Semi-Industrial Fluorination of β-Keto Esters with SF₄: Safety vs Efficacy

S. A. Trofymchuk et al.

Abstract

The possibility of deoxofluorination of β-keto esters using SF₄ was investigated. The scope and limitation of the reaction were determined. The efficient method for the synthesis of β,β-difluorocarboxylic acids was elaborated based on the reaction. The set of mentioned acids, being the perspective building blocks for medicinal chemistry, were synthesized on multigram scale. The safety of SF₄ use was discussed. The described method does not improve upon the safety of using SF₄, but practical recommendations for working with the reagent are proposed. Despite the hazards of using toxic SF₄, a significant increase of efficacy in the synthesis of medicinal-chemistry-relevant building blocks, based on the reaction, in comparison with earlier described approaches is shown.

Key words organofluorine compounds, deoxofluorination, sulfur tetrafluoride, β-keto esters, β,β-difluorocarboxylic acids, building blocks

There are many efficient reagents for organic synthesis known from the classical textbooks, but by no means are all of them popular among chemists for real application in laboratory practice. Gaseous or volatile compounds which possess extremely high toxicity, like CH₃N₂, HCN, COCl₂, and MeNCO, are among the most characteristic examples. The Bhopal disaster, where approximately 200,000 people were exposed to MeNCO and around 20,000 died as a result, has clearly demonstrated such reagents as actually dangerous.¹ Nevertheless, unique properties of SF₄ in substitution of carbonyl oxygen with two fluorine atoms are very attractive. This is making development of more safe and convenient SF₄-based analogues like DAST (Et₂NSF₃) and XtalFluor-E ([Et₂N⁺=SF₂]BF₄⁻) or other similar reactants like fluoramine reagents (FAR) very important.¹⁰ Such replacement of reagents is successful, but it does not always happen. Fluorination of carboxylic acids to CF₃ derivatives is one of the
most known examples to the contrary. This process proceeds smoothly under SF₄ treatment, but in the case of DAST or XtalFluor-E the reaction stops at the fluoroanhydride formation step. There is only one successful example described – Fluolead (4-tert-Butyl-2,6-dimethylphenylsulfur trifluoride), which is used for fluorination of carboxylic acids to CF₃ derivatives instead of SF₆. However, Fluolead is a rather expensive reagent, therefore this approach does not find further application. In this work we describe another example of utilizing SF₄ as unique deoxofluorinative reagent, like cited above. As a part of our ongoing efforts on design and synthesis of advanced reagents for medicinal chemistry and especially functionalized gem-difluoro derivatives, we chose β-keto esters, the precursors for β,β-difluorocarboxylic acids, promising building blocks for medicinal chemistry, as substrates for the fluorination.

The products of deoxofluorination of β-keto esters are corresponding β,β-difluorocarboxylic acids, building blocks of high value to medicinal chemistry. Some recent representative examples A–F of such building blocks from medicinal chemistry programs related to different therapeutics areas are shown in Figure 1. In spite of wide use of β,β-difluorocarboxylic acids as building blocks by big pharma and biotech companies, direct and efficient approaches to their synthesis are still unknown. The analysis of compounds presented in the literature reveals, that many of them are known, but available only from commercial sources without any information about synthetic routes and procedures.

The first attempts of deoxofluorination of β-keto esters were made in the early 1980s by L. M. Yagupol’ski and co-workers. As were shown in these seminal researches, the reaction was accompanied by side dehydrofluorination processes, the impact of which could be decreased by reducing the temperature (Scheme 1). Therefore, the reaction in HF media at room temperature could be considered as preparative. Nevertheless, all attempts to replace SF₄ by DAST failed. Unexpectedly, in this reaction DAST, introducing an additional fluorine into the molecule, formally oxidizes the substrate. In our previous investigations we also tried to optimize the reaction and replaced SF₄ with DAST-type reagents, but all our attempts failed as well. In consequence an alternative synthetic route was proposed. The strategy was based on three-step transformation of the ester function into a nonacceptor CH₂OAc group, which allowed DAST-based deoxofluorination. The further deacylation/oxidation led to desired β,β-difluorocarboxylic acids. In spite of successful realization of the strategy additional six-step sequence was needed, so the total yields were in 14–16% range. Such avoiding of SF₄ is justified for the small-scale synthesis but inefficient for the further scale-up. Therefore, we decided to test diverse deoxofluorination reactions of β-keto esters with hazardous SF₄ in autoclave conditions and scale them up to hundred grams.

