Access to Unprotected β-Fluoroalkyl β-Amino Acids and their α-Hydroxy Derivatives

Volodymyr Sukach,*[‡,†] Serhii Melnykov,[#,¤] Sylvain Bertho,[†] Iryna Diachenko,[†] Pascal Retailleau,[§] Mykhailo Vovk,[#] Isabelle Gillaizeau*[,†]

[‡] Le Studium Loire Valley Institute for Advanced Studies, 1, rue Dupanloup, 45000 Orléans, France

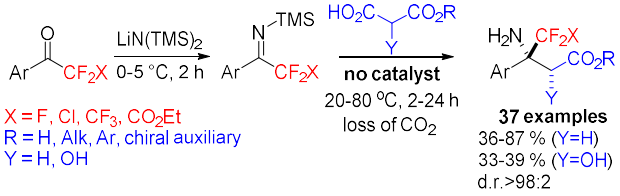
[†] Institute of Organic and Analytical Chemistry, ICOA UMR 7311 CNRS, Université d'Orléans, rue de Chartres, 45100 Orléans, France

[#] Institute of Organic Chemistry of NAS of Ukraine, 5, Murmanska Str., Kyiv, Ukraine

[¤] Enamine LTD, 78 Chervonotkats'ka str., Kyiv 02094, Ukraine

[§] Institut de Chimie des Substances Naturelles, CNRS UPR 2301, Université Paris-Sud, Université Paris-Saclay, avenue de la terrasse, 91198 Gif-sur-Yvette, France

Supporting Information Placeholder



ABSTRACT: Unprotected β-(het)aryl-β-fluoroalkyl β-amino acids and their α-hydroxy derivatives can be readily obtained using a decarboxylative Mannich-type reaction without protection/deprotection steps. This protocol utilizes lithium hexamethyldisilazide and (het)arylfluoroalkyl ketones to generate NH-ketimine intermediates. The mild reaction conditions allow the preparation of original fluorinated β-amino acids as useful building blocks in a practical and scalable manner.

β-Amino acids are the most prominent non-proteinogenic amino acids[1] and are found as a structural motif in many natural products[2] or biologically active molecules such as β-lactam antibiotics (Figure 1).[3] They are key synthetic precursors for important marketed pharmaceutical products (i.e. sitagliptin, paclitaxel).[4] Fluorinated analogues of amino acids have received considerable attention in recent years due to their potential in preparing bioactive molecules with remarkable properties.[5-7]β-Amino acids bearing a fluoroalkyl group at β-position are of particular interest as unique intermediates in the design of bioactive peptide mimetics or enzyme inhibitors. 3-Amino-4,4,4-trifluorobutanoic acid[8] has been incorporated into partially modified retropeptides exhibiting a β-turn-like conformation,[9] into peptidomimetics which inhibit MMP[10] and, more recently, into oligo-β-peptides which are able to form significantly more stable helices due to the effects of CF_3 groups.[11] β-Substituted derivatives of β-fluoroalkyl-β-amino acids are scarce.[12] The synthesis of racemic 3-amino-4,4,4-trifluoro-3-phenylbutanoic acid was first described in 1991 by Kukhar's group via a hetero Diels-Alder cycloaddition using ketene (Scheme 1a).[13] However, harsh reaction conditions or substrate scope limitations call for the development of new routes.

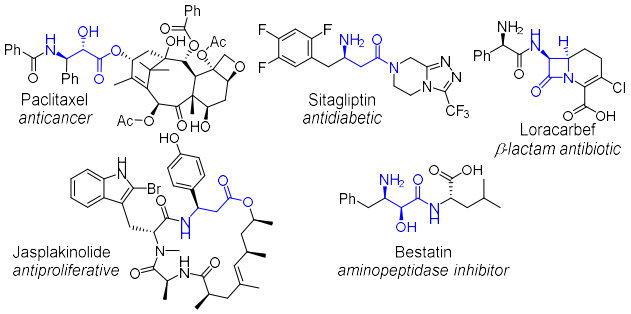
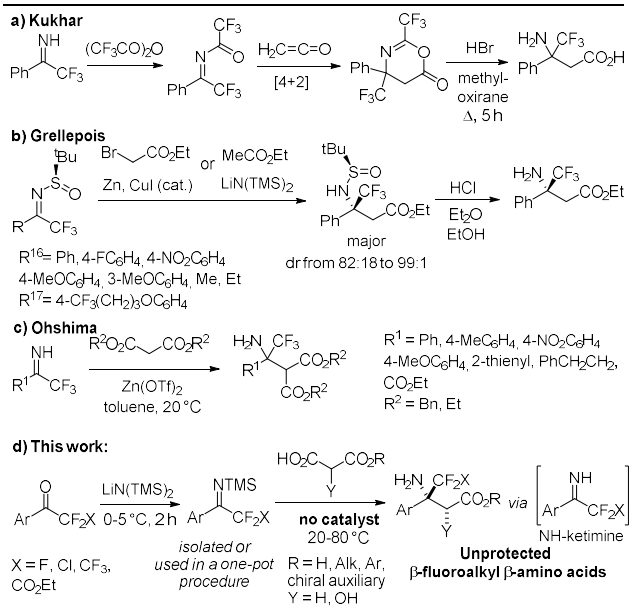


