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A practical synthesis of 2,2-difluoro-3-amino-propanoic acid (α,α-difluoro-β-alanine)

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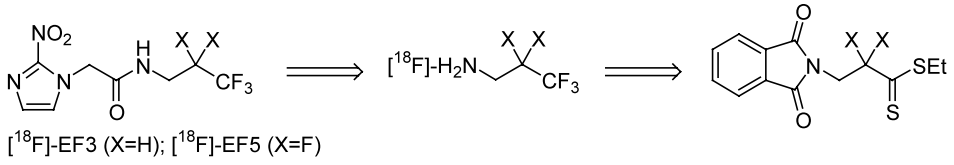
Abstract—Reformatsky reaction of ethyl bromodifluoroacetate with *N*,*N*-(dibenzyl)-1*H*-benzotriazolyl-1-methylamine gave fully protected α,α-difluoro-β-alanine. Hydrogenolysis and hydrolysis furnished α,α-difluoro-β-alanine. Further transformation into *N*-phthalimido-α,α-difluoro-β-alanine was described.

In the course of a medicinal chemistry program dedicated to the synthesis and validation of [^{18}F]-labeled radiopharmaceuticals, we needed 2,2-difluoro-3-amino-propanoic acid (**4**). Indeed, the *N*-phthalimidodithioester derivative of this acid (Scheme 1; X = F) was considered as the starting material towards [^{18}F] radiolabeled 2,2,3,3,3-pentafluoropropylamine, the building block for the preparation of [^{18}F]-EF5 (nitroimidazolyl marker for PET detection of hypoxia).[1,2] [^{18}F]-Trifluorination by an oxidative fluorodesulfurization reaction has already been successfully exploited in the radiosynthesis of [^{18}F]-EF3 (Scheme 1; X = H).[3]

Fluorine-containing aminoacids are useful molecules for the construction of various biologically active compounds, and, for this reason, a lot of methods have been developed for their preparation.[4–6] Amongst them, Reformatsky-type reactions[5] with halodifluoroacetates are usually applied for the synthesis of β-substituted α,α-difluoro-β-aminoacids.[7–10] Surprisingly, this method has not been reported yet from the preparation of the simplest term, namely α,α-difluoro-β-alanine (**4**). To our knowledge, this particular compound was previously described in a single publication[11] it was obtained in four steps from 2,2-difluorosuccinic acid with an overall yield of 13%. We thus decided to investigate an alternative route, potentially more efficient, based on the Reformatsky-type strategy.

N,*N*-(Bis-phenylmethyl)-benzotriazolyl-1-methylamine (**1**), easily prepared from benzotriazole, formaldehyde and dibenzylamine,[12] is known to react with organometallic reagents[13] as an iminium salt,[14,15] and therefore has been considered as a choice reagent for the introduction of a CH_2–$N(Bn)_2$ motif onto zinc–enolate derived from ethyl bromo-difluoroacetate (**2**). Thus, we investigated the reaction of **1** with **2** (Scheme 2) in the presence of zinc dust activated with chlorotrimethylsilane. In refluxing THF (usual conditions of Reformatsky-type coupling reactions[13]), we recovered ethyl *N*,*N*-(dibenzyl)-2,2-difluoro-3,3-aminopropanoate (**3**) in about 70% yield, together with side products resulting from reduction of **2** (ethyl difluoroacetate) and debenzylation of **1**. The critical role of temperature on the occurrence of side-products in zinc–enolate alkylation has been pointed out.[16] We screened reaction



Scheme 1.

