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FELLOWSHIP FINAL REPORT

Exploring the effects of trifluoromethyl group in the design of organocatalysts, enzyme inhibitors and in the conformational control of saturated nitrogen-containing heterocycles

Volodymyr Sukach,[1,2,3] Sergii Melnykov,[3,4] Sylvain Bertho,[2] Pascal Retailleau,[5] Mykhailo Vovk, Isabelle Gillaizeau[2]

[1] Le Studium Loire Valley Institute for Advanced Studies, 1, rue Dupanloup, 45000 Orléans, France
[2] Institute of Organic and Analytical Chemistry, ICOA UMR 7311 CNRS, Université d'Orléans, rue de Chartres, 45100 Orléans, France
[3] Institute of Organic Chemistry of NAS of Ukraine, 5, Murmanska Str., Kyiv, Ukraine
[4] Enamine LTD, 78 Chervonotkats'ka str., Kyiv 02094, Ukraine
[5] Institut de Chimie des Substances Naturelles, CNRS UPR 2301, Université Paris-Sud, Université Paris-Saclay, avenue de la terrasse, 91198 Gif-sur-Yvette, France

REPORT INFO

Fellow: Volodymyr SUKACH
From Institute of Organic Chemistry of NAS of Ukraine
Host laboratory in region Centre-Val de Loire: Institute of Organic and Analytical Chemistry, ICOA UMR 7311 CNRS, Université d'Orléans

Host scientist: Pr. Isabelle GILLAIZEAU
Period of residence in region Centre-Val de Loire: 03/11/2017-02/11/2018

ABSTRACT

The fluoroalkyl group plays an important role in the design of novel pharmacologically active agents since its introduction into organic compounds often leads to improved potency, stability and activity. Herein we wish to report an application of fluoroalkyl ketimines in decarboxylative Mannich reaction with a focus on the chemistry of unprotected NH-ketimines and heterocyclic ketimines. This study addresses the influence of the N-unprotected form of the ketimine function on the efficiency and selectivity of decarboxylative addition of malonic acid and its derivatives. The methods developed provide straightforward access to a range of valuable fluoroalkyl β-amino acids and their derivatives promising as novel organofluorine building blocks.

Keywords :
Organofluorine compounds, trifluoromethyl group, decarboxylative addition, ketimines, b-amino acids

1- Introduction

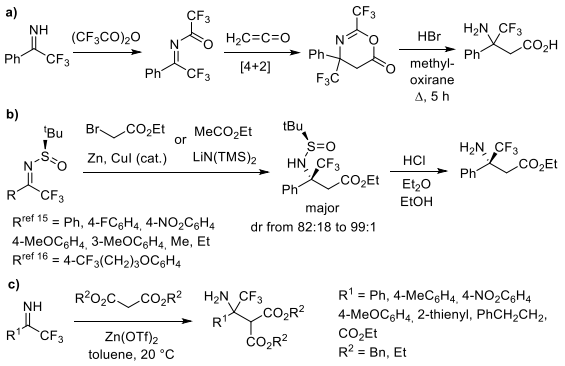
β-Amino acids are the most prominent non-proteinogenic amino acids.[1] This structural motive occurs in the bioactive natural products, including carnosine, jasplakinolide, dolastatins, paclitaxel, bleomycin, *etc*,[2] as well as β-lactam antibiotics.[3] As close analogues to the more common α-amino acids, the essential building blocks of the proteins, β-amino acids have attracted considerable interest in biochemistry and chemical biology. This is due to numerous reports showing that integration of a single or multiple β-amino acid subunits into synthetic or natural proteins confers them significantly altered remarkable in many aspects conformational properties, biological and pharmacological activity.[4] Modified β-amino acids residues are also frequent in complex bioactive small molecules and marketed pharmaceutical products. Sitagliptin, maraviroc, otamixaban are representative

examples of important drugs for which β-amino acids are key synthetic precursors. [5]

Incorporation of fluorine or, more specifically, fluoroalkyl group, into organic molecules has become a fruitful and currently almost routine strategy for developing better drug candidates with improved cell penetration, metabolic stability, toxicity profile and potency.[6] Accordingly, fluorinated amino acids demonstrate significant physiological activity and are widely used for the design of rationally modified proteins, PET imaging agents and drugs.[7] A variety of β-amino acid derivatives containing fluorine substituent(s) have been investigated as well in attempts to combine useful characteristics of the both β-amino acids and organofluorine compounds for more efficient peptidomimetics and enzyme inhibitors.[8]

