Electronic Supplementary Material (ESI) for Chemical Communications
This journal is © The Royal Society of Chemistry 2011

Supporting Information to Accompany:

Sultone opening with [^{18}F]fluoride : an efficient ^{18}F-labelling strategy for PET imaging

Sébastien Schmitt, Cédric Bouteiller, Louisa Barré and Cécile Perrio*

Laboratoire de Développements Méthodologiques en Tomographie par Emission de Positons, CEA/DSV/I2BM/CI-NAPS UMR6232, CNRS, Université de Caen Basse-Normandie, Centre Cyceron, Boulevard Henri Becquerel, 14074 Caen cedex, France

perrio@cyceron.fr

Contents

This journal is © The Royal Society of Chemistry 2011

[Texte]

1. Materials and general methods

Reagents and solvents. All reagents were purchased from Fluka or Sigma-Aldrich and were used without further purification. Anhydrous THF, DMF and acetonitrile were obtained from an Mbraun SPS-800 solvents delivery system. HPLC quality solvents were purchased from Merck or SDS.

Spectroscopy. ^{1}H, ^{13}C and ^{19}F NMR spectra were measured on a Brucker DRX 400, at 400 MHz (^{1}H), 100.6 MHz (^{13}C) and 376.4 MHz (^{19}F) or on a Brucker DPX 250, at 250 MHz (^{1}H), 62.5 MHz (^{13}C) and 235 MHz (^{19}F). Samples were dissolved in an appropriate deuterated solvent ($CDCl_3$, acetonitrile-d_3, methanol-d_4, D_2O or DMSO-d_6). Chemical shifts are reported as parts per million (ppm) using tetramethylsilane (TMS) as internal standard or by reference to proton resonances resulting from incomplete deuteration of the NMR solvent. Coupling constants are given in Hz and coupling patterns are abbreviated as: s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quadruplet), m (mutiplet), dd (doublet of doublet), ddd (doublet of doublet of doublet) and dtt (doublet of triplet of triplet). Mass spectra (MS) were obtained on a Varian GCMS Saturn 2000 spectrometer by electronic impact (EI) or on a Waters Q-TOF micro spectrometer by electrospray ionisation (ESI). High-resolution mass spectra (HRMS) were obtained on a Waters Q-TOF micro spectrometer by ESI. Relative intensities are given in brackets. Infrared spectra were recorded on a Thermo Nicolet 350 FT-IR ATR spectrophotometer and peaks are given in cm^{-1}. Melting points were determined on a Barnstead Electrothermal IA 9100 melting point apparatus and are uncorrected. Elemental analyses were performed on a ThermoQuest analyser CHNS and were within ± 0.4% of the calcd values.

Chromatography. Thin Layer Chromatography (TLC) was run on pre-coated aluminium plates of silica gel $60F_{254}$ (Merck) and Rf were established using an UV-lamp at 254 nm or by ninhydrin or phosphomolybdic acid hydrate spray reagent. Radioactive TLC was measured using an Instant Imager® Packard apparatus. Liquid chromatography was performed on 40-63 mesh silica gel 60 (Merck) columns. High Performance Liquid Chromatography (HPLC) was carried out by means of a Waters 600 pump and controller, a Waters 717 plus autosampler, and a Waters 996 photodiode arrays detector (210-800 nm). Two chromatographic systems were used for the purification and quality control.

This journal is © The Royal Society of Chemistry 2011

System A: semi-preparative HPLC (MS C18, Waters Bondapak, 7.8 x 300 mm, 10 µm) with acetonitrile and aqueous trifluoroacetic acid (TFA, 0.1%, pH 2) [20% acetonitrile (15 min), then linear gradient from 20 to 80% acetonitrile (20 min), then 80% acetonitrile (5 min), then linear gradient from 80 to 20% acetonitrile (5 min) and 20% acetonitrile (5 min)] at a flow rate of 3 mL/min. UV detection was achieved from 210 to 750 nm.

System B: analytical HPLC (Nucleodur 100-3 Hilic, Macherey-Nagel, 150 x 4.6 mm, 3 µm) with acetonitrile and aqueous ammonium acetate ($AcNH_4$, 100 mM, pH 6) [linear gradient from 97 to 70% acetonitrile] at a flow rate of 1 mL/min. UV detection was achieved at 220 nm.