Firstly, we tested the reaction of deoxofluorination by SF₄ with and without addition of HF at different temperatures and different ethylacetocacetate/SF₄ ratios using the simplest ethylacetocacetate (1a) as a model compound. It was found that in the absence of HF, the reaction proceeded nonselectively with predominant dehydrofluorination to the product 3 at 100 °C, as well as at 25 °C. The fraction of dehydrofluorination was dramatically decreased by addition of HF to the system, and at 25 °C a significant selectivity of formation of β,β-difluorocarboxylic ester 2a was achieved (Scheme 1). Further optimization showed that the most favorable was the amount of HF of 0.8 mL per 1 g of ethylacetoacetate, the ratio of SF₄/keto ester = 1.7:1, and the reaction time of 10 h. Using these conditions, we performed

![Figure 1](image-url)
the reaction on 100 g scale of ethylacetoacetate in 1.2 L Hastelloy autoclave. The level of dehydrofluorination was less than 5% and as a result the desired β,β-difluoroacrylic ester 2a was isolated in preparative 70% yield.

For the investigation of scope and limitation of the developed protocol, a diverse set of substrates were chosen. Acetoacetic ester derivatives 1a–g, their mono- and dialkyl-substituted analogues 1h–k and 1l–o, respectively, functionalized acetoacetic ester derivatives 1p–s and cyclic β-keto esters 1t–y were presented among them. The nonenolizable dialkylated derivatives 1h–k were added to the set for checking the influence of possible enol formation as the reaction occurs. Also, the set of functionalized acetoacetic esters 1p–s were tested for the group-tolerance determination, and derivatives 1t–y to examine the impact of conformational restriction (Figure 2).

These substrates were tested in deoxofluorination reaction with SF₄/HF system according to the aforementioned optimized protocol for ethylacetoacetate (1a).¹⁹ The procedure appeared to be suitable for most β-keto esters except for the substrates highlighted in boxes in Figure 2. Treatment of compounds 1d, 1r, and 1s with SF₄/HF led to complex undefined mixture of products, the desired dehydrofluorinated compounds were not observed. The cyclopropane derivative 1d probably decomposed via cyclopropylmethyl/cyclobutyl cation rearrangement, which we had observed during fluorinations earlier.²⁰ Decomposition of 1r in the reaction conditions was unexpected due to our previous successful experience with DAST fluorination of TFA-protected amino ketones,¹⁸ while decomposition of the substrate 1s was anticipated. According to our previous expertise fluorination of compounds containing PhCH₂O fragment by SF₄ led to debenzylation with subsequent unselective decomposition. It should be noted that compound 1w, bearing an ether fragment, also did not give the desired product in the SF₄/HF system. In this case the compound having m/z [M⁺] = 286 in GC–MS and m/z [M + 1] = 287 in positive mode in APCI HPLC MS was observed as a major product, but we were not able to determine its structure based on these results as well as on NMR data. Nevertheless, the product 1w was successfully deoxofluorinated by SF₄ in the absence of HF at 60 °C in 61% preparative yield,²¹ which was a rare exception to our procedure. The rate of dehydrofluorination in this case was less than 10%. Substrates 1e, 1j, and 1v also reacted unselectively under the optimized conditions, but the corresponding deoxofluorinated products were registered at about 10%, making the proce-

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**Scheme 1** The synthesis of β,β-difluoroacrylic acid

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**Figure 2** The set of substrates for SF₄ based deoxofluorination
dure nonpreparative. The results of deoxofluorination of β-keto esters 1 are summarized in Table 1. The preparative yields obtained using the above-mentioned substrate set are high (from 55–90%) and comparable for both enolizable and nonenolizable keto esters. Considerable rate of dehydrofluorination was observed in the case of using substrates 1u (up to 20%), 1c, 1h (up to 10%), and 1b, 1i (up to 5%).

