Selective and Effective Fluorination of Organic Compounds in Water using Selectfluor™ F-TEDA-BF₄

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General

¹H, ¹⁹F and ¹³C NMR spectra were recorded on Varian Inova 300 (¹H 300 MHz, ¹⁹F 285 MHz, ¹³C 75 MHz) and Varian EM360 L (¹⁹F 56.4 MHz) spectrometers in CDCl₃. Chemical shift are reported in ppm from TMS (¹H and ¹³C) and CCl₃F (¹⁹F) as internal standards. Data are reported as follows: chemical shift, multiplicity, coupling constants, integration, and assignment. MS spectra were obtained on an Autospec Q instrument under electron impact (EI) conditions at 70 eV. IR spectra were recorded on Perkin-Elmer 1310 spectrometer. Standard KBr pellet procedures were used to obtain IR spectra of solids, while a film of neat material on NaCl window was used to obtain IR spectra of liquid products. Melting points were determined on Buchi 535 apparatus and are uncorrected. Selectfluor™ F-TEDA-BF₄ was purchased from Apollo, Genapol LRO from Clariant, while other material from Sigma-Aldrich. All commercial samples were used as received.

1,1-Difluoro-2(1H)-naphthalenone¹ (3, Scheme 1)

Yield 78% (from MeOH); yellow crystals; mp 48-50 °C (mp¹ 50 °C); ¹H NMR (300 MHz, CDCl₃): δ 6.23(dt, 1H, J_{HH}=10 Hz, H_{HF}=2 Hz, H3), 7.20-8.06(m, 5H, ArH and H4); ¹⁹F NMR(56.4 MHz, CDCl₃): δ -101.5(d, J=2 Hz); ¹³C NMR(75 MHz, CDCl₃): δ 107.3(d, J_{CF}=244.7 Hz, C1), 123.2(C4), 127.6(t, J_{CF}=8.5 Hz, C3), 130.0, 131.0, 132.0, and 145.8(C_{ArH}), 130.2(t, J_{CF}=8.1 Hz, C4a), 133.2(t, J_{CF}=23.6 Hz, C4b), 187.4(t, J_{CF}=24.4 Hz, CO); MS(EI, 70eV): m/z 180(M⁺, 60%), 152(75), 151(100), 133(52), 114(60); IR(KBr): ν(cm⁻¹) 1694, 1252, 1042, 835, 770.

4a-Fluoro-5,6,7,8-tetrahydro-(4aH)-naphthalen-2-one² (5, Scheme 1)

Yield 73.5% (flash chromatography, SiO₂, n-hexane); unstable liquid; ¹H NMR (300 MHz, CDCl₃): δ 1.0-3.0(m, 8H, H5-H9); 6.08(broad s, 1H, H1), 6.20(d, 1H, J_{HH}=10.0 Hz, H3);

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6.83(dd, 1H, $J=10.0$ Hz, $J_{\text{HF}}=6.0$ Hz, H4); ^{19}F NMR(56.4 MHz, CDCl_3): δ -158.0(dm, $J_{\text{FH}}=40.0$ Hz); ^{13}C NMR(75 MHz, CDCl_3): δ 20.4, 27.2 and 32.0(C6, C7, and C8), 38.1(d, $J_{\text{CF}}=25.8$ Hz, C5), 87.4(d, $J_{\text{CF}}=164.5$ Hz, C4a), 124.0(d, $J_{\text{CF}}=6.1$ Hz, C1), 129.2(d, $J_{\text{CF}}=8.2$ Hz, C3), 146.0(d, $J_{\text{CF}}=22.0$ Hz, C4), 158.8(d, $J_{\text{CF}}=18.7$ Hz, C4b), 185.6(d, $J_{\text{CF}}=4.7$ Hz, CO); MS(EI, 70eV): m/z 166(M^+ , 100%), 151(20), 146(22), 138(66), 125(34), 109(65), 96(59); IR(neat): $\nu(\text{cm}^{-1})$ 2942, 2862, 1671, 1641, 1439, 1299, 1267, 1076, 954, 884, 809.

