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Synthesis of a Fluorinated Analog of 1-Aminocyclopropane Carboxylic Acid

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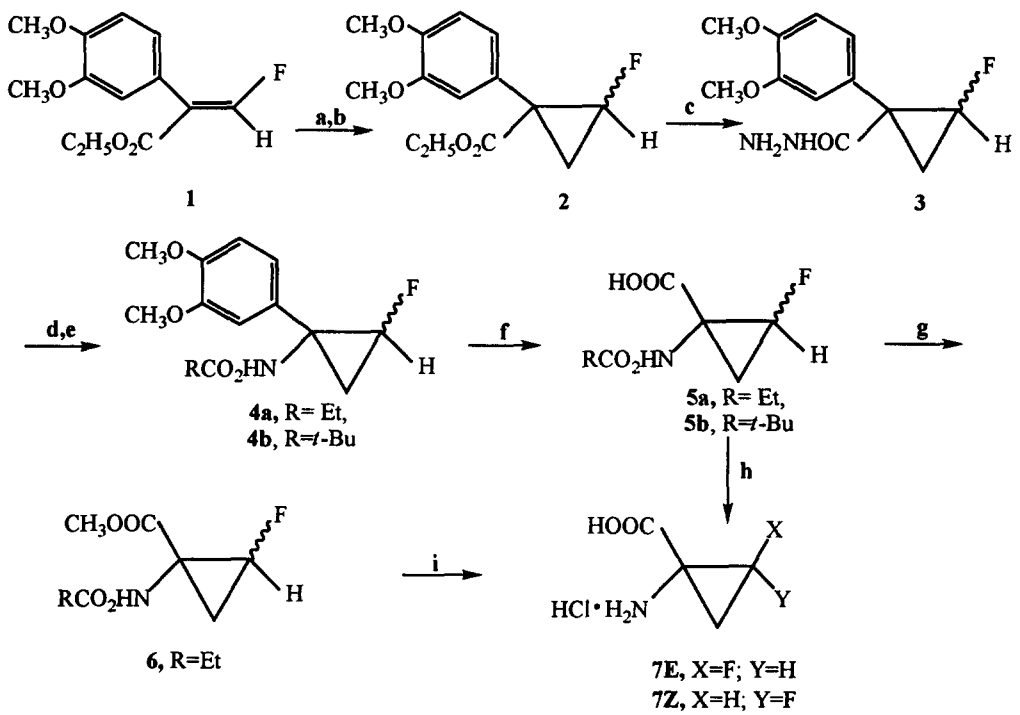
ABSTRACT: A convenient synthesis of 2-fluoro-1-aminocyclopropane-1-carboxylic acid is described. Cyclopropanation of ethyl 2-(3,4-dimethoxyphenyl)-3-fluoroacrylate followed by Curtius rearrangement, oxidative cleavage of the aromatic ring, and deprotection, produced the α-amino acid. Published by Elsevier Science Ltd.

The physiological importance of cyclopropyl α-amino acids has stimulated considerable research, including for example, their use as tools in enzyme mechanistic studies and in the synthesis of conformationally restricted peptides.[1,2] 1-Aminocyclopropane-1-carboxylic acid (ACC), found in apples, pears and many other plant tissues,[3] is an intermediate in the biosynthesis of the fruit ripening hormone ethylene.[4] Recently, ACC has been shown to act as a potent glycine agonist on the *N*-methyl-D-aspartate (NMDA) receptor ion channel.[5] Activation of NMDA receptor, a subtype of the glutamate receptors, has been implicated in epilepsy and hypoxic/ischemic brain damage.