Keywords: difluoro-β-alanine; benzotriazolyl-1-methylamine; Reformatsky reaction.
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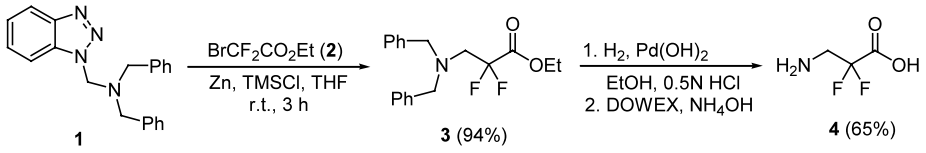
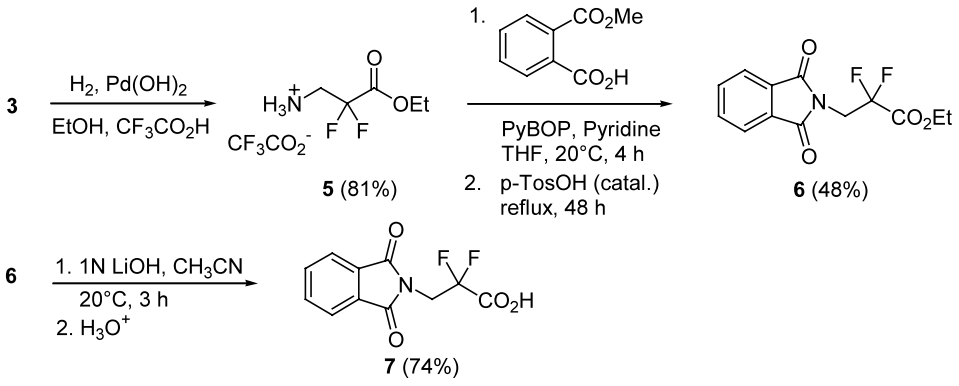


Scheme 2.



Scheme 3.

temperatures from 0 to 70°C and found that maintaining the reaction mixture at room temperature was simply the best condition: product **3** was formed in nearly quantitative yield within 3 h (94% isolated yield, after purification).[17] The next step was the deprotection of the *N*-dibenzyl moiety by catalytic hydrogenation. Performing the reaction in aqueous EtOH–HCl led to the simultaneous hydrolysis of the ester function; α,α-difluoro-β-alanine (**4**) recovered as the hydrochloride salt was neutralized by chromatography on a cation-exchange resin (65% yield).[18] Thus, by our process, 2,2-difluoro-3-amino-propanoic acid (**4**) could be easily obtained in two steps with an overall yield of 61% (Scheme 2).

We also examined the possibility to selectively prepare either carboxyl-protected or amino-protected derivatives of **4** (Scheme 3). Palladium-catalyzed hydrogenolysis of precursor **3** in dry ethanol containing trifluoroacetic acid gave free-amino β-aminoester **5** as the trifluoroacetate salt in 81% yield.[19] For the preparation of phthalimide **6**, we used 2-(methoxycarbonyl)benzoic acid activated by PyBOP (benzotriazol-1-yl-oxy-tris-pyrrolidinophosphonium hexafluorophosphate), as previously described.[3,20] Ethyl *N*-(phthalimido)-2,2-difluoro-3-amino-propanoate (**6**) was isolated in 48% yield after chromatography.[21] Lastly, saponification of **6** furnished *N*-(phthalimido)-2,2-difluoro-3-amino-propanoic acid (**7**) in 74% yield.[22] The corresponding dithioester (see Scheme 1), required as radiolabeling precursor, could be obtained following known procedures.[23,24]

