Chemistry of 4-fluoroglutamic acid. Part 1. A critical survey of its syntheses: an attempt to optimize reaction conditions for large-scale preparation*

V. Tolman

Institute of Nuclear Biology and Radiochemistry, Czechoslovak Academy of Sciences, Vídeňská 1083, 14220 Prague 4 (Czechoslovakia)

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Abstract

Synthetic methods for the preparation of 4-fluoroglutamic acid (**1**) are reviewed. The utility of every method for routine laboratory work is evaluated with respect to the accessibility of starting materials and reagents, the overall yields and also from the viewpoint of safety. Optimum reaction conditions are given for the selected pathway, suitable for large-scale synthesis.

Introduction

In the wide family of the many kinds of amino acid analogues, the fluorinated amino acids represent a specific group of compounds with some characteristic features. Due to the small difference in the length of the C–F and C–H bonds (1.33 Å and 1.08 Å, respectively), the fluorinated amino acids may be considered to be the structural mimics of their non-fluorinated counterparts. On the other hand, the extreme electronegativity of fluorine, as illustrated by its standard electrode potential (2.65 V, referred to the H^+/H couple as zero) strongly polarizes the C–F bond(s), thus resulting in the principal change in polarity of the whole molecule. Both these factors, e.g. the geometrical similarity to and the electrophysical difference from the parent amino acids, predetermine the behaviour of fluorinated amino acids in most biological systems. This markedly differentiates these compounds from other groups of amino acid analogues.

4-Fluoroglutamic acid (**1**) is a very interesting representative of the monofluorinated aliphatic amino acids. As a derivative of the widely distributed glutamic acid, **1** is expected to act by diverse ways in most enzymatic systems involving glutamic acid. Moreover, sterically homogeneous forms of **1** may serve in the chemical laboratory as the 'building blocks' for the syntheses of many other sterically defined fluorinated amino acids and other fluoro compounds. With these facts in mind, we decided to undertake a detailed

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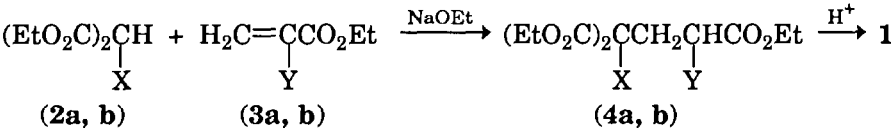
study on the chemistry of **1**, the results of which will be described in this series of papers.

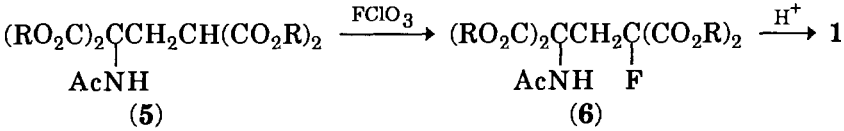
Theoretical

The first synthesis of **1**, published just 30 years ago [1], was based on the Michael addition of diethyl acetamidomalonate (**2a**) on ethyl 2-fluoroacrylate (**3a**) to give the adduct **4a**, which on acid hydrolysis yielded **1**. An analogous preparation of **1**, which appeared only one year later [2], utilized the same principle but was applied in the 'reverse mode'; the five-carbon chain of **1** was constructed by addition of 2-fluoromalonate (**2b**) to 2-acetamidoacrylic ester (**3b**), giving **4b** as the key intermediate.



2a–4a: X = NHAc, Y = F
2b–4b: X = F, Y = NHAc

A short synthesis of **1**, developed in our laboratory [3] and independently by Russian workers [4], makes use of the three-carbon condensation between formaldehyde, malonic and acetamidomalonic ester [5], followed by fluorination of the tetraester **5** by perchloryl fluoride, which gives rise to the fluoro derivative **6**.



lit. [3]: R = Me
lit. [4]: R = Et

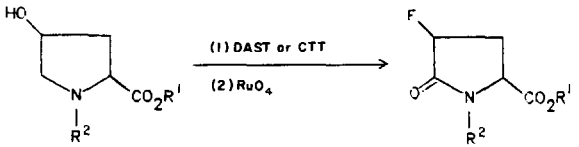
In order to prepare **6** directly, unsuccessful attempts were made to substitute the malonic ester by diethyl fluoromalonate in the synthesis of **5**. No trace of acid **1** was found by TLC after hydrolysis of the crude reaction mixture [6].

Another access to **1** through the ester **4a** had been realized with ethyl 3-chlorolactate (**7a**) as the starting material [7]. The chloro ester in its O-protected form **7b** was used to alkylate diethyl acetamidomalonate, yielding crude **8a**. Acid cleavage of the ether group gave the hydroxy ester **8b**, which on treatment with 2-chloro-1,1,2-trifluoroethyldiethylamine (CTT) [8] furnished **4a**.

$$ClCH_2\underset{\underset{O-X}{|}}{CHCO_2Et} \xrightarrow{2a} (EtO_2C)_2\overset{\overset{AcNH}{|}}{C}CH_2\underset{\underset{O-X}{|}}{CHCO_2Et} \xrightarrow{CTT} \mathbf{4a} \xrightarrow{H^+} \mathbf{1}$$