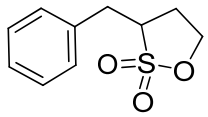
Radioisotope production and radiochemistry. No-carrier-added aqueous [^{18}F]fluoride was produced by the ^{18}O[p,n]^{18}F nuclear reaction of a target consisting of ^{18}O-enriched water (97%, Eurisotop) irradiated with a 18 MeV proton beam (IBA Cyclone 18/9 cyclotron). Radiosyntheses using fluorine-18 were performed in fume hoods equipped of 5 cm lead-shielded wall and lead-shielded glass screens. In those conditions, starting radioactivity of [^{18}F]-fluoride was under 10 mCi (370 MBq). Solid phase extraction cartridges were preconditioned with methanol (5 mL) and water (5 mL). Radioactivity quantities were determined using dose calibrator (Capintec R15C) for radiochemical samples.

2. Synthesis of the starting sultones 1-6 and *bis*-sultone 13

General procedure for sultones 1-5 and 13[1-2]

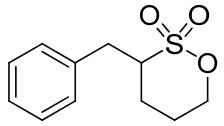
A solution of n-butyllithium (1 equiv.) in hexane was added dropwise under nitrogen to a stirred solution of propane or butane sultone (1 equiv.) in THF at -78 °C. After stirring for 15 min, benzylbromide, ethyl benzoate (1 equiv) or 1,4-bis(bromomethyl)benzene (0.5 equiv) was added dropwise to the vigorously stirred solution. The mixture was stirred at -78 °C for 2 h, allowed to warm to 0 °C and then treated with water. DCM was added and the organic phase was washed with water and brine, dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by column chromatography over silica gel (pentane/diethyl ether 50/50) to yield the titled compound.

3-Benzyl-[1,2]oxathiolane 2,2-dioxide 1 [75732-43-3]



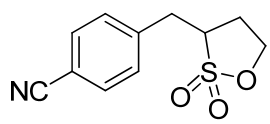
Obtained from propane sultone (340 mg, 2.8 mmol) and benzylbromide (478 mg, 2.8 mmol) as a white solid (440 mg, 74%). Mp 70 °C (lit. 54-56 °C). Rf 0.27 (pentane/diethyl ether 50/50). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38-7.25 (m, 5H), 4.48-4.43 (m, 1H), 4.38-4.32 (m, 1H), 3.58-3.50 (m, 1H), 3.44-3.39 (m, 1H), 2.93-2.87 (m, 1H), 2.54-2.47 (m, 1H), 2.41-2.35 (m, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 136.4, 129.4, 129.2, 127.8, 67.3, 56.9, 34.9, 29.6. IR (cm^{-1}) 2955, 2923, 1494, 1456, 1334, 1191, 1153, 783, 723, 703, 620. ESI^+/MS/MS m/z (%) 213.1 ($[M+H]^+$, 45), 131.1 (100). ESI^+/HRMS calcd for $C_{10}H_{11}O_3S$ 213.0585; found 213.0592. Anal. calcd for $C_{10}H_{12}O_3S$ C, 56.58, H, 5.70, S, 15.11; found C, 56.93, H, 6.04, S, 15.46. HPLC (System A) R_t 28.8 min.

3-Benzyl-[1,2]oxathiane 2,2-dioxide 2



Obtained from butane sultone (500 mg, 3.7 mmol) and benzylbromide (633 mg, 3.7 mmol) as a white solid (833 mg, 90%). Mp 125 °C. Rf 0.46 (pentane/diethyl ether 50/50). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38-7.28 (m, 3H), 7.23-7.21 (m, 2H), 4.63-4.57 (m, 1H), 4.51-4.47 (m, 1H), 3.54 (dd, J = 4.0 Hz et J = 13.8 Hz, 1H), 3.32-3.26 (m, 1H), 2.82-2.75 (m, 1H), 2.08-2.01 (m, 1H), 1.99-1.81 (m, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 136.2, 129.7, 129.3, 127.6, 74.1, 61.1, 34.4, 27.8, 24.4. IR (cm^{-1}) 1347, 1165, 939, 913, 901, 783, 718, 597, 531. ESI^+/MS/MS m/z (%) 227.2 ($[M+H]^+$, 100), 145.2 (57). ESI^+/HRMS calcd for $C_{11}H_{13}O_3S$ 227.0742; found 227.0738. Anal. calcd for $C_{11}H_{14}O_3S$, 0.4 H_2O C, 56.58, H, 6.39; found C, 56.78, H, 6.62. HPLC (System A) R_t 31.2 min.