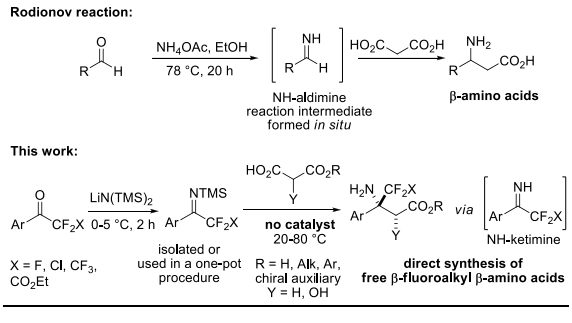
β-Amino acids bearing a fluoroalkyl group at β-position are of particular interest. 3-Amino-4,4,4-trifluorobutanoic acid[9] has been incorporated into partially modified retropeptides exhibiting β-turn-like conformation,[10] into peptidomimetics which inhibit MMP[11] and, more recently, into oligo-β-peptides which are able to form significantly more stable helices due to the effect of CF_3 groups.[12] β-Substituted derivatives of the β-fluoroalkyl-β-amino acids were scarce.[13] The synthesis of racemic 3-amino-4,4,4-trifluoro-3-phenylbutanoic acid was first described in 1991 by Kukhar group.[14] The method showed some drawbacks associated with the use of hazardous ketene in hetero Diels-Alder reaction and harsh conditions for the adduct hydrolysis (Scheme 1a). In 2013, Grellepois[15] published the first diastereo- and enantioselective synthesis of β-alkyl(aryl)-β-trifluoromethyl-β-amino acid derivatives based on CuI-catalyzed Reformatsky reaction (Scheme 1b). Enantiopure N-*tert*-butanesulfinyl trifluoromethyl ketimines generated *in situ* from stable precursors were thus advantageously used. Similar report, using lithium enolate, can be witnessed giving rise to promising MGAT2 inhibitors[16] and modulators of mGluR4.[17] In a recent communication from Oshima's group, catalytic Mannich-type reaction with various (di)ketones and dialkyl malonates was investigated using trifluoromethyl NH-ketimines as electrophiles (Scheme 1c).[18] However, the method required strong metal-based Lewis acid catalyst and isolation of hardly accessible NH-ketimines.

Scheme 1. Literature methods for preparation of β-substituted β-trifluoromethyl-β-amino acids



The literature survey clearly pointed out the lack of simple and flexible protocols for accessing β-(het)aryl-β-fluoroalkyl-β-amino acids that may limit their broader synthetic application. Despite the highlighted above existing methods, only the simplest β-amino acid possessing β-phenyl substituent has been characterized so far.[14] That is in striking contrast to non-β-fluoroalkylated analogues which are readily available in one step by the Rodionov reaction, three component decarboxylative condensation of aldehydes, malonic acid (MA) and ammonium acetate.[19] The Rodionov method does not provide the corresponding β-aryl-β-fluoroalkyl-β-amino acids when arylfluoroalkyl ketones are used instead of aldehydes.

Scheme 2. Access to β-fluoroalkyl-β-amino acids *via* a modified Rodionov reaction



In the context of our studies on trifluoromethyl NH-ketimines,[20] we were curious if the Rodionov reaction is possible using these compounds. Herein, we present the first decarboxylative addition of MA, its half esters or tartronic acid to generated *in situ* fluoroalkyl NH-ketimines as an attractive and direct access to free unprotected β-fluoroalkyl-β-amino acid derivatives (Scheme 2). Our approach complements the mechanistically similar Rodionov reaction, postulated to proceed *via* formation of the NH-aldimines,[19] by introducing previously challenging fluorinated ketones as a new class of substrates.

2- Experimental details

General methods. All manipulations were conducted under argon (1atm). The reactions were monitored by ^{19}F NMR spectra of the reaction mixture samples or thin-layer chromatography (TLC) using silica gel gel (60 F254) plates (compounds were visualized using a UV lamp (254 nm) and/or by potassium permanganate stain). Flash column chromatography was carried out on silica gel 60 (230-400 mesh, 0.040-0.063 mm). Melting points (mp [°C]) were taken on samples in open capillary tubes and are uncorrected. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a spectrometer at 400 MHz (^{13}C: 101 MHz; ^{19}F: 376 MHz). Chemical shifts are given in parts per million from tetramethylsilane (^{1}H NMR) or CCl_3F (^{19}F NMR) as internal standard. High-resolution accurate mass measurements (HRMS) were recorded with a Maxis Bruker 4G instrument and were performed in positive mode with an ESI source on a Q-TOF mass spectrometer with an accuracy tolerance of 2 ppm by the "Fédération de Recherche" ICOA/CBM (FR2708) platform. Compounds **1a-z** were provided by Sigma-Alrich, Fluorochem or Enamine LTD and used as received.