<table>
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<th>Entry</th>
<th>Substrate</th>
<th>Fluorination</th>
<th>Scale (mol)</th>
<th>Yield (%)</th>
<th>Protocol</th>
<th>Bp (°C/mmHg)</th>
<th>Hydrolysis</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Protocol</th>
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<td>B2</td>
<td>95–97/0.3b</td>
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The reaction was scaled up to 50–150 g (0.3–0.9 mol) of starting material from one synthetic run without changing the protocol. Such amounts required operating with significant quantity, up to 175 g, of SF₄ for one run. These operations were performed in the special well-ventilated laboratory with strictly limited staff access due to safety reasons. The staff always wear the personal-protection equipment including single-filter, full-face masks during operation in accordance with international safety regulations.²² The damper technique applied for loading of SF₄ into the autoclave was shown in Figure 3. The standardized damper chambers were used, which contained 25±1 g of SF₄ at atmospheric pressure. The excess of SF₄, along with the other gaseous byproducts, is vented from the autoclave through a KOH solution after the reaction is complete.

All obtained β,β-difluoroesters 2 were subjected to subsequent hydrolysis into the corresponding acids. Taking into account unsustainability of enolizable β,β-difluoroesters to fluorine anion elimination,²³ the acidic conditions were chosen for hydrolysis. In the case of nonenolizable β,β-difluoroesters 2e,f and 2l–o more convenient alkali hydrolysis was applied.²⁴ The corresponding acids were obtained in good preparative yields under both conditions (Table 1).

The next milestone of the investigation was the elaboration of an efficient method for the synthesis of Medicinal chemistry relevant difluorinated cyclic amino acid derivatives type 11 starting from readily available compounds type 12 (Scheme 2). Earlier, this methodology was applied only for the 3,3-difluoroproline derivative 11c. Recently, the preparative deoxofluorination of the corresponding precursor, where PG = Cbz and R = t-Bu, was described using DAST as a reagent.²⁶ The approaches to derivatives of amino acids 11b and 11c were also described based on another methodology. The 3,3-difluoroisonipecotic acid derivatives were obtained via multistep synthesis starting from ethyl bromodifluoroacetate as CF₂ moiety source.²⁷ In the case of 4,4-difluoro-β-proline the core was assembled...
by [3+2] cycloaddition of azomethine ylide with benzyl 3,3-difluoroacrylate.²⁸

At first, we chose the NBn-protected compounds 12a–d as potential substrates for deoxofluorination. These compounds were examined in a standard protocol with SF₄ in HF. Among them substrates 12a–c gave the corresponding difluoro derivatives 11a–c in good preparative yields (from 68–83% on 0.6 mol scale of starting materials). But compound 12d unexpectedly gave dehydrofluorinated compound 13d as the major product under the reaction conditions according to ¹⁹F NMR and ¹H NMR analysis of the reaction mixture and the crude product (Scheme 2). Unfortunately, all attempts to isolate the reactive compound 13d in a pure state failed. The deprotected fluorinated amino acids 14 could be quantitatively hydrolyzed in acidic conditions²⁹ to the corresponding acids 16 as hydrochloric salts. It was illustrated by the synthesis of Bn-protected amino acids 16a,b. Amino acids 11a,b were formed by catalytic hydrogenation of Bn-protected derivatives 16a,b at room temperature and 1 atm hydrogen pressure over Pd on carbon in MeOH–H₂O media³⁰ as hydrochloric salts. These compounds were easily transformed into Boc-
protected derivatives 18ab\(^{34}\) that are more convenient for utilizing as building blocks in parallel synthesis in comparison with Bn-protected derivatives. The orthogonal benzyl deprotection from the compound type 14 could be also accomplished by catalytic hydrogenation.\(^{32}\) It was demonstrated by synthesis of the amino ester 15c. In the case of 4,4-difluoro-\(\beta\)-proline derivatives replacement of Bn protection group with TFA in substrate proceeded smoothly in SF\(_4\)/HF system according to protocol A1 at room temperature (Scheme 3). The desired \(\beta\)-\(\beta\)-difluoronitriles 22a, 22j, and 22t were formed in moderate to good yields (46–78%) on 0.15–0.3 mol scale. The possibility of hydrolysis of such nitriles was demonstrated on the intermediate 22j. The acid 10j was obtained through acidic hydrolysis of nitrile 22j by H\(_2\)SO\(_4\) at 90 °C\(^{35}\) in 74% yield.