Figure 1. β-Amino acids in bioactive compounds

In 2013, Grellepois[14] published the first diastereo- and enantioselective synthesis of β-alkyl(aryl)-β-trifluoromethyl-β-

amino acid derivatives based on a CuI-catalyzed Reformatsky reaction (Scheme 1b). Enantiopure N-*tert*-butanesulfinyl trifluoromethyl ketimines generated *in situ* from stable precursors were thus advantageously used. Similar reports, using lithium enolate, gave rise to promising MGAT2 inhibitors[15] or modulators of mGluR4.[16] Recently, Ohshima investigated a catalytic Mannich-type reaction with various (di)ketones and dialkyl malonates using trifluoromethyl NH-ketimines as electrophiles (Scheme 1c).[17] However, it required a strong metal-based Lewis acid catalyst and isolation of hardly accessible NH-ketimines, weakening its synthetic potential. Furthermore, this group also reported a catalytic enantioselective decarboxylative Mannich-type reaction of N-unprotected ketimines from isatins, providing N-unprotected 3-tetrasubstituted 3-aminooxindole derivatives.[18]

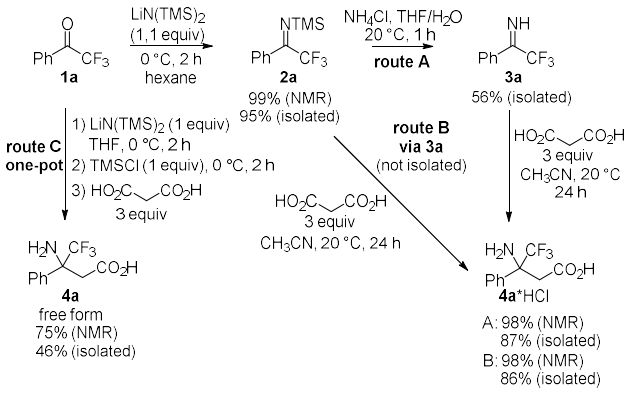
Scheme 1. Preparation of β-substituted β-trifluoromethyl-β-amino acids



The literature survey clearly pointed out the lack of simple and flexible protocols for accessing β-(het)aryl-β-fluoroalkyl-β-amino acids, which may limit their broader synthetic application. Despite the above-mentioned existing methods, only the simplest β-amino acid possessing a β-phenyl substituent has been characterized so far.[13] This is in striking contrast to β-substituted analogues which are readily available in one step by the Rodionov reaction,[19] a three-component decarboxylative reaction of aldehydes, malonic acid (MA) and ammonium acetate. However, this approach suffers from limitations, providing a major challenge to develop sustainable alternatives.[20] In the context of our studies on trifluoromethyl NH-ketimines,[21] we present herein the first decarboxylative addition of malonic acids to generate *in situ* fluoroalkyl NH-ketimines as an attractive and direct access to unprotected β-fluoroalkyl-β-amino acids that has heretofore remained unexplored. Our approach complements the mechanistically similar Rodionov reaction, postulated to proceed *via* formation of the NH-aldimines,[19b] by introducing as a new class of substrates challenging fluoroalkyl ketones.