Synthesis of compounds 4a-y. General procedure (GP). Step 1. Reaction of ketones 1a-y with lithium hexamethyldisilazide. Preparation of crude compounds 2a-y. A solution of ketone **1a-y** (1.50 mmol, 1 equiv) in anhydrous hexane (10 mL) was cooled to 0-5 °C in ice water bath and lithium hexamethyldisilazide solution (1.0 M in hexanes, Sigma-Aldrich, 1.65 mL, 1.1 equiv) was added at stirring *via* syringe over 5 min under argon atmosphere. The reaction mixture was stirred for 20 min at 0-5 °C and for 2 h at room temperature. After that the mixture was cooled to 0-5 °C in ice water bath and cold water (5 mL) was added under vigorous stirring. The resulted mixture was stirred for 5 min at 0-5 °C. Organic layer was separated, washed with brine (2×10 mL), dried over anhydrous magnesium sulfate, filtered and solvents were removed under vacuum. The residual liquid or oil was dried at 35-40 °C and 15 Torr for 1 h. The crude compound **2a-y** thus obtained was used immediately in the next step without additional purification.

Step 2. Reaction of crude compounds 2a-y with malonic acid. Synthesis of compounds 4a-y. The crude compound **2a-y** was dissolved in anhydrous acetonitrile (1 mL), then malonic acid (312 mg, 3.0 mmol) was added and the mixture was stirred at 80 °C for 2 h. After cooling, the reaction mixture was treated as specified for each example. The yields are calculated based on starting ketone **1a-y**.

Representative products:

3-Amino-4,4,4-trifluoro-3-phenylbutanoic acid (4a). Following the **GP**, using 1-phenyl-2,2,2-trifluoroethanone **1a** (261 mg, 1.5 mmol, 1 equiv). The reaction mixture obtained according to **GP** was evaporated to dryness and the residue was dissolved in aqueous hydrochloric acid (10 % w/w, 3 mL). The solution was evaporated to dryness. The residue was treated with ethyl acetate (3 mL). The white solid was collected by filtration, washed with ethyl acetate (3×3 mL), dried under vacuum and dissolved in distilled water (5 mL). A solution of sodium hydrocarbonate (115 mg, 1.37 mmol, 1 equiv) in distilled water (3 mL) was added to this solution. The mixture was stirred at room temperature for 1 h. The precipitate was collected by filtration, washed with distilled water (3×3 mL) and dried in vacuum to give free **4a** as a white solid (263 mg, 71 % starting from **1a**). Mp 174–176 °C. ^{1}H NMR (400 MHz,

DMSO-d_6): 7.66 (d, J = 7.4 Hz, 2H), 7.4 – 7.35 (m, 3H), 5.02 (br s, 3H), 3.26 (d, J = 16.0 Hz, 1H), 2.95 (d, J = 16.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.1, 138.1, 128.55, 128.51, 127.52, 126.7 (q, J = 287 Hz), 60.5 (q, J = 26 Hz), 39.6. ^{19}F NMR (376 MHz, DMSO-d_6): δ –77.7 (s).

3-Amino-4,4,4-trifluoro-3-(thiophen-2-yl)butanoic acid (4v). Following the **GP** using 2,2,2-trifluoro-1-(thiophen-2-yl)ethanone **1v** (270 mg, 1.50 mmol, 1 equiv). The reaction mixture obtained according to **GP** was treated as described for preparation of free **4a**. White solid (248 mg, 69 %). Mp 127–129 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.53 (d, J = 4.7 Hz, 1H), 7.22 (s, 1H), 7.04 (t, J = 4.0 Hz, 1H), 6.14 (br s, 3H), 3.08 (d, J = 15.7 Hz, 1H), 2.93 (d, J = 15.7 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 170.9, 143.2, 127.5, 127.1, 126.9, 126.1 (q, J = 286 Hz), 59.7 (q, J = 28 Hz), 40.8. ^{19}F NMR (376 MHz, DMSO-d_6): δ –78.5 (s). HRMS (ESI+): calcd for $C_8H_9F_3NO_2S$ $[M+H]^+$: 240.0300, found 240.0298.