In designing analogs of biologically important molecules, the replacement of a carbon-hydrogen bond with a carbon-fluorine bond often has dramatic effects on biological activity.[6] However, there were no reports in the literature of fluorinated analogs of ACC. The mono ring-chlorinated derivative was reported by Stammer et al.[7a] and the bromo-and iodo-analogs were recently reported by Tamm et al..[7b]

We report here our synthesis of 2-fluoro-1-aminocyclopropane-1-carboxylic acid (FACC). Our approach is based on the cyclopropanation of the key fluoro-substituted acrylate intermediate **1**, prepared in good yield as reported by Bey et al..[8] A 1,3 dipolar addition of diazomethane to the fluoro-substituted acrylate **1** produced pyrazolines quantitatively (Scheme). The photochemical extrusion of N_2 by irradiation in acetone (Rayonet® photochemical reactor model RMR 400; 3500 Å) gave the cyclopropyl esters **2** in good yields (90%).[9] A mixture of (*E* and *Z*)-diastereoisomers was obtained with the *E*-isomer as the major product (3:1). The cyclopropyl esters **2** were then converted to the hydrazides[10] (**3**) in essentially quantitative yield by reaction with hydrazine monohydrate in absolute ethanol at room temperature. The *E*-isomer **3** precipitated upon concentration of the solution and was thus readily separated. Curtius rearrangement of the hydrazides **3** resulted in the *N*-carbamates[11] **4**, via *in situ* alcoholysis of the derived isocyanates formed in refluxing absolute alcohol. Aromatic oxidation of **4** was carried out using RuO_4[12] prepared *in situ* from $RuCl_3$ (Method A) in a carbon tetrachloride/acetonitrile/water system with excess $NaIO_4$ as a cooxidant.[13] Subsequently, ozonolysis over dry silica gel[15] proved to be a more suitable aromatic oxidative route to the

protected amino acid. The *tert*-butyloxycarbonyl (Boc) group was initially employed for its facile removal, however the ethoxycarbonyl group gave better yields with an oxidative workup in H_2O_2 (Method B). Using the dry silica gel modification (Method C) to obtain the acid product directly, the Boc protecting group was more convenient. The protected fluoro amino acid could be cleanly isolated from byproducts using reversed-phase (C_{18}) silica gel and water. The Boc group was rapidly removed at room temperature with 3N HCl/EtOAc, in contrast to the severe conditions required for removal of the ethoxycarbonyl group. Diazomethane converted the acid **5a** to the methyl ester, a step which facilitated characterization. The *N*-ethoxycarbonyl methyl ester **6** was isolated as a pale yellow oil.[14]



SCHEME

(a) slight excess CH_2N_2, ether, 0°C, 16h, (b) hν, acetone, 48h, (90%); (c) NH_2NH_2-H_2O, absolute ethanol, 25°C, 16-24h, (99%); (d) 1N HCl, O°C, 15 min, dropwise addn $NaNO_2$ (1.5 eq), 15 min, (e) reflux absolute alcohol (ethanol or *t*-butanol), overnight, (55%); (f) Method A-CCl_4, CH_3CN, H_2O (1:1:2.5), $NaIO_4$ (12 eq), $RuCl_3$ (cat.), 25°C, 16h; Method B- i) CH_2Cl_2, excess O_3,15 min, ii), H_2O_2, reflux, 1h, (95%); Method C-addn of **4** to dry silica gel (10g/1mol), excess O_3, 15 min; (g) excess CH_2N_2, ether, 0°C, 1h, (96%); (h), R=*t*-Bu, 3N HCl/ethyl acetate, 30 min, R=Et, HBr/HOAc (30%), 50°C, 8-12h, Dowex, 1N HCl; (i) HBr/HOAc (30%), reflux, 8-12h, Dowex, 1N HCl.

Complete hydrolysis of **6** was accomplished in a refluxing solution of hydrogen bromide (30%) in acetic acid and gave the hydrobromide salt of **7**. Ring opened products were indicated under the reflux conditions that were needed for complete removal of the methyl ester. However, refluxing was found not to be nescessary to

completely remove the ethoxycarbonyl protecting group from **5a** and gentle heating prevented the formation of ring opened products. The proton NMR spectrum of **7** and the intermediate flurocyclopropyl compounds, showed the expected characteristic ABX pattern. The two diastereoisomers were distinguishable in the NMR spectrum and the ratios of (E/Z) could be determined by simple proton integration. Ion exchange chromatography over Dowex gave the pure hydrochloride of two diastereoisomers **7E** and **7Z** (1N HCl as eluant) or the free amino acid (cold 1N NH_4OH as eluant). The single isomer of the precipitated hydrazide **3** provided for the convenient preparation of **7E**.[16] This approach can thus provide a general route to the synthesis of fluorinated cyclopropyl amino acids and also affords a stereospecific preparation of the *E*-isomer. Preliminary biological studies of FACC showed comparable potencies as the parent ACC at the NMDA receptor. As a fluoromethylene amino acid, FACC may serve as an inhibitor of PLP-dependant enzymes associated with ethylene biosynthesis, and will be investigated in this regard.