10 β -Fluoro-1,4-estradien-3,17-dione³ (7, Scheme 1)

Yield 73.5% (flash chromatography, SiO_2 , n-hexane); white crystals, mp 138.2-140.2 °C; (mp³ 143-144 °C); ^1H NMR (300 MHz, CDCl_3): δ 0.8-3.1(m, 18H), 6.1(s, 1H, H1), 6.22(d, 1H, $J_{\text{HH}}=10.0$ Hz, H2), 7.0(dd, 1H, $J=10.0$ Hz, $J_{\text{HF}}=7.5$ Hz, H1); ^{19}F NMR(56.4 MHz, CDCl_3): δ -166.0(dd, $J_{\text{FH}}=30.0$, $J_{\text{FH}}=7.5$ Hz); MS(EI, 70eV): m/z 288(M^+ , 79), 247(30), 231(32), 163(51), 159(69), 149(77), 126(100), 107(53), 93(55); IR(KBr): $\nu(\text{cm}^{-1})$ 2945, 2861, 1732, 1670, 1289, 1249.

2-Fluoro-1-phenylethanol⁴ (9a, Scheme 2)

Yield 87% (flash chromatography, SiO_2 , CH_2Cl_2); liquid product; ^1H NMR (300 MHz, CDCl_3): δ 3.15(broad s, 1H, OH), 4.4(dm, 2H, $J_{\text{HF}}=47.0$ Hz, H2), 4.95(ddd, 1H, $J=14.3$ Hz, $J=8.1$ Hz, $J=3.3$ Hz, H1), 7.3(m, 5H, ArH); ^{19}F NMR(56.4 MHz, CDCl_3): δ -221.3(td, $J=47.0$ Hz, $J=14.3$ Hz); ^{13}C NMR(75 MHz, CDCl_3): δ 72.8(d, $J_{\text{CF}}=19.8$ Hz, C1), 87.0(d, $J_{\text{CF}}=175.0$ Hz, C2), 126.5, 128.2, and 128.8(C_{ArH}), 138.5(d, $J_{\text{CF}}=8.0$ Hz, C_{Ar}); MS(EI, 70eV): m/z 140(M^+ , 8%), 107(100), 79(76), 77(45); IR(neat): $\nu(\text{cm}^{-1})$ 3402, 2940, 1490, 1435, 1005, 695.

2-Fluoro-1,1-diphenylethanol⁴ (9b, Scheme 2)

Yield 87% (flash chromatography, SiO_2 , CH_2Cl_2); white crystals, mp 65.0-66.7 °C; ^1H NMR (300 MHz, CDCl_3): δ 3.08(broad s, 1H, OH), 4.7(d, 2H, $J_{\text{FH}}=48.0$ Hz, H2), 7.07-7.57(m, 10H, ArH); ^{19}F NMR(56.4 MHz, CDCl_3): δ -218.7(t, $J=48.0$ Hz); ^{13}C NMR(75 MHz, CDCl_3): δ 77.9(d, $J_{\text{CF}}=19.2$ Hz, C1), 87.2(d, $J_{\text{CF}}=180.2$ Hz, C2), 126.5, 127.9, and 128.4(C_{ArH}), 142.4(C_{Ar}); IR(KBr): $\nu(\text{cm}^{-1})$ 3564, 3029, 2967, 1491, 1449, 1171, 996, 696.

1-Fluoro-2-phenyl-2-propanol⁵ (9c, Scheme 2)

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Yield 86% (flash chromatography, SiO₂, CH₂Cl₂); liquid product; ¹H NMR (300 MHz, CDCl₃): δ 1.63(d, 3H, J=2 Hz, H₃), 2.53(broad s, 1H, OH), 4.47(d, 2H, J=49 Hz, H₁), 7.26-7.63(m, 5H, ArH); ¹⁹F NMR(56.4 MHz, CDCl₃): δ -223.3(tq, J=49.0 Hz, J=2 Hz); ¹³C NMR(75 MHz, CDCl₃): δ 25.2(d, J=3.8 Hz, C₃), 73.9(d, J=18.9 Hz, C₂), 89.6(d, J=177.8 Hz, C₁), 125.2, 127.5 and 128.4(C_{ArH}), 143.2(C_{Ar}); MS(EI, 70eV): m/z 139(M-Me, 12%), 137(19), 121(100), 105(28), 91(38), 77(40).