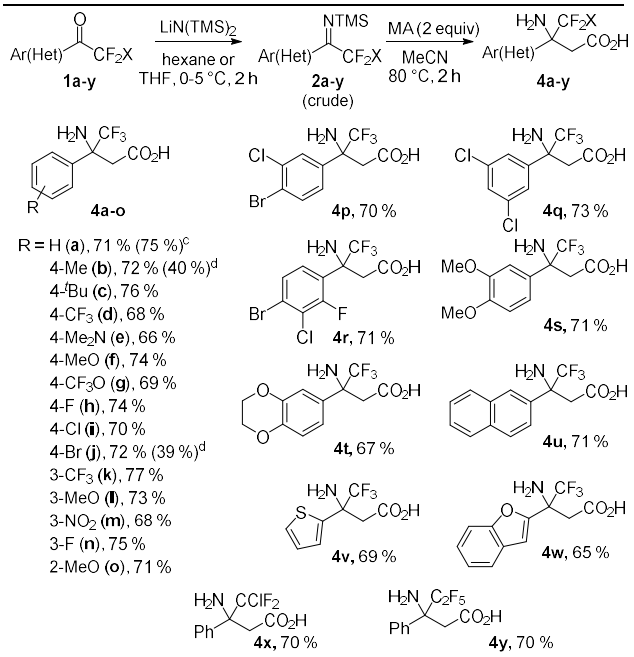
Initially, we attempted to synthesize the starting NH-ketimine **3a**, used as a model substrate, from the corresponding trifluoromethyl ketone **1a** *via* the N-TMS derivative **2a** to avoid the use of highly toxic trifluoroacetonitrile or of triphenylphosphine imine which is not readily available (Scheme 2, route **A**).[22] Compound **2a** was isolated in almost quantitative yield according to the known procedure using lithium hexamethyldilazide (LiHMDS).[23] Removal of the TMS group was achieved upon acidic treatment affording **3a** in 56% isolated yield after distillation. Then, we first studied the reaction of **3a** with MA. To our delight the addition of MA (3 equiv) in anhydrous acetonitrile proceeded smoothly to full completion in 24 hours at room temperature. The concurrent decarboxylation of the initially formed MA adduct (not shown in scheme 2, but see the mechanism discussion below) occurs much faster since it could not be detected in the reaction mixture by ^{19}F NMR monitoring. In these conditions, 3-amino-4,4,4-trifluoro-3-phenylbutanoic acid **4a** was formed in quantitative NMR yield and precipitated from acetonitrile. After a simple workup, **4a** was isolated as hydrochloride salt in 87% yield.

Scheme 2. Preliminary synthesis of β-amino acid 4a from ketone 1a using LiHMDS



We also demonstrated that 3-amino-4,4,4-trifluoro-3-phenylbutanoic acid **4a** could be obtained in higher overall yield directly from **2a** (route **B**). In this case the cleavage of the N-TMS bond is likely to quickly occur in presence of malonic acid leading to the *in situ* formation of the reactive NH-ketimine **3a**. It is worth noting that a one-pot procedure can also be advantageously used (route **C**). In this case, the equimolar amount of TMSOLi, resulting from the transformation of ketone to ketimine, was quenched with TMSCl before MA addition to prevent TMSOH formation. Its dimerization with concomitant water release may result in hydrolysis of **3a**.[24] Gratifyingly, the one-pot protocol directly led to the unprotected amino acid **4a** which precipitates from the reaction mixture. However, in this case the yield of pure isolated product **4a** dropped to 46% due to the still poorly controlled partial hydrolysis of *in situ* formed **3a** to ketone **1a** (see SI). Since the best yield of unprotected β-amino acid **4a** was observed using method **B**, various conditions were then screened from N-TMS ketimine **2a** (see SI section). A series of common solvents were next examined, revealing that a short heating of the reaction mixture in acetonitrile (2h at 80 °C) in presence of 2 equiv of MA was best suited to the reaction.

Scheme 3. Scope of ketones 1a-y in the synthesis of β-fluoroalkyl β-amino acids 4a-y[a,b]

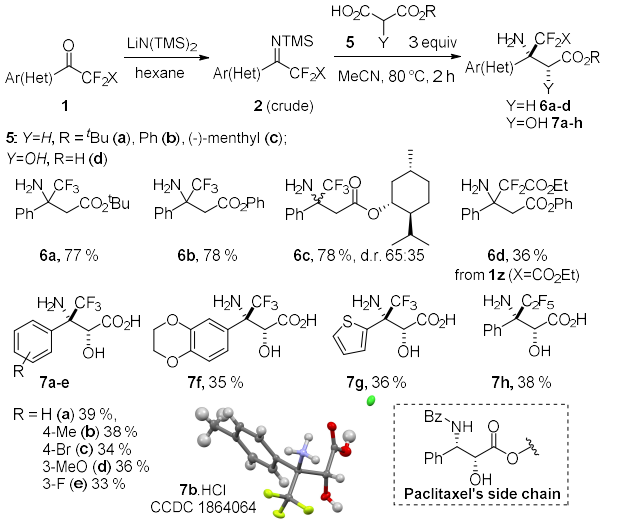


Reaction conditions: [a]Method **B** was used with isolation of crude N-TMS ketimines **2a-y** unless otherwise specified; syntheses were performed on 1.5 mmol scale in 1 mL of CH_3CN. [b]Isolated yields were calculated based on the corresponding starting ketones **1a-y**. [c]Reaction was performed on 10 mM scale. [d]One-pot procedure **C** was used with addition of TMSCl (1 equiv, 0-5 °C, 2 h at r.t.) before addition of MA (see SI for experimental details).