Acknowledgements

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17. Synthesis and characterization of **3**: to a suspension of zinc dust (0.921 g, 14.2 mmol) in dry THF (10 mL), stirred under argon atmosphere, was added chlorotrimethylsilane (0.905 mL, 0.769 g, 7.09 mmol) followed, 10 min later, by ethyl bromodifluoroacetate (1 mL, 1.583 g, 4.57 mmol). After 10 min, **1** (2.35 g, 7.08 mmol) in THF (5 mL) was added dropwise. After 3 h at rt, the mixture was poured on aqueous 5% $NaHCO_3$ (10 mL) and filtered on Celite 545. The layers were separated and the aqueous phase was extracted with EtOAc (3×10 mL). The organic layers were combined and washed with 1N HCl (20 mL), then dried over $MgSO_4$. After evaporation of the solvent, the residue was diluted in ether; the solid formed was removed by filtration and ether was evaporated. Distillation of the oil (pressure 3×10^{-3} mBar, temperature = 115–120°C) give **3** (2.21 g, 94%) as a colorless oil. $R_f = 0.47$ (EtOAc:hexane, 5:95). ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 1.22$ (t, 3H, $J = 7.2$ Hz, CH_3); 3.15 (t, 2H, $J = 13.1$ Hz, CH_2CF$_2$); 3.68 (s, 4H, CH_2Ph); 4.18 (q, 2H, $J = 7.2$ Hz, CH_2O); 7.24–7.35 (m, 10H$_{arom.}$); ^{19}F NMR (282 MHz, $CDCl_3$/$CFCl_3$) $\delta = -106.32$ (t, $J_{F-H} = 13.8$ Hz, CH$_2$CF_2); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 13.73$ (*C*H$_3$); 53.81 (t, $J_{C-F} = 26.1$ Hz, *C*H$_2$CF$_2$); 58.47 (*C*H$_2$); 62.53 (*C*H$_2$); 116.16 (t, $J_{C-F} = 251.4$ Hz, *C*F$_2$); 114.48, 129.26, 129.51, 159.67 (C$_{arom.}$); 160.28 (t, $J_{C-F} = 30.5$ Hz, *C*=O); HRMS (M+1) calcd for $C_{19}H_{21}NO_2F_2 = 334.160545$; found: 334.161861.
18. Synthesis and characterization of **4**: compound **3** (2.07 g, 6.2 mmol) was dissolved in a solution of EtOH: 0.5N HCl (1:1) (10 mL) and $Pd(OH)_2$ (20 wt.% on carbon) (0.217 g, 1.55 mmol) was added. After stirring for 36 h under H_2 atmosphere, the catalyst was removed by filtration on Celite 545. The mixture was diluted with ether (5 mL); the aqueous phase was isolated and evaporated to give a colorless oil which precipitated in chloroform to give the hydrochloride as a white solid (0.61 g, 65%). Distilled water was added, the mixture was adsorbed on cation-exchange resin (DOWEX 50X2 400) and the resin was washed with water (until water came out neutral), then with 1.5 M aqueous NH_4OH to recover the β-amino acid. Concentration of the aqueous solution afforded quantitatively **4** as a white solid. (for analytical data, see Ref. 11).
19. Synthesis and characterization of **5**: to a solution of **3** (1 g, 3.02 mmol) in EtOH (4 mL) and trifluoroacetic acid (0.28 mL, 3.62 mmol) was added $Pd(OH)_2$ (20 wt.% on carbon) (0.105 g, 0.151 mmol). After 36 h of stirring under H_2 atmosphere, the solution was filtered on Celite 545 and the solvent was evaporated to afford **5** as a colorless oil (0.646 g, 81%). ^{1}H NMR (200 MHz, D_2O) $\delta = 1.33$ (t, 3H, $J = 7.2$ Hz, CH_3); 3.80 (t, 2H, $J = 15.6$ Hz, CH_2CF$_2$); 4.41 (q, 2H, $J = 7.2$ Hz, CH_2); ^{19}F NMR (282 MHz, DMSO-d_6) $\delta = -73.48$ (s, CF_3CO$_2$H); −107.75 (t, $J = 16$ Hz, CF_2); ^{13}C NMR (50 MHz, DMSO-d_6) $\delta = 40.34$ (t, $J_{C-F} = 21.1$ Hz, *C*H$_2$CF$_2$); 112.58 (t, $J_{C-F} = 250.8$ Hz, *C*F$_2$); 116.77 (q, $J_{C-F} = 294.4$ Hz, *C*F$_3$); 158.97 (t, $J_{C-F} = 33$ Hz, CF$_3$*C*=O); 161.26 (t, $J_{C-F} = 30.5$ Hz, CF$_2$*C*=O); MS (APCI, CH_4-NO_2): $m/z = 154.14$ (M+1).