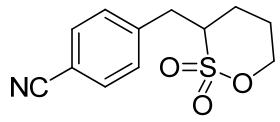
3-(4-Cyanobenzyl)-[1,2]oxathiolane 2,2-dioxide 3



Obtained from propane sultone (100 mg, 0.82 mmol) and 4-cyanobenzyl bromide (161 mg, 0.82 mmol) as a white solid (123 mg, 63%). Mp 78 °C. Rf 0.35 (diethyl ether). ^{1}H NMR

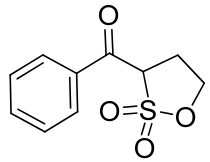
($CDCl_3$, 400 MHz) δ 7.67 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 4.51-4.46 (m, 1H), 4.45-4.35 (m, 1H), 3.56-3.52 (m, 1H), 3.45-3.40 (m, 1H), 3.06-3.00 (m, 1H), 2.58-2.55 (m, 1H), 2.41-2.35 (m, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 141.7, 133.2, 130.1, 118.8, 112.1, 67.1, 56.4, 35.2, 29.8. IR (cm^{-1}) 2226, 1608,1331, 1166, 1153, 867, 781, 589, 549. Anal. calcd for $C_{11}H_{11}NO_3S$, 0.5 H_2O C, 53.64, H, 4.91; found C, 53.95, H, 5.37. HPLC (System A) R_t 25.5 min.

3-(4-Cyanobenzyl)-[1,2]oxathiane 2,2-dioxide 4



Obtained from butane sultone (1.1 g, 8.1 mmol) and 4-cyanobenzyl bromide (1.58 g, 8.1 mmol) as a white solid (1.2 g, 57%). Mp 104 °C. Rf 0.41 (diethyl ether). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.67-7.64 (m, 2H), 7.37-7.28 (m, 2H), 4.60-4.51 (m, 2H), 3.54-3.51 (m, 1H), 3.32-3.28 (m, 1H), 2.91-2.85 (m, 1H), 2.08-1.86 (m, 4H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 141.9, 133.0, 130.5, 118.9, 111.8, 74.2, 60.5, 34.9, 28.2, 24.3. IR (cm^{-1}) 2947, 2228, 1331, 1162, 940, 918, 901, 833, 792, 588, 543. Anal. calcd for $C_{12}H_{13}NO_3S$, H_2O C, 53.52, H, 5.61, N, 5.20; found C, 53.64, H, 5.63, N, 4.91. HPLC (System A) R_t 27.4 min.

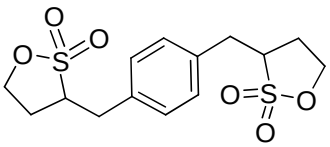
3-Benzoyl-[1,2]oxathiolane 2,2-dioxide 5



Obtained from propane sultone (610 mg, 5.0 mmol) and ethylbenzoate (750 mg, 5.0 mmol) as a white solid (340 mg, 30%). Mp 64 °C. Rf 0.41 (pentane/ethyl acetate 80/20). ^1H NMR ($CDCl_3$, 400 MHz) δ 8.09-8.08 (m, 2H), 7.70-7.66 (m, 1H), 7.66-7.54 (m, 2H), 5.15-5.11 (m, 1H), 4.68-4.63 (m, 1H), 4.58-4.52 (m, 1H), 3.33-3.25(m, 1H), 2.78-2.69 (m, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 187.6, 135.2, 134.8, 129.2, 129.1, 68.2, 59.8, 26.9. IR (cm^{-1}) 2992, 1688, 1595, 1579, 1149, 1335, 1292, 1181, 1148, 965, 873, 785, 727, 603. ESI^+/HRMS calcd for $C_{10}H_{10}O_4S$ 226.0300; found 226.0302. (System A) R_t 28.5 min.