With the optimized conditions in hand, the scope of this two-step reaction was examined with respect to the ketone derivatives **1a-y** (Scheme 3). The reaction proceeded smoothly with a wide functional group tolerance. Initially, the effect of the substituents on the aromatic ring of arylfluoroalkyl ketone (**1a-u**) was investigated. Both electron-donating (i.e. alkoxy, alkyl or dialkylamino groups) and withdrawing groups (i.e. halogen, trifluoroalkyl or nitro groups) with different substitution patterns were tolerated thus giving the corresponding quaternary β-(het)aryl-β-fluoroalkyl-β-amino acids in good yields (**4a-u**). In addition, heteroaryl substituted ketones **1v-w** were also suitable for this reaction, providing the original β-hetaryl β-trifluoromethyl β-amino acids **4v-w**. Introduction of the $CClF_2$ and C_2F_5 groups led to the hitherto unknown β-fluoroalkyl β-amino acids **4x-y**. Additionally, the alternative one-pot procedure (method **C**) was applied to ketones **1b,j** affording the attempted products **4b,j** in lower yields. A variety of original unprotected β-fluoroalkyl β-amino acids were thus readily furnished in synthetically useful yields without any chromatographic purification steps and in a convenient and easy way for scale-up (preparation of **4a** was achieved in 75 % yield under optimal conditions on a 10 mM scale). There are also a great many uses for β-fluoroalkyl β-amino acids which can be transformed to a variety of useful compounds.

Subsequently, we explored the use of substituted MA in this decarboxylative Mannich-type reaction with ketimines **2** (Scheme 4). To our delight, a range of malonic acid half esters **5a-d** were suitable for the reaction leading to β-amino esters **6a-d** (Y=H) in moderate to good yield which demonstrated the remarkable scope of this method. Installation of a chiral auxiliary derived from optically pure (–)-menthol in the starting compound **5c** led to β-amino esters **6c** with 65:35 d.r. Compound **6d** featuring an ethoxycarbonyldifluoromethyl group was obtained in moderate yield from the corresponding ethyl 2,2-difluoro-3-oxo-3-phenylpropanoate **1z**. Noticeably, α-hydroxy-β-amino acids are important naturally occurring compounds primarily known as components of the taxane family of anticancer drugs.[25] Their corresponding β-aryl-β-fluoroalkyl derivatives remain elusive and represent an attractive synthetic target owing to the presence of the fluorinated functional group. We attempted to further confirm the broad generality and effectiveness of the developed method by involving commercially available α-hydroxymalonic (tartronic) acid **5d** (Scheme 4, Y=OH) as substrate. **5d** (3 equiv) reacted smoothly with the corresponding crude N-TMS ketimines **2** under the reaction conditions and afforded the desired products **7a-h** as single diastereomers (>98:2 d.r.), albeit in lower yields, directly upon simple workup of the reaction mixture and crystallization. ^{19}F NMR analysis revealed that in the reaction of **2a** with **5d** a mixture of diastereomeric products (83:17 d.r.) was initially formed in 80 % NMR yield (see SI). The (2*R**,3*S**) relative configurations of the chiral centers in products **7a-h** were unambiguously proved by the XRD study of **7b**.[26] Consequently, the 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.[7c,27]

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

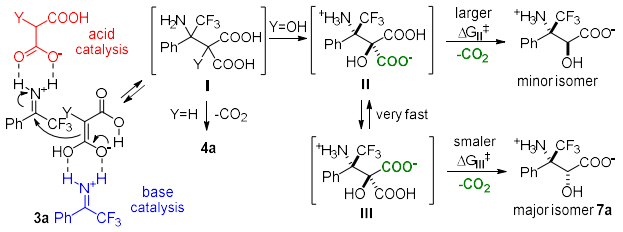


[a]Isolated yields were calculated from the corresponding starting ketones **1**. For compounds **7** the structures and yields refer to isolated major diastereomers with >98:2 d.r.