Finally, the reaction of deoxofluorination of \(\beta\)-keto esters and \(\beta\)-keto nitriles by SF\(_4\) in anhydrous HF media was investigated. The scope and limitation of the reaction were determined. Substrates having steric hindrance at the keto group, bearing ArCH\(_2\)OH–, –NHTFA, and fragments capable of cationic-like rearrangements, are out of the scope of the procedure. The reaction was scaled up to 0.9 mol of starting material using 1200 mL Hastelloy autoclave. Work with such quantity of SF\(_4\) required a special technique and equipment, which was also demonstrated. The promising building blocks for medicinal chemistry, \(\beta\)-difluorinated acids, were produced by hydrolysis of the appropriate esters on 100 g scale. Despite the serious difficulties of using toxic, hazardous SF\(_4\) towards special lab space, equipment, personal protection, and staff skills, the elaborated methods are substantially more efficient in comparison with multistep sequences based on less hazardous fluorine sources. Moreover, the proposed protocol can be easily introduced into the production cycle at industrial facilities that use SF\(_4\).

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**Supporting Information**

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610744.

**References and Notes**


(19) Deoxofluorination Protocol A1

The keto ester 1 (1 mol) was placed in a Hasseltel autoclave (1200 mL) and cooled with liquid nitrogen. Anhydrous hydrogen fluoride (1 mL per 0.01 mol of the keto ester) was added. The autoclave was evacuated and SF6 (about 1.7 equiv) was condensed into it. The autoclave was warmed up to room temperature and was stirred on a magnetic stirrer overnight. Gaseous products were released, the solution was removed from the autoclave and poured onto ice, the oil obtained was extracted with MTBE, the extracts were combined and washed with aqueous solution of Na2CO3, dried, evaporated and distilled. In the case of obtaining an admixture of monofluoroalkane during the fluorination (substrates 1a-c, i, u), the crude product was dissolved in dichloromethane/water mixture before purification.


(21) Deoxofluorination Protocol B1

The keto ester 1 (1 equiv) was placed in a Hasseltel autoclave (1200 mL), cooled with liquid nitrogen, vacuumed, and SF6 was condensed into it (about 1.7 equiv). The autoclave was warmed up to room temperature and stirred at 60 °C on a magnetic stirrer for 48 h. Gaseous products were released, the solution was poured from the autoclave onto ice, and the oil formed was extracted with MTBE. The extracts were washed with aqueous solution of Na2CO3 and dried. The residue was evaporated and purified with potassium permanganate (as in protocol A) and distilled. The bp and yields of products 2 are given in Table 1.


A mixture of the ester 2 (1 equiv), formic acid (4 equiv), and 20% hydrochloric acid (3 equiv of HCl) was stirred at 100°C for 16 h. The solid residue was washed with dichloromethane (for the substance 2p, the precipitated product was filtered off and washed with cold water). The extracts were dried, evaporated, and distilled. The bp and yields of products 10 are given in Table 1.

Representative Examples

3,3-Difluorobutanoic Acid (10a)

1H NMR (400 MHz, CDCl3): δ = 9.70 (br, 1 H), 2.97 (t, J = 13.9 Hz, 2 H), 1.77 (t, J = 18.7 Hz, 3 H). 13C NMR (151 MHz, CDCl3): δ = 173.2 (t, J = 7.8 Hz), 120.7 (t, J = 23.9 Hz), 42.9 (t, J = 29.3 Hz). 19F NMR (376 MHz, CDCl3): δ = –87.2. EIMS (70eV): m/z (%) = 122 (1), 107 (12), 104 (21), 89 (41), 76 (12), 65 (100), 64 (11), 63 (10), 60 (62), 59 (23), 45 (44), 43 (14), 42 (23), 40 (12), 39 (10).

