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New Efficient Syntheses of α-Difluoromethyl- and α-Trifluoromethyl-Ornithine

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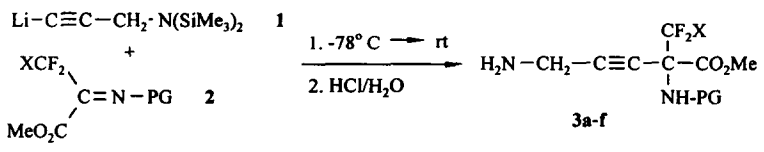
Abstract: A new efficient method for the preparation of ornithine derivatives **3-5** is described. The key step of the synthesis is the regioselective alkylation of imine **2** with propargyl amine **1**.

Amino acid decarboxylases are important enzymes involved in the biosynthetic pathways of endogenous biogenic amines such as γ-aminobutyric acid (GABA), histamine and putrescine. The diamine putrescine and the polyamines spermidine and spermine play a major role in the regulation of growth processes, including tumor growth[1]. Consequently, *L*-ornithine decarboxylase, which catalyzes the conversion of *L*-ornithine into putrescine, is regarded as a crucial target for developing new chemotherapeutic agents for cancer treatment.

In 1978, Kollonitsch et al. reported that α-fluoromethyl analogues of amino acids were potent and selective irreversible inhibitors of amino acid decarboxylases[2]. Since, there have been further reports on biologically active α-mono- and α-difluoromethyl substituted α-amino acids as irreversible inhibitors of amino acid decarboxylases[3]. Among them 2-(difluoromethyl)ornithine discovered by Bey et al.[4] seems to be a superior drug possessing a broad spectrum of biological activity including anticancer activity. It is clinically used for the treatment of African sleeping disease and of *Pneumocystis carinii* pneumonia, the most frequent opportunistic infection associated with the acquired immune deficiency syndrome (AIDS)[5].

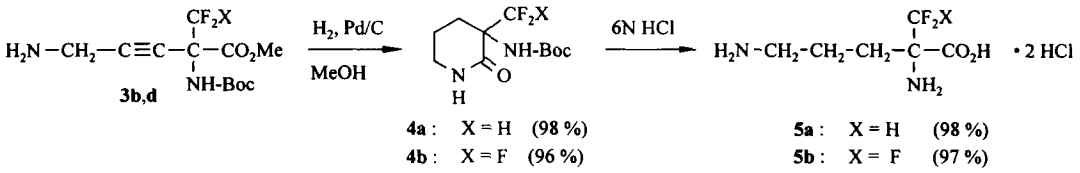
We have recently reported on a preparative efficient access to α-difluoromethyl and α-trifluoromethyl substituted α-amino acids based on the amidoalkylation of carbon nucleophiles with highly electrophilic imines of methyl 3-halo-3,3-difluoropyruvates[6].

In this context we now found that readily available lithium N,N-bis(trimethylsilyl)aminomethyl acetylide **1**[7] smoothly reacts with alkoxycarbonyl imines of difluoropyruvates **2**[6a] in tetrahydrofuran to give quantitatively the corresponding adducts **3**[8].



3a :	X = H, PG = Cbz	(89 %)
3b :	X = H, PG = Boc	(93 %)
3c :	X = F, PG = Cbz	(95 %)
3d :	X = F, PG = Boc	(91 %)
3e :	X = Cl, PG = Cbz	(94 %)
3f :	X = Cl, PG = Boc	(87 %)

Hydrogenation of **3** is accomplished in methanol within 24 hours and followed by spontaneous lactamization yielding the 2-piperidone derivative **4**[9] in high yield. Simultaneous cleavage of the Boc group and ring opening of **4** under acidolytic conditions (6 N HCl, 80° C, 3 h) affords the desired ornithine derivatives **5**[10].



4a: X = H (98 %)
4b: X = F (96 %)

5a: X = H (98 %)
5b: X = F (97 %)

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8. **3b**: ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H, C*Me*$_3$), 1.62 (br.s, 2H, N*H*$_2$), 3.48 (s, 2H, NC*H*$_2$), 3.86 (s, 3H, OC*H*$_3$), 5.51 (br.s, 1H, N*H*), 6.21 (t, $^2J_{HF}$ = 56.0 Hz, 1H, C*H*F$_2$). ^{13}C NMR ($CDCl_3$) δ 28.56, 31.89, 54.23, 59.88 (t, $^2J_{CF}$ = 24.4 Hz), 73.32, 81.86, 88.73, 112.23 (t, $^1J_{CF}$ = 262.0 Hz), 154.29, 166.35. ^{19}F NMR ($CDCl_3$) δ - 50.48 (dd$_{ABX}$, $^2J_{FF}$ = 276.2 Hz, $^2J_{FH}$ = 56.0 Hz, 1F, C*F*$_2$H), - 47.90 (dd$_{ABX}$, $^2J_{FF}$ = 276.2 Hz, $^2J_{FH}$ = 56.0 Hz, 1F, C*F*$_2$H).
3c: ^{1}H NMR (d_6-acetone) δ 2.91 (br.s, 2H, N*H*$_2$), 3.81 (s, 3H, OC*H*$_3$), 4.11 (s, 2H, NC*H*$_2$), 5.12 (d$_{AB}$, $^2J_{HH}$ = 12.0 Hz), 5.16 (d$_{AB}$, $^2J_{HH}$ = 12.0 Hz), 7.41 (m, 5H, Ph), 8.09 (br.s, 1H, N*H*). ^{13}C NMR (d_6-acetone) δ 40.39, 53.97, 60.91 (q, $^2J_{CF}$ = 32.6 Hz), 67.51, 72.81, 86.89, 123.71 (q, $^1J_{CF}$ = 285.5 Hz), 128.67, 128.88, 129.24, 137.38, 155.31, 164.06. ^{19}F NMR (d_6-acetone) δ 3.32 (s, 3F, C*F*$_3$).
9. **4b**: ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H, C*Me*$_3$), 1.98 (m, 2H, C*H*$_2$), 2.61 (m, 2H, C*H*$_2$), 3.41 (m, 2H, NC*H*$_2$), 5.61 (br.s, 1H, N*H*), 6.71 (br.s, 1H, N*H*). ^{13}C NMR ($CDCl_3$) δ 18.77, 27.10, 28.17, 41.86, 60.62 (q, $^2J_{CF}$ = 26.8 Hz), 80.67, 124.75 (q, $^1J_{CF}$ = 287.7 Hz), 154.03, 166.24. ^{19}F NMR ($CDCl_3$) δ 5.04 (s, 3F, C*F*$_3$).
10. **5b** x 2HCl: ^{1}H NMR (D_2O) δ 1.51 (m, 2H, C*H*$_2$), 2.03 (m, 2H, C*H*$_2$), 2.91 (m, 2H, NC*H*$_2$). ^{13}C NMR (D_2O) δ 20.97, 27.21, 38.79, 65.41 (q, $^2J_{CF}$ = 28.2 Hz), 123.18 (q, $^1J_{CF}$ = 283.9 Hz), 166.28. ^{19}F NMR (D_2O) δ 3.48 (s, 3F, C*F*$_3$). Anal. Calcd. for $C_6H_{11}F_3N_2O_2$ x 2HCl : C 26.37, H 4.80, N 10.25; Found: C 26.38, H 5.00, N 10.15.

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