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21. Synthesis and characterization of **6**: to a suspension of PyBOP (0.437 g, 0.84 mmol) in THF (2 mL) was added a solution of 2-(methoxycarbonyl)benzoic acid (0.144 g, 0.802 mmol) in THF (2 mL) and pyridine (0.094 mL, 0.090 g, 1.15 mmol). The mixture was stirred at rt for 45 min. **5** (0.204 g, 0.764 mmol) in THF (2 mL) was introduced in one portion followed by a slow addition of pyridine (0.467 mL, 0.453 g, 5.73 mmol). After stirring at rt for 4 h, a catalytic amount of *p*-TsOH was added before refluxing for 48 h. After cooling to rt, the solution was poured on aqueous 5% $NaHCO_3$ (10 mL) and extracted with EtOAc (3×10 mL). The organic layer was dried ($MgSO_4$) and concentrated before purification by flash chromatography on silica gel (hexane:EtOAc 70:30 ($R_f = 0.56$)) to afford **6** as a white solid. Yield 48% (0.45 g); mp = 89.5–90.5°C; ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 1.35$ (t, 3H, $J = 7.1$ Hz, CH_3); 4.32 (t, 2H, $J = 13$ Hz, CH_2CF$_2$); 4.34 (q, 2H, $J = 7.1$ Hz, CH_2); 7.74–7.93 (m, 4H$_{arom.}$); ^{19}F NMR (282 MHz, $CDCl_3$/$CFCl_3$) $\delta = -109.70$ (t, $J_{F-H} = 12.8$ Hz, CH$_2$CF_2); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 13.83$ (*C*H$_3$); 40.29 (t, $J_{C-F} = 29.5$ Hz, *C*H$_2$CF$_2$); 63.54 (O*C*H$_2$CH$_3$); 112.10 (t, $J_{C-F} = 253.8$ Hz, *C*F$_2$); 123.80, 131.89 and 134.46 (*C*$_{arom.}$); 162.63 (t, $J_{C-F} = 31.1$ Hz, CF$_2$*C*=O), 167.08 (s, 2×N-*C*=O); MS (APCI, CH_4-NO_2): $m/z = 284.1$ (M+1), 256.1, 238, 210.3.
22. Synthesis and characterization of **7**: to a solution of **6** (0.172 g, 0.607 mmol) in acetonitrile (3 mL) was added 1N LiOH aqueous solution (3 mL). The mixture was stirred for 3 h at rt. After evaporation of the solvent, the residue was diluted with water (5 mL) and washed with ether (10 mL). The aqueous phase was treated with 1N HCl aqueous solution (until pH 1) and extracted with EtOAc (3×10 mL). The organic layer was dried ($MgSO_4$) and concentrated to give **7** (0.21 g, 74%) as a hygroscopic white solid. Mp = 140–141.5°C; ^{1}H NMR (200 MHz, $(CD_3)_2CO$) $\delta = 4.09$ (t, 2H, $J = 14.4$ Hz, CH_2CF$_2$); 7.49–7.94 (m, 4H$_{arom.}$); ^{19}F NMR (282 MHz, $(CD_3)_2CO$/$CFCl_3$) $\delta = -109.719$ (t, $J_{F-H} = 14.9$ Hz, CH$_2$CF_2); ^{13}C NMR (50 MHz, $(CD_3)_2CO$) $\delta = 42.89$ (t, $J_{C-F} = 28$ Hz, *C*H$_2$CF$_2$); 114.88 (t, $J_{C-F} = 249.1$ Hz, *C*F$_2$); 128.92, 130.51, 130.94, 132.60, 137.19 and 139.16 (*C*$_{arom.}$); 164.78 (t, $J_{C-F} = 30.6$ Hz, *C*=O), 167.90 and 170.53 (s, N-*C*=O); MS (APCI, CH_4-NO_2): $m/z = 254.5$ (M−1), 291.5, 146.2. Anal. calcd for $C_{11}H_7NO_4F_2 \cdot 1.75H_2O$: C, 46.08; H, 3.69; N, 4.88. Found: C, 46.46; H, 3.58; N, 5.03.
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