2,2-Difluorocyclopentanecarboxylic Acid (10t)

1H NMR (400 MHz, CDCl3): δ = 3.93 (t, J = 16.0 Hz, 2 H), 4.03 (br, 1 H), 2.48–2.12 (m, 2 H). 13C NMR (151 MHz, CDCl3): δ = –92.6 (d, J = 22.9 Hz), –100.8 (d, J = 22.9 Hz). EIMS (70eV): m/z (%) = 150 [M]+ (1), 130 (7), 115 (11), 110 (13), 109 (17), 91 (10), 82 (14), 77 (21), 73 (100), 66 (13), 65 (11), 59 (11), 55 (33), 51 (14), 45 (15), 41 (20), 39 (20).

Hydrolysis Protocol B2

A mixture of the ester 2 (1 equiv) and sodium hydroxide (1.5 equiv) in 50% aqueous ethanol (2 L per 1 mol) was boiled until the reaction was completed (check by NMR). The catalyst was filtered off, and the filtrate was evaporated. The solid residue was washed with MTBE to obtain hydrochloride of the acid 16.2b

Representative Examples

1-Benzyl-4,4-difluoropiperidine-3-carboxylic Acid Hydrochloride (16a·HCl)

H NMR (400 MHz, DMSO-d6): δ = 13.47 (s, 1 H), 12.13 (s, 1 H), 7.64 (d, J = 6.7 Hz, 2 H), 7.51–7.40 (m, 3 H), 4.41 (s, 2 H), 3.88–3.66 (m, 1 H), 3.54 (d, J = 12.7 Hz, 1 H), 3.37 (s, 1 H), 3.28 (t, J = 17.2 Hz, 1 H), 3.16 (t, J = 12.4 Hz, 1 H), 2.72–2.52 (m, 1 H), 2.39 (t, J = 14.8 Hz, 1 H). 13C NMR (126 MHz, CDCl3): δ = 167.3, 131.8, 130.2, 130.0, 129.3, 119.5 (t, J = 247.6 Hz), 58.8, 49.4, 48.0, 45.2, 31.2. 19F NMR (376 MHz, DMSO-d6): δ = –98.3 (d, J = 237.1 Hz), –110.0 (d, J = 237.1 Hz). LC-MS (negative mode): m/z = 254 [M–HCl + H]+.

1-Benzyl-3,3-difluoropiperidin-4-carboxylic Acid Hydrochloride (16b·HCl)

1H NMR (400 MHz, DMSO-d6): δ = 11.81 (br, 2 H), 7.63 (s, 2 H), 7.53–7.36 (m, 3 H), 4.55–4.17 (m, 2 H), 4.34–3.95 (m, 2 H), 2.18 (s, 2 H). 13C NMR (151 MHz, DMSO-d6): δ = 169.0, 132.2, 130.1, 129.4, 129.2, 118.4 (t, J = 246.2 Hz), 59.4, 53.1, 49.6, 45.0, 22.4. 19F NMR (376 MHz, DMSO-d6): δ = –100.9 (d, J = 243.0 Hz), –106.3 (d, J = 255.7 Hz). LC-MS (positive mode): m/z = 256 [M+HCl + H]+.

Debenzylation Protocol A3

10% Pd on carbon (0.1 g for 1 g of 16) was added to the solution of a compound 16 in MeOH–H2O (2:1, 10 mL of mixture for 1 g of 16), and the mixture was hydrogenated at room temperature and atmospheric pressure until the reaction was completed (check by NMR). The catalyst was filtered off, and the filtrate was evaporated dry. The crude product was washed with MTBE–acetone mixture affording the desired compounds 11, which were then treated by a saturated solution of HCl in dioxane and isolated in pure form as hydrochloride; mp (11a·HCl) 185 °C; mp (11b·HCl) 188 °C.