3- Results and discussion

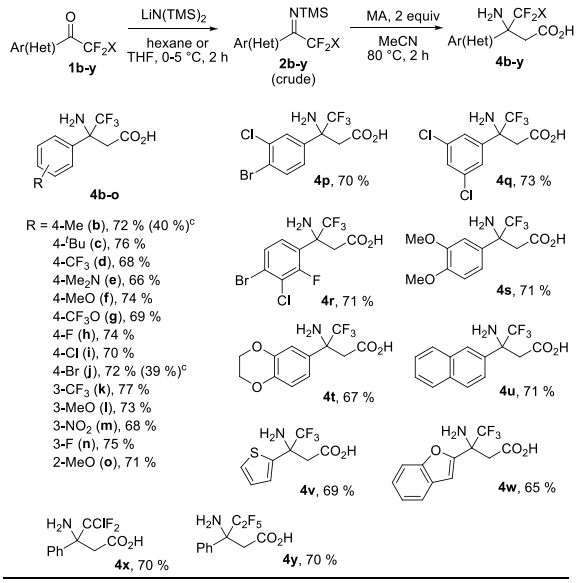
Initially, we attempted to synthesize the starting NH-ketimine **3a**, used as a model substrate, from the corresponding trifluoromethyl ketone **1a** *via* the N-TMS derivative **2a** to avoid the usage of highly toxic trifluoroacetonitrile or hardly available triphenylphosphine imine.[18,21] Compound **2a** was isolated in almost quantitative yield according to known procedure using lithium hexamethyldilazide (LiHMDS).[22] Then, we first studied **3a** interaction with MA to mimic the Rodionov reaction with preformed and stable NH-ketimine. To our delight the addition of MA (3 equiv) in anhydrous acetonitrile smoothly proceeded to full completion in 24 hours at room temperature. In these conditions 3-amino-4,4,4-trifluoro-3-phenylbutanoic acid **4a** was formed in quantitative NMR yield and precipitated from acetonitrile. After simple workup, **4a** was isolated as hydrochloride salt in 87% yield.

In the next experiment, we directly introduced into reaction with MA the N-TMS ketimine **2a** and found that there were no significant differences in reactivity of the new substrate and in yield of the product. This finding substantially simplifies the preparation of **4a** by eliminating the unnecessary and yield reducing TMS group deprotection step. The cleavage of N-Si bond is likely to quickly occur by action of the MA leading to *in situ* formation of the reactive NH-ketimine **3a**.

To make the procedure even shorter we tested a one-pot protocol. After preparation of TMS protected ketimine **2a** using 1 equiv of LiHMDS in THF we allowed it to react with MA in the same reaction flask without isolation Gratifyingly, one-pot protocol directly led to **4a** which precipitated from the resulted THF solution as free amino acid and could be easily purified by simple washing with THF and water. However, in this case yield of the pure isolated product dropped to 46%.

Next we started the optimization study by investigating the addition of MA to the N-TMS ketimine **2a** and selected acetonitrile and 2 h heating with 2 equiv of MA as optimal conditions to evaluate the scope and limitations of the addition reaction, at first, with respect to both aryl(hetaryl) and fluoroalkyl substituents of the ketone substrate **1** (Scheme 3).

Scheme 3. Scope of ketone substrates in the synthesis of β-fluoroalkyl β-amino acids 4b-y

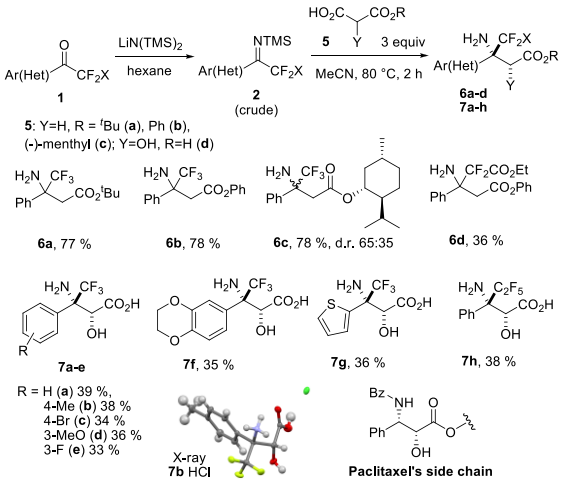


The two-step general protocol with isolation of the crude N-TMS ketimines **2b-y** demonstrated tolerability to common halogen, (halo)alkyl,

alkoxy, nitro and dialkylamino substituents R at the *para* or *meta* position(s) of the aryl group (products **4b-u**). In total, 24 previously not described free β-fluoroalkyl β-amino acids were directly synthesized in good to high yields. All compounds were isolated without chromatographic purification steps in a preparatively convenient and scalable way.

Next we studied the analogous reactions with substituent variations at the accessible sites of MA (Scheme 4). Starting from malonic acid half *t*-butyl and half phenyl esters **5a,b** (3 equiv), β-amino esters **6a,b** were successfully prepared in high yields in similar conditions.