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9. Major *E*-isomer **2** : ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18(t, *J*=7Hz, 3H, $C\underline{H}_3$), 1.70(ddd, *J*=23Hz, *J*=6.5 Hz, *J*=3.5Hz, 1H, ΔC$\underline{H}$), 1.86(ddd, *J*=6.5Hz, *J*=6.5Hz, *J*=6.5Hz, 1H, ΔC$\underline{H}$), 3.87(s, 3H, $OC\underline{H}_3$), 3.89(s, 3H, $OC\underline{H}_3$), 4.10(q, *J*=7Hz, 2H, $C\underline{H}_2$), 5.07(ddd, *J*=65Hz, *J*=6.5Hz, *J*=3.5Hz, 1H, ΔC$\underline{H}$F), 6.8-6.94(m, 3H, Ar$\underline{H}$). GC-MS(EI) *m/z*=268; 268(100), 251(43), 230(2), 221(27), 205(5), 177(5), 145(8), 131(2), 115(1), 103(1), 91(2), 73(1). Anal. Calcd. for $C_{14}H_{17}O_4F$: C, 62.67; H, 6.39; F, 7.08; Found: C, 62.33; H, 6.63; F, 7.24.

10. Major *E*-isomer **3**: mp of 124-26°C. IR (KBr) 3418 cm^{-1}, 3374 , 3300, 3195, 2984, 2938, 2840, 1660, 1640, 1575, 1575, 1500, 1251, 1227, 1173, 1138, 1024, 910, 818. ^1H NMR (300 MHz,$CDCl_3$) δ 1.59(ddd, *J*=23Hz, *J*=-6.5Hz, *J*=3.5Hz, 1H, ΔCH), 1.91(ddd, *J*=6.2Hz, *J*=6.5Hz, *J*=6.5Hz, 1H, ΔCH), 3.78(s, 2H, NH_2), 3.89(s, 3H, OCH_3), 3.91(s, 3H, OCH_3), 5.10(ddd, *J*=66Hz, *J*=6.2Hz, *J*=3.5Hz, 1H, ΔCHF), 6.63(s, 1H, NH), 6.86(s, 1H, ArH), 6.90(d, *J*=8Hz, 1H, ArH), 6.96(d, *J*=8Hz, 1H, ArH). GC-MS(EI) *m/z*=254; 254(40), 239(24), 223(16), 192(100), 164(21), 149(32), 109(18), 83(13), 63(21). Anal. Calcd. for $C_{12}H_{15}O_3N_2F$: Calcd. C, 56.68; H, 5.95; N, 11.02; F, 7.47; Found: C, 56.52; H, 6.09; N, 11.06; F, 7.15.
11. Major *E*-isomer **4a**: mp 121-22 °C. IR(KBr) 3328 cm^{-1}, 2994, 2974, 2937, 2917, 2838, 1691(s), 1591, 1508(s), 1458, 1348, 1259, 1228, 1180, 1145, 1114, 1078, 1051, 1022, 965, 865, 807. ^1H NMR (300 MHz,$CDCl_3$) δ 1.24 ppm(t *J*=7Hz, 3H, CH_3), 1.49(m, 1H, ΔCH), 1.67(ddd, *J*=23Hz, *J*=3Hz, *J*=8Hz, 1H, ΔCH), 3.88(s, 3H, OCH_3), 3.90(s, 3H, OCH_3), 4.13(q, *J*=7Hz, 2H, CH_2), 4.78(br d, *J*=66Hz, 1H, ΔCHF), 5.15(br s, 1H, NH), 6.85(d, *J*=8Hz, 1H, ArH), 7.06(br d, *J*=8Hz, 2H, ArH). GC-MS(EI) *m/z*=283; 283(20), 254(60), 252(50), 210(20), 180(30), 164(100), 148(30), 79(20), 51(20). Anal. Calcd. for $C_{14}H_{18}O_4NF$: Calcd. C, 59.36; H, 6.41; N, 