Representative Examples

4,4-Difluoropiperidine-3-carboxylic Acid Hydrochloride (11a·HCl)

1H NMR (400 MHz, D2O): δ = 3.56–3.18 (m, 5 H), 5.12–4.21 (m, 2 H), 4.85–4.09 (m, 2 H); NH, OH not observed due to exchange. 13C NMR (151 MHz, D2O): δ = 168.8, 132.0, 129.4, 129.5, 118.2 (s, J = 246.7 Hz), 59.8, 53.1, 49.6, 45.0, 22.4. 19F NMR (376 MHz, D2O): δ = –98.9 (d, J = 247.7 Hz), –106.7 (d, J = 247.6 Hz). LC-MS (positive mode): m/z = 166 [M+HCl + H]+.

3,3-Difluoropiperidine-4-carboxylic Acid Hydrochloride (11b·HCl)

1H NMR (400 MHz, DMSO-d6): δ = 10.56 (br, 3 H), 3.64 (dt, J = 13.9 Hz, 13.4 Hz). 19F NMR (376 MHz, D2O): δ = –99.8 (d, J = 244.7 Hz), –106.7 (d, J = 247.6 Hz). LC-MS (positive mode): m/z = 166 [M+HCl + H]+.
Debenzylation Protocol D2

Boc-Protection Protocol A4

Synlett

J

17.1, 9.3 Hz, 1 H), 3.47 (dd, J = 27.4, 12.9 Hz, 1 H), 3.38–3.22 (m, 1 H), 3.18 (d, J = 12.6 Hz, 1 H), 3.01 (t, J = 12.1 Hz, 1 H), 2.12 (d, J = 14.9 Hz, 1 H), 1.99 (q, J = 12.4, 11.9 Hz, 1 H). 13C NMR (126 MHz, DMSO-d6): δ = 169.4, 118.3 (t, J = 247.4 Hz), 46.2 (dd, J = 36.1, 28.6 Hz), 45.2 (t, J = 21.1 Hz), 41.0, 22.9 (d, J = 5.2 Hz). 19F NMR (376 MHz, DMSO-d6): δ = -101.4 (d, J = 234.8 Hz), -100.7 (d, J = 234.8 Hz). LC-MS (positive mode): m/z = 180 [M–HCl+H]+.

(31) Boc-Protection Protocol A4

The Boc₂O (1.2 equiv) was added to the stirred mixture of compound 11 (1 equiv), NaHCO₃ (3.5 equiv) in THF–H₂O (1:1, 10 mL of mixture for 1g of 11). The resulting suspension was stirred at room temperature overnight. The THF was distilled at rotor evaporator (20 mmHg, 40 °C). The suspension formed was filtered, and the mother liquor was extracted with MTBE. The combined extracts were dried with Na₂SO₄ and evaporated to give the desired Boc-protected product 18; mp (18a) 185 °C; mp (18b) 188 °C.

Representative Examples

4,4-Difluoropiperidine-3-carboxylic Acid Hydrochloride

(11a·HCl)

1H NMR (400 MHz, DMSO-d6): δ = 12.95 (s, 1 H), 3.86–3.41 (m, 4 H), 3.05–2.90 (m, 1 H), 2.36–2.17 (m, 1 H), 1.91 (q, J = 9.8, 6.1 Hz, 1 H), 1.39 (s, 9 H). 13C NMR (126 MHz, DMSO-d6): δ = 169.5, 153.8, 125.5–117.2 (m), 79.9, 47.6, 44.0, 43.2, 32.1, 28.3. 19F NMR (376 MHz, DMSO-d6): δ = 95.9 (dm, J = 238.8 Hz), -100.1 (dm, J = 242.1 Hz), -103.3 (dm, J = 245.8 Hz). LCMS, negative mode, m/z: 264 [M–H]-.