1,1-Diphenyl-2-fluoro-1-propanol⁶ (9d, Scheme 2)

Yields 85% (flash chromatography, SiO₂, CH₂Cl₂); white crystals, mp 102-104 °C (mp⁶ 104 °C); ¹H NMR (300 MHz, CDCl₃): δ 1.24(dd, 3H, J=24.5 Hz, J=6.2 Hz, H₃), 2.52(broad s, 1H, OH), 5.61(dq, 1H, J=46.5 Hz, J=6.2 Hz, H₂), 7.1-7.85(m, 10H, ArH); ¹⁹F NMR(56.4 MHz, CDCl₃): δ -180.82(tq, J=46.5 Hz, J=2 Hz); ¹³C NMR(75 MHz, CDCl₃): δ 15.0(d, J=21.6, C₃), 79.1(d, J=20.3 Hz, C₁), 92.5(d, J=175.5 Hz, C₂), 125.8, 126.8, 127.0, 127.3, and 128.0(C_{ArH}), 142.6 and 144.5(C_{Ar}); MS(EI, 70eV): m/z 230(M⁺, 1%), 201(14), 183(100), 105(95), 77(70).

2,2-Difluoro-1,1-diphenylethanol⁴ (9e, Scheme 2)

Yield 84% (flash chromatography, SiO₂, CH₂Cl₂); liquid product; ¹H NMR (300 MHz, CDCl₃): δ 2.82(broad s, 1H, OH), 6.20(t, 1H, J_{HF}=55.1 Hz, H₂), 7.3(m, 6H, ArH), 7.4(m, 4H, ArH); ¹⁹F NMR(56.4 MHz, CDCl₃): δ -128.2(t, J=51.2 Hz); ¹³C NMR(75 MHz, CDCl₃): δ 78.0(t, J_{CF}=20.9 Hz, C₁), 116.9(t, J_{CF}=250.2 Hz, C₂), 127.0, 128.1 and 128.2(C_{ArH}), 148.8(C_{Ar}); MS(EI, 70eV): m/z 234(M⁺, 1%), 183(100), 105(86), 77(60); IR(neat): ν(cm⁻¹) 3550, 3450, 1495, 1450, 1080, 700.

A mixture (81% by flash chromatography; SiO₂ CH₂Cl₂) of

d,l-threo-1-Fluoro-2-hydroxy-1,2-diphenylethane⁷ (11) ¹H NMR (300 MHz, CDCl₃): δ 2.8(broad s, 1H, OH), 4.86(dd, 1H, J_{HF}=12.5 Hz, J_{HH}=7.5 Hz, H₂), 5.36(dd, 1H, J_{HF}=47.6 Hz, J_{HH}=7.5 Hz, H₁), 7.0-7.4(m, 10H, ArH); ¹⁹F NMR(285 MHz, CDCl₃): δ -181.2(dd, J_{FH}=47.6 Hz, J_{FH}=12.5 Hz)

and

d,l-erythro-1-Fluoro-2-hydroxy-1,2-diphenylethane⁷ (12) ¹H NMR (300 MHz, CDCl₃): δ 2.3(broad s, 1H, OH), 4.93(dd, 1H, J_{HF}=12.5 Hz, J_{HH}=5.5 Hz, H₂), 5.46(dd, 1H, J_{HF}=47.6 Hz, J_{HH}=5.5 Hz, H₁), 7.0-7.4(m, 10H, ArH); ¹⁹F NMR(285 MHz, CDCl₃): δ -181.2(dd, J_{FH}=45.8 Hz, J_{FH}=12.5 Hz);

MS(EI, 70eV): m/z calcd. for C₁₄H₁₃FO: 216.0955; measured m/z: 216.0950; m/z 216(M⁺, 2%), 199(3), 191(1), 109(38), 105(100), 79(65), 77(40).