4.94; Found: C, 59.29 ; H, 6.59; N, 4.76. Major *E*-isomer **4b**: mp 118-19 °C. IR(KBr) 3360 cm^{-1}, 3013, 2989, 2976, 2935, 2837, 1732, 1690(s), 1592, 1523, 1496, 1369, 1346, 1262(s), 1144(s), 1049, 1022(s), 970, 879, 866, 848, 807. ^1H NMR (300MHz,$CDCl_3$) δ 1.27 (ddd *J*=66Hz, *J*=3Hz, *J*=8Hz, 1H, ΔCH), 1.42(s, 9H, $(CH_3)_3$), 1.65(ddd, *J*=23Hz, *J*=3Hz, *J*=8Hz, 1H, ΔCH), 3.88(s, 3H, OCH_3), 3.89(s, 3H, OCH_3), 4.89(ddd, *J*=66Hz, *J*=3Hz, *J*=8Hz, 1H, ΔCHF), 5.03(br s, 1H, NH), 6.85(d, *J*=8Hz, 1H, ArH), 7.02(d, *J*=8Hz, 1H, ArH), 7.11(s, 1H, ArH). GC-MS(EI) *m/z*=311; 311(5), 255(20), 224(30), 210(20), 180(20), 164(20), 148(10), 92(5), 57(100). Anal. Calcd. for $C_{16}H_{22}O_4NF$: C, 61.72; H, 7.12; N, 4.50; F, 6.10; Found: C, 61.69; H, 7.12; N, 4.38; F, 6.44.
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14. Maior *E*-isomer **6a:** IR (neat) 3346 cm^{-1}, 2982, 2960, 2913, 2853, 1735, 1711, 1523, 1440, 1370, 1331, 1257, 1205, 1178, 1143, 1096, 1070, 873, 822, 783. ^1H NMR (300 MHz,$CDCl_3$) δ 1.27 ppm(t *J*=7Hz, 3H, CH_3), 1.90(m, 1H, ΔCH), 2.35(ddd, *J*=23Hz, *J*=8Hz, *J*=5Hz, 1H, ΔCH), 3.80(s, 3H, $COOCH_3$), 4.15(q, J=7Hz, 2H,CH_2) 4.80(ddd,*J*=59Hz, *J*=8Hz, *J*=5Hz 1H, ΔCH), 5.19(br s, 1H, NH). HRMS; (FAB+) Calcd for $C_8H_{13}O_4NF$ *m/z*=206.0829, Found 206.0832. Anal. Calcd. for $C_8H_{12}O_4NF$: Calcd. C, 46.83; H, 5.89; N, 6.82; Found: C, 46.97; H, 5.66; N, 6.75.
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16. The hydrochloride **7E** gave a characteristic ninhydrin color reaction, Mp ~250 (dec.). IR(KBr) 3425 cm^{-1} (br), 3243, 3049, 2961, 2809, 2608, 2571, 2500, 2045(br), 1965 (br), 1718(s), 1652, 1630, 1577, 1540, 1508, 1447, 1407(s), 1270, 1197, 1168(s), 1111, 1069, 1036, 989, 923, 883, 841, 815, 780, 737. ^1H NMR (300MHz, D_2O ref. at 4.65 ppm) δ 1.65(ddd, *J*=5Hz, *J*=4Hz, *J*=7.5Hz, 1H, ΔCH), 2.18(ddd, *J*=23Hz, *J*=9Hz, *J*=5Hz, 1H, ΔCH), 5.05(ddd, *J*=61Hz, *J*=8Hz, *J*=5Hz, 1H, ΔCHF). CI-MS (NH_3) 154(M+35) 137 (M+18), 120(M+1), 119, 117. HRMS; (FAB+) Calcd for $C_4H_7O_2NF$ *m/z*=120.0461, Found 120.0464.

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