) in the presence of hydroquinone at 140° for 15 h. We obtained 4.25 g (54%) of the adduct with bp 86-87° (10 mm); n_D^{20} 1.4459; d_4^{20} 1.0602. Found: C 63.70; 64.00; H 8.16; 8.00; F 10.76; 11.06%. C₁₀H₁₅FO₂. Calculated: C 64.50; H 8.12; F 10.20%. Infrared spectrum: ν_{max} 1660 (w) (C = C), 1745 (C = O) cm⁻¹.

Ethyl Ester of 1-Fluoro-2-methylcyclohexanecarboxylic Acid. The adduct obtained in the preceding experiment was hydrogenated in the same manner as the adduct of (I) with butadiene. From 4.2 g of substance was obtained 3.6 g of the hydrogenation product with bp 82-83° (9 mm); n_D^{20} 1.4366; d_4^{20} 1.0262. Found: C 63.33; 63.36; H 8.83; 9.03; F 9.84; 9.72%. C₁₀H₁₇FO₂. Calculated: C 63.79; H 9.10; F 10.9%. Infrared spectrum: ν_{max} 1740, 1755 (C = O) cm⁻¹.

Condensation of (I) with Isoprene. From 3.45 g of isoprene and 5.9 g of (I) in the presence of hydroquinone (140°, 10 h) was obtained 6.6 g (70.6%) of the ethyl ester of 1-fluoro-4-methyl- Δ^3 -cyclohexenecarboxylic acid, bp 95-96° (10 mm); $n_D^{18.5}$ 1.4511; $d_4^{18.5}$ 1.0602. Found: C 64.61; 64.64; H 8.26; 8.32; F 9.40; 9.61%. $C_{10}H_{15}FO_2$. Calculated: C 64.50; H 8.12; F 10.20%. Infrared spectrum: ν_{max} 1680 (w) (C = C), 1745, 1760 (C = O) cm⁻¹.

Condensation of (I) with Cyclopentadiene. In a sealed glass ampul was heated a mixture of 2.9 g of cyclopentadiene and 5.2 g of (I) in the presence of hydroquinone at 80° for 6 h. We obtained 5.15 g of the adduct with bp 82-84° (9 mm); n_D^{20} 1.4559; d_4^{20} 1.1212. Found: C 64.33; 64.53; H 6.91; 6.92; F 10.04; 9.85%. C₁₀H₁₃FO₂. Calculated: C 65.20; H 7.11; F 10.31%. Infrared spectrum: ν_{max} 1660 (w) (C = C), 1745 (C = O) cm⁻¹.

A mixture of 3.5 g of the obtained adduct and 17 ml of 10% aqueous KOH solution was heated for 1.5 h, after which the neutral impurities were extracted with ether, while the aqueous solution was acidified with HCl to Congo red and extracted with ether. The ether extract was dried over MgSO₄, and the ether was distilled off. Vacuum-distillation of the residue gave 2.4 g of a mixture of the endo- and exo-isomers of 1-fluoro-2,5-endomethylene- Δ^3 -cyclohexenecarboxylic acid with bp 117-120° (10 mm) (the material crystallizes at room temperature). The mixture was dissolved in 90 ml of 0.5 N NaHCO₃ solution, to the solution was added a solution of 0.76 g of I₂ and 1.5 g of KI in 45 ml of water, and the whole was allowed to stand in the dark for a day. Then the obtained precipitate was filtered, washed in succession with Na₂S₂O₃ solution and water, and dried in vacuo. We obtained 0.45 g of the iodolactone with mp 90-92° (from alcohol). Found: C 33.99; 33.70; H 2.77; 2.78; F 6.64; 6.78%. C₈H₈FIO₂. Calculated: C 34.06; H 2.86; F 6.74%.

The aqueous solution was acidified with HCl and extracted with ether, the ether solution was dried over MgSO₄, the ether was distilled off, and the residue was vacuum-distilled. Exo-1-fluoro-2,5-endomethylene- Δ^3 -cyclohexenecarboxylic acid has bp 120-121° (10 mm) and mp 54-56° (from heptane). Found: C 61.25; 61.01; H 5.60; 5.63; F 12.02; 12.02%. C₈H₉FO₂. Calculated: C 61.53; H 5.81; F 12.25%. The acid was converted in conventional manner to the ethyl ester, which was identified by GLC to be one of the isomers of the adduct of cyclopentadiene with (I).

<u>Cycloaddition of (I) to Tetrafluoroethylene</u>. In a 50-ml stainless steel autoclave was heated a mixture of 5.9 g of (I), 5 g of tetrafluoroethylene, and 0.1 g of hydroquinone in 5 ml of heptane at 170-175° for 14 h. The heptane was distilled off, while the residue was vacuum-distilled. We obtained 4.8 g (38.5%) of the ethyl ester of 1,2,2,3,3-pentafluorocyclobutanecarboxylic acid with bp 62-63° (55 mm); n_D^{20} 1.3600; d_4^{20} 1.3522. Found: C 38.71; 38.71; H 3.23; 3.28%. $C_7H_7F_5O_2$. Calculated: C 38.54; H 3.23%. Infrared spectrum: ν_{max} 1760 (C = O) cm⁻¹. Cycloaddition of (I) to Trifluorochloroethylene. In the same manner as in the preceding experiment, from 5.9 g of (I) and 5.8 g of trifluorochloroethylene was obtained 3.17 g of the cycloadduct with bp 82-83° (30 mm); n_D^{20} 1.3920; d_4^{20} 1.3912. Found: C 39.94; 36.04; H 3.13; 3.21%. C₇H₇F₄ClO₂. Calculated: C 35.84; H 3.01%. Infrared spectrum: ν_{max} 1760 (C = O) cm⁻¹.

<u>Gas</u> – Liquid Chromatography. The carrier gas was helium, the solid phase was Chromosorb W, the liquid phase was Rheoplex 400 (15%), and the detector was based on the heat conductivity. The purity of the obtained compounds was analytically checked on this phase, and the endo- and exo-isomers of the adduct of (I) with cyclopentadiene are separated on it. The geometric isomers of the cycloadduct of (I) with trifluorochloroethylene are separated if 20% diethylene glycol succinate is used as the liquid phase. We were unable to chromatographically separate the geometric isomers of the adduct of (I) with piperylene.

CONCLUSIONS

Ethyl α -fluoroacrylate was introduced into the diene synthesis reaction with butadiene, isoprene, piperylene, and cyclopentadiene, and into the cycloaddition reaction with tetrafluoroethylene and trifluoro-chloroethylene.

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