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2-Fluoro-1-indanone⁸ (14a, Scheme 4)

Yield 90% (flash chromatography, SiO₂, CH₂Cl₂); white crystals; mp 57-59 °C (mp⁸ 55-57 °C); ¹H NMR (300 MHz, CDCl₃): δ 3.5(n, 2H, H3), 5.3(ddd, 1H, J=54 Hz, J=8 Hz, J=4 Hz, H2), 7.6(m, 4H, ArH); ¹⁹F NMR(56.4 MHz, CDCl₃): δ - 193.0(ddd, J=54 Hz, J=24 Hz, J=8 Hz); ¹³C NMR(75 MHz, CDCl₃): δ 33.3(d, J=21.4 Hz, C3), 90.2(d, J=189.8 Hz, C2), 124.4, 126.7, 128.2 and 136.4(C_{ArH}), 133.6 and 149.6(d, J=5.8 Hz, C_{Ar}), 199.8(d, J=14.8 Hz, CO); MS(EI, 70eV): m/z 150(M⁺, 100%), 149(38), 122(77), 121(28), 104(18), 191(28), 76(31); IR(KBr): ν(cm⁻¹) 1720, 1462, 1084, 907, 764.

2-Fluoro-3,4-dihydronaphthalen-1(2H)-one⁸ (14b, Scheme 4)

Yield 88.5% (flash chromatography, SiO₂, CH₂Cl₂); white crystals; mp 38-39.5 °C (mp⁸ 37-38 °C); ¹H NMR (300 MHz, CDCl₃): δ 2.45(m, 2H, H4), 3.2(m, 2H, H3), 5.1(ddd, 1H, J=50 Hz, J=10 Hz, J=6 Hz, H2), 7.2-8.2(m, 4H, ArH); ¹⁹F NMR(56.4 MHz, CDCl₃): δ - 191.0(ddd, J=54 Hz, J=24 Hz, J=8 Hz); MS(EI, 70eV): m/z 164(M⁺, 30%), 118(100), 90(85), 89(32); IR(KBr): ν(cm⁻¹) 1703, 1601, 1227, 1080, 930, 754.

2,2-Difluoro-2,2-diphenyl-1,3-propanedione⁸ (16a, Scheme 5)

Yield 67% (flash chromatography, SiO₂, CH₂Cl₂); white crystals; mp 55-57 °C (mp⁸ 55-57 °C); ¹H NMR (300 MHz, CDCl₃): δ 7.36(m, 3H), 8.23(m, 2H); ¹⁹F NMR(56.4 MHz, CDCl₃): δ - 102.7(s); ¹³C NMR(75 MHz, CDCl₃): δ 112.7(t, J=265.7 Hz, C2), 127.2, 128.4, 128.8, 130.0, 132.4, 135.0, 187.3(t, J=27.2 Hz, CO); MS(EI, 70eV): m/z 260(M⁺, 1%), 241(2), 105(100), 77(70); IR(KBr): ν(cm⁻¹) 3069, 1698, 1593, 1450, 1138, 941, 887, 719.

Ethyl 2,2-difluoro-3-oxo-3-phenylpropanoate⁹ (16b, Scheme 5)

Yield 85.5% (flash chromatography, SiO₂, CH₂Cl₂); liquid product; ¹H NMR (300 MHz, CDCl₃): δ 1.4(t, 3H, J=7.2 Hz, Me), 4.4(q, 2H, J=7.2 Hz, OCH₂), 7.7(m, 3H), 8.2(m, 2H); ¹⁹F NMR(56.4 MHz, CDCl₃): δ -108.5(s); ¹³C NMR(75 MHz, CDCl₃): δ 13.7(Me), 63.7(OCH₂), 109.9(t, J=264.5, C2), 128.8, 130.0 and 135.0(C_{ArH}), 131.0(C_{Ar}), 161.8(t, J=31.0 Hz, COOEt), 185.8(t, J=27.2 Hz, CO); MS(EI, 70eV): m/z 183(M-OEt, 1%), 155(2), 105(100), 77(50); IR(neat): ν(cm⁻¹) 1780, 1610, 1320, 1175, 925, 690.