7a : X = H **8a** : X = Bu^t
7b : X = Bu^t **7b** : X = H

None of these methods permits any stereoselectivity in the preparation of **1**, the product being always the mixture of racemic diastereomers. However, a stereospecific synthesis of **1** has been developed quite recently [9], starting from the optically pure forms of both *trans*- and *cis*-4-hydroxyprolines (**9a**). After conventional protection of the carboxy and imino groups, compounds **9b** were first fluorinated either by diethylaminosulphur trifluoride (DAST) or CTT and then oxidized by ruthenium tetroxide to give the respective 4-fluoro-5-pyrrolidone-2-carboxylic esters (**10**). Acid hydrolysis then gave **1**; thus, from *trans*-L-**9a** the *threo*-L form of **1** was prepared, whereas *cis*-D-**9a** gave, by the same reaction sequence, the *erythro*-D-**1**.



9a: $R^1 = R^2 = H$
9b: $R^1 = Me$, $R^2 = Ac$

10: $R^1 = Me$, $R^2 = Ac$

For the purpose of our work, we required large amounts (over 100 g) of racemic **1**. None of the above-mentioned methods [1–4, 7] was suitable for the large-scale, economic and safe production of this compound. Esters of 2-fluoroacrylic acid, as well as those of fluoromalonic acid, are fairly difficult to prepare in substantial quantities. This makes the original versions of the first two syntheses [1, 2] hardly applicable for multigram preparations of **1**. The major drawback of the third synthesis [3] is the very hazardous character of perchloryl fluoride, confirmed by the author's own bad experience; one cautionary event years ago forced this laboratory to abandon this otherwise promising pathway. Finally, Bergmann's synthesis [7] was also unsuitable for our purposes due to its low overall yield, giving no advantage in comparison with the original method of Hudlický [1].

Discussion

Having compared all the above-mentioned synthetic methods, we have preferred the principle of the first synthesis [1], together with some improvements. The major limitation of the original pathway was the laborious preparation of **3a**, isolated in only 17% yield. We introduced [10, 11] another access to **3a**, which made use of a stable crystalline precursor, ethyl 2-fluoro-3-(4′-toluenesulphonyloxy)propionate. Treatment of this compound with potassium phthalimide on a vacuum line resulted in an entirely quantitative

yield of **3a**, which was over 99% pure (GC). This was immediately subjected to Michael addition of **2a** to afford the ester **4a** in yields ranging from 80% to 88%. The final isolation of **1** after acid hydrolysis of **4a** has been modified by the use of pyridine instead of silver oxide for neutralization and by completing the crystallization of **1** by adding ethanol, so increasing the yield of the hydrolytic step up to 80% of **1**.

Experimental

*Preparation of ethyl 2-fluoroacrylate (**3a**)*

An intimate mixture of ethyl 2-fluoro-3-(4'-toluenesulphonyloxy)-propionate (14.4 g, 0.05 mol) (prepared according to Tolman and Špronglová [10] except that only 1.4 equiv. of 4-toluenesulphonyl chloride was used) and potassium phthalimide (22.1 g, 0.15 mol) was placed in a flat-bottom vacuum flask connected to a trap cooled to −78 °C. The system was evacuated to 15 mmHg under protection from moisture and the reaction flask slowly heated to 100–120 °C, when the main amount of **3a** distilled into the trap. The reaction was completed in 15 min heating at 150 °C, giving 5.9 g (100% yield) of **3a** which was over 99% GC pure. To avoid any loss of material, this product was used in the subsequent step without redistillation. A sample had a boiling point of 107–109 °C (lit. reports b.p., 110 °C [1], 106–107 °C [11]).

*Michael addition of diethyl acetamidomalonate to **3a***

Sodium metal (100 mg) and **2a** (10.85 g, 0.05 mol) were dissolved in absolute ethanol (22 ml) on slight warming. Compound **3a** (5.9 g, 0.05 mol) was added over 2 min to the cooled solution, the reaction mixture allowed to stand at laboratory temperature for 5 h and refrigerated (5 °C) overnight. The separated crystals of **4a** were filtered, washed with cold ethanol and dried in a desiccator: yield, 14.7 g (88%); m.p., 99–101 °C (crude). Hudlický [1] reports 58.7% (crude), 50.7% (pure) (m.p., 103–104° C).

*Preparation of 4-fluoroglutamic acid (**1**)*

A mixture of **4a** (67.0 g, 0.2 mol) and 6 N hydrochloric acid (175 ml) was refluxed for 5 h, evaporated *in vacuo*, the residue taken up in water (40 ml) and evaporated again to remove most of the hydrogen chloride; this operation was repeated three times. The remainder was dissolved in water (33 ml) and pyridine (28 ml) was slowly added to the solution, followed by careful dilution with ethanol (190 ml in total, added during the course of 6–8 h) to achieve complete crystallization of **1**. After being refrigerated overnight, the mixture was filtered and the product repeatedly washed with ethanol to remove chloride ions, then with ether and dried. Yield, 26.4 g (80%) of **1**; m.p., 167–170 °C. Hudlický [1] reports 61% yield of crude 1.

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