In agreement with the previously reported literature results,[28] a proposed mechanism for the decarboxylative addition of MA and tartronic acid to NH-ketimine **3a** is outlined in Scheme 5. First, it should be noted that the rate of **4a** formation is not sensitive to the presence of organic acid or base catalysts (TFA, TfOH, pyridine, Et_3N, *etc*, including chiral organocatalysts). We suppose that in this case a mutual substrate catalysis is observed since **3a** itself is a weak organic base while MA is mildly acidic (pK_a^1 = 2.83). Therefore, both substrates are capable of activating each other's corresponding electrophilic (C=N bond) or nucleophilic (CH_2 group) centers, thus causing

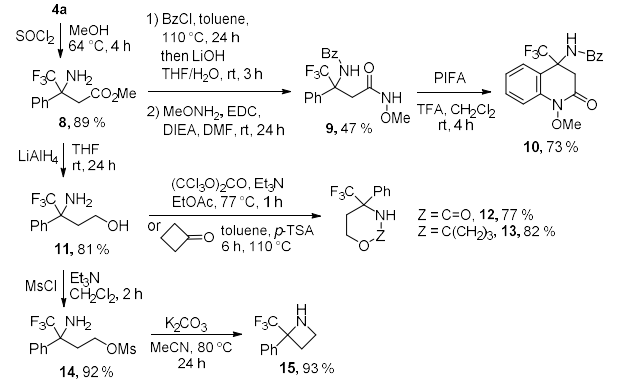
externally added catalyst inefficiency. The reactive C-nucleophilic species generated from malonic (tartronic) acid is assumed to be enolate monoanion (approximate $pK_a^{CH} = 13 – 14$ for MA).[29] In the first step, its reversible addition to protonated ketimine **3a** gives rise to intermediate **I**. Then irreversible decarboxylation of **I** leads to **4a** (Y=H). In the case of tartronic acid addition (Y=OH), preferential formation of the major diastereomer **7a** is determined, according to the classic Curtin-Hammett principle, by the relatively large difference in $\Delta G_{II}^{\ddagger}$ and $\Delta G_{III}^{\ddagger}$ energies of the transition states derived from the respective most populated conformers **II** and **III** which are stabilized by the intramolecular electrostatic interaction and hydrogen bonding between *syn*-clinal NH_3^+ and COO^-/COOH groups. These mechanistic assumptions imply that intermediates **II** and **III** should undergo rapid reversible interconversion by proton transfer and slower irreversible decarboxylation (presumably via the leaving CO_2^- group and the formation of a noncyclic anionic transition state)[30] into diastereomeric products.

Scheme 5. Proposed mechanistic pathways for the decarboxylative addition of malonic or tartronic acid to 3a



To demonstrate the utility of this reaction and gain access to molecular diversity, we performed a short-step synthesis of the novel relevant 4-amino-4-(trifluoromethyl)-3,4-dihydroquinolin-2(1H)-one derivative **10** as an attractive scaffold for medicinal chemistry (Scheme 6).[31] The key cyclization step of the N-methoxy amide **9** in the proposed synthetic sequence was achieved with phenyliodine bis(trifluoroacetate) (PIFA) in good yield.[32] In addition, reduction of the methyl ester **8** into amino alcohol **11** and its subsequent cyclocondensation with triphosgene or cyclobutanone provided derivatives of 1,3-oxazinan-2-one **12** and 5-oxa-9-azaspiro[3.5]nonane **13**, respectively. 2-Phenyl-2-(trifluoromethyl)azetidine **15** can be readily prepared from the corresponding mesylate **14** in excellent yield.

Scheme 6. Application of β-amino acid 4a to the synthesis of original heterocyclic systems



In summary, we reported a new and simple method for the preparation of a range of original β-aryl(hetaryl)-β-fluoroalkyl β-amino acids and their analogous α-hydroxy derivatives with high diastereoselectivity. The generality of this approach was demonstrated and it opens the way to organofluorine building blocks otherwise challenging to prepare. The reaction occurred in smooth reaction conditions and without any chromatographic purification steps via a decarboxylative Mannich-type reaction involving NH-ketimine intermediate which could be isolated. Further experiments are in progress to study the scope of this process.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, NMR data and crystal structure of the products (PDF file).

Accession Codes

CCDC 1864064 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Authors

* E-mail: isabelle.gillaizeau@univ-orleans.fr
* E-mail: vsukach@gmail.com

ORCID

Isabelle Gillaizeau: 0000-0002-7726-3592
Pascal Retailleau: 0000-0003-3995-519X
Volodymyr Sukach: 0000-0002-2891-343X
Mykhailo Vovk: 0000-0001-7739-670X

Notes

The authors declare no competing financial interest.

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