Scheme 4. Synthesis of β-fluoroalkyl β-amino esters 6a-d and α-hydroxy-β-amino acids 7a-h



α-Hydroxy-β-amino acids are important naturally occurring compounds primarily known as components of the taxane family of anticancer drugs.[23] Their β-aryl-β-fluoroalkyl derivatives remain elusive and represent an attractive synthetic target owing to the presence of the fluorinated functional motive. We attempted to further confirm the versatility of the developed methodology by involving commercially available α-hydroxymalonic (tartronic) acid **5d** (Scheme , Y=OH) as reaction substrate potentially leading to new α-hydroxy derivatives of β-fluoroalkyl-β-amino acids. Despite the presence of the additional nucleophilic center, hydroxyl group, **5d** (3 equiv) reacted with corresponding crude N-TMS ketimines **2** in previously optimized conditions and readily afforded the desired products **7a-h** as single diastereomers (>98:2 d.r.) in 33-39 % yields. The (2*R**,3*S**) relative configurations of the chiral centers in products **7a-h** was unambiguously proved by XRD study of **7b**. Consequently, obtained compounds **7** are the first racemic β-fluoroalkyl analogues of Paclitaxel's side chain amino acid, (2*R*,3*S*)-α-hydroxy β-phenylalanine.[8c,24]

4- Conclusion

In summary, our report establishes a new and general methodology for convenient preparation of β-aryl(hetaryl)-β-fluoroalkyl β-amino acids and their previously not known α-hydroxy derivatives. The provided protocols may stimulate wider utilization of these β-amino acids as now readily available basic organofluorine building blocks.

5- Perspectives of future collaborations with the host laboratory

In our future collaborations we will focus on the study of specific effects of trifluoromethyl group that provide novel tools in molecular design of pharmacologically promising nitrogen containing heterocyclic compounds. This work has established a collaboration between experienced scientists in the area of computational chemistry and methodological synthesis representing both IOCH NAS of Ukraine (Pr. A. Rozhenko, Pr. M. Vovk) and ICOA, University of Orleans in France (Pr. Isabelle Gillaizeau).

The diverse structures of our original fluoroalkyl substituted compounds are under investigation in the *in silico* fragment-based design of novel protein kinase inhibitors where we pay special attention to the trifluoromethyl substituent as a unique structural feature to achieve specific attractive interactions with protein targets. This study has been initiated in collaboration with Pr. P. Bonnet (Structural Bioinformatics and Chemoinformatics of the ICOA).

6- Communications in the framework of the fellowship

Oral communications:

1. Sukach, V.A. 4-Trifluoromethylpyrimidin-2(1H)-ones in organocatalytic decarboxylative addition of malonic acid and its derivatives. Journées de la Section Régionale Centre-Ouest (SCF), Université de La Rochelle, La Rochelle (France), February 7-9, 2018.

2. Sukach, V.A. Fluoroalkyl ketimines in decarboxylative Mannich reaction, Le Studium Conference: Progress in Organofluorine Chemistry, Orléans (France), October 15-17, 2018.

Posters:

1. Sukach, V.A., Melnykov, S.V., Vovk, M.V., Gillaizeau, I. A modification of the Rodionov reaction for the synthesis of β-fluoroalkyl β-amino acids, XXII International Conference on Organic Synthesis, Florence (Italy), September 16-21, 2018.

2. Sukach, V.A., Melnykov, S.V., Vovk, M.V., Gillaizeau, I. Le Studium Conference: Progress in Organofluorine Chemistry, Orléans (France), October 15-17, 2018.

3. Sukach, V.A., Bertho, S., Melnykov, S.V., Vovk, M.V., Diachenko, I., Gillaizeau, I. Synthesis of β-fluoroalkyl β-amino acids via a modification of the Rodionov reaction, Carbohydrate and Fluorine Symposium, Poitiers (France), October 18-19, 2018.

4. Sukach, V.A., Melnykov, S.V., Vovk, M.V., Bertho, S., Gillaizeau, I. β-Fluoroalkyl β-amino acids – effective reagents for preparation of 3,4-dihydroquinolin-2(1H)-one derivatives, 8th International Conference "Chemistry of Nitrogen Containing Heterocycles", Kharkiv (Ukraine), November 12-16, 2018.

5. Melnykov, S.V., Sukach, V.A., Tkachuk, V.M., Vovk M.V. Organocatalytic decarboxylative addition of malonic acid, its derivatives and ketoacetic acids to 4-(trifluoromethyl)pyrimidin-2(1H)-ones, 8th International Conference "Chemistry of Nitrogen Containing Heterocycles", Kharkiv (Ukraine), November 12-16, 2018.

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