2,2-Difluoro-1,3-indandione¹⁰ (18, Scheme 5)

Yield 74% (flash chromatography, SiO₂, CH₂Cl₂); yellow crystals, mp 116.5-118.6 °C; (mp¹⁰ 117-118 °C); ¹H NMR (300 MHz, CDCl₃): δ 8.2(m); ¹⁹F NMR(56.4 MHz, CDCl₃): δ -

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125.8(s); ^{13}C NMR(75 MHz, CDCl_3): δ 104.0(t, $J=264.2$ Hz, C2), 128.8 and 138.2(C_{ArH}), 139.2(t, $J=4.4$ Hz, C_{Ar}), 185.8(t, $J=23.9$ Hz, CO); MS(EI, 70eV): m/z 182(M^+ , 90%), 104(100), 76(60); IR(KBr): $\nu(\text{cm}^{-1})$ 1761, 1732, 1196, 1112, 939, 737.

2-Acetyl-2-fluoro-3,4-dihydronaphthalen-1(2H)-one¹¹ (20, Scheme 5)

Yield 91% (flash chromatography, SiO_2 , CH_2Cl_2); white crystals; mp 33.5-35 °C ; ^1H NMR (300 MHz, CDCl_3): δ 2.40(dddd, 1H, $J=18.5$ Hz, $J=12.3$ Hz, $J=8.2$ Hz, $J=5.6$ Hz, H3), 2.41(d, 3H, $J=5.3$ Hz, Me), 2.6(dddd, 1H, $J=18.5$ Hz, $J=13.3$ Hz, $J=5.6$ Hz, $J=5.3$ Hz, H3'), 3.12(m, 2H, H4H4'), 7.24(d, 1H, $J=7.4$ Hz, H8), 7.32(dd, 1H, $J=7.4$ Hz, $J=7.9$ Hz, H7), 7.52(dd, 1H, $J=9.1$ Hz, $J=7.9$ Hz, H6), 8.0(d, 1H, $J=9.1$ Hz, H5); ^{19}F NMR(285 MHz, CDCl_3): δ -161.1(ddq, $J=13.3$ Hz, $J=12.3$ Hz, $J=5.3$ Hz); ^{13}C NMR(75 MHz, CDCl_3): δ 24.7(d, $J=7.7$ Hz, C4), 26.4(Me), 31.2(d, $J=21.9$ Hz, C3), 97.5(d, $J=192.8$ Hz, C2); 126.9, 127.8, 128.8, and 134.4(C_{ArH}), 130.4 and 143.5(C_{Ar}), 190.3(d, $J=18.1$ Hz, COMe), 205.3(d, $J=30.2$ Hz, CO); MS(EI, 70eV): m/z 186(M-HF, 12%), 164(24), 163(20), 85(64), 84(100); IR(KBr): $\nu(\text{cm}^{-1})$ 2925, 1730, 1693, 1352, 1315, 1241, 720.

Ethyl-2-fluorocyclopentan-1-on-2-carboxylate¹² (22, Scheme 5)

Yield 87% (flash chromatography, SiO_2 , CH_2Cl_2); liquid product; ^1H NMR (300 MHz, CDCl_3): δ 1.3(t, 3H, $J=7.2$ Hz, Me), 2.1-2.6(m, 6H, H3H4H5), 4.3(q, $J=7.2$ Hz, OCH_2); ^{19}F NMR(56.4 MHz, CDCl_3): δ -165.0(tm, $J=25.2$ Hz); ^{13}C NMR(75 MHz, CDCl_3): δ 13.8(Me), 17.9(d, $J=2.7$ Hz, C4), 33.7(d, $J=21.5$ Hz, C3), 35.5(C5), 62.1(OCH_2), 94.4(d, $J=199.7$ Hz, C2), 167.2(d, $J=27.7$ Hz, COOEt), 207.5(d, $J=16.8$ Hz, CO); MS(EI, 70eV): m/z 174(M^+ , 16%), 146(17), 117(43), 101(40), 91(100), 73(47).

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