1-(tert-butoxycarbonyl)-3,3-difluoropiperidine-4-carboxylic acid (18b)

1H NMR (400 MHz, DMSO-d6): δ = 12.86 (s, 1 H), 4.02 (s, 1 H), 3.77 (d, J = 13.8 Hz, 1 H), 3.45–3.37 (m, 1 H), 3.18–2.98 (m, 2 H), 1.89 (dt, J = 13.6, 4.1 Hz, 1 H), 1.80–1.66 (m, 1 H), 1.40 (s, 9 H). 13C NMR (126 MHz, chloroform-d): δ = 170.2 (d, J = 2.4 Hz), 154.2, 119.1 (t, J = 249.7 Hz), 80.1, 49.2, 48.2, 46.8 (t, J = 21.5 Hz), 28.4, 25.7. 19F NMR (376 MHz, DMSO-d6): δ = -103.3 (dd, J = 239.2, 172.0 Hz), -112.5 (dd, J = 239.6, 101.1 Hz). LCMS, negative mode, m/z: 264 [M–H]-.

(32) Debenzylation Protocol D2

10% Pd on carbon (0.1g for 1 g of 14c) was added to the solution of compound 14c (as hydrochloride) in EtOH (10 mL for 1g of 14c), and the mixture was hydrogenated at room temperature and atmospheric pressure until the consumption of hydrogen ceased. The catalyst was filtered off, and the filtrate was evaporated and dried. The crude product was washed by MTBE affording the desired compound 15c. Then crude compound 15c was treated by a saturated solution of HCl in dioxane and isolated in pure form as hydrochloride; mp (15c·HCl) 95 °C.

Representative Example

Ethyl 3,3-Difluoropyrrolidine-2-carboxylate Hydrochloride (15c·HCl)

1H NMR (400 MHz, DMSO-d6): δ = 10.76 (s, 2 H), 4.94 (dd, J = 17.4, 9.2 Hz, 1 H), 4.44–4.19 (m, 2 H), 3.55–3.36 (m, 2 H), 2.78–2.52 (m, 2 H), 1.25 (t, J = 7.1 Hz, 3 H). 13C NMR (126 MHz, DMSO-d6): δ = 163.3 (d, J = 27.2 Hz), 126.9 (dd, J = 257.5, 250.4 Hz), 63.4, 62.7 (dd, J = 33.1, 28.7 Hz), 42.3 (d, J = 5.8 Hz), 33.4 (t, J = 24.1 Hz), 14.3. 19F NMR (376 MHz, DMSO-d6): δ = -98.3 (d, J = 234.8 Hz), -100.7 (d, J = 234.8 Hz). LC-MS (positive mode): m/z = 180 [M–HCl+H]+.


TFA-Deprotection Protocol E2

A solution of 20d (1 equiv) in 1 M HCl in EtOH (prepared from AcCl (4 equiv) and EtOH) was stirred at 40 °C for 4 h. The solution was evaporated dry, and the crude product was washed by MTBE affording the desired compound 15d. Then crude compound 15d was treated by a saturated solution of HCl in dioxane and isolated in pure form as hydrochloride; mp (15d·HCl) 116 °C.

(35) Hydrolysis Protocol F2

A mixture of nitrile 22j (1 mol) and conc sulfuric acid (3 mL per 1 g of nitrile) was heated to 90 °C and stirred for 1 h, diluted with water (10 mL per 1 g of nitrile), and boiled overnight. After cooling, the product was extracted with dichloromethane, the extracts were dried, evaporated, and distilled; bp (10j) 91–92 °C/0.3 mmHg.

Representative Example

3,3-Difluoro-2-phenylbutanoic Acid (10j)

1H NMR (400 MHz, CDCl₃): δ = 10.56 (br, 1 H), 7.43 (dd, J = 6.7, 3.0 Hz, 2 H), 7.37 (d, J = 3.6 Hz, 3 H), 4.15 (t, J = 12.2 Hz, 1 H), 1.65 (t, J = 19.0 Hz, 3 H). 13C NMR (151 MHz, CDCl₃): δ = 174.5 (d, J = 7.0 Hz), 131.4 (t, J = 3.5 Hz), 129.5, 128.8, 128.7, 122.04 (t, J = 244.6 Hz), 58.4 (t, J = 26.9 Hz), 21.6 (t, J = 26.3 Hz). 19F NMR (376 MHz, CDCl₃): δ = -89.7 (d, J = 248.0 Hz), -92.4 (d, J = 248.0 Hz). LCMS (negative mode): m/z = 199 [M–H]-.