[Texte]

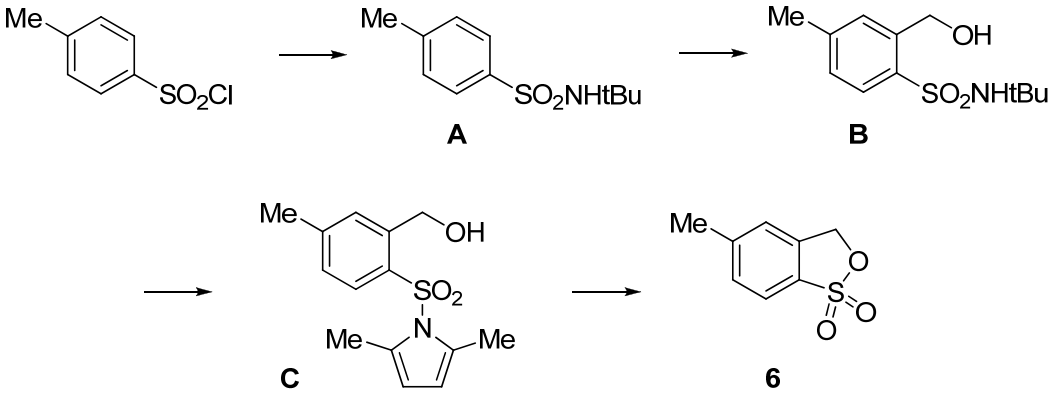
3,3'-[1,4-phenyl-bis(methylene)]bis(1,2-oxathiolane-2,2-dioxide) 13



Obtained from propane sultone (1.83 g, 15 mmol) and 1,4-bis(bromomethyl)benzene (1.98 g, 7.5 mmol) as a white solid (884 mg, 34%). Mp 208 °C. Rf 0.65 (ethyl acetate). ^{1}H NMR (CD_3CN, 400 MHz) δ 7.28 (m, 4H), 4.45-4.34 (m, 2H), 4.32-4.30 (m, 2H), 3.66-3.62 (m, 2H), 3.22-3.17 (m, 2H), 2.98-2.92 (m, 2H), 2.56-2.48 (m, 2H), 2.35-2.25 (m, 2H). ^{13}C NMR (CD_3CN, 100.6 MHz) δ 135.3, 134.7, 131.7, 129.7, 68.4, 57.1, 34.4, 29.9. IR (cm^{-1}) 2933, 1518, 1444, 1335, 1254, 1159, 988, 877, 785, 614. ESI$^+$/MS/MS m/z (%) 347.16 ($[M+H]^+$, 100%), 265.17 (35%), 253.16 (80%), 247.15 (10%), 201.19 (30%), 183.17 (15%). ESI$^+$/HRMS calcd for $C_{14}H_{19}O_6S_2$ 347.0623; found 347.0633. HPLC (System B) R_t 1.6 min.

Synthesis of sultone 6[3-4]

Sultone **6** was prepared from methylbenzenesulfonyl chloride according to the following reaction scheme :



***N-tert*-Butyl-4-methylbenzenesulfonamide A**

To a stirred solution of 4-methylbenzenesulfonyl chloride (5 g, 26.2 mmol) in dry DCM (100 mL) was added triethylamine (5.53 mL, 39.37 mmol). The resulting mixture was cooled to 0 °C and *tert*butylamine (4.46 mL, 39.37 mmol) was added. The resulting mixture was stirred at 0 °C for 1 h and for 24 h at RT. The reaction was quenched by the addition of aqueous HCl (2.0 M, 25 mL). The organic fraction was separated and washed with aqueous HCl (2 M, 2X250 mL), brine (250 mL), dried ($MgSO_4$) and concentrated in vacuo to yield the titled

compound as a white solid (5.1 g, 86%). Mp 114 °C. Rf 0.50 (DCM). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.03-6.77 (m, 2H), 6.52-6.21 (m, 2H), 5.33 (s, 1H), 1.54 (s, 3H), 0.45 (s, 9H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 143.1, 141.0, 129.8, 127.3, 54.8, 30.5, 21.9. IR (cm^{-1}) 3261, 1299, 1136, 1094, 995, 816, 657, 551. ESI^+/MS/MS m/z (%) 228.1 ($[M+H]^+$, 25), 172.1 (100), 155.0 (12). ESI^+/HRMS calcd for $C_{11}H_{18}NO_2S$ 228.1058; found 228.1057. Anal. calcd for $C_{11}H_{17}NO_2S$ C, 58.12, H, 7.54, N, 6.16, S, 14.11; found C, 58.23, H, 7.86, N, 6.30, S, 14.37.

***N*-tert-Butyl-2-hydroxymethyl-4-methylbenzenesulfonamide B [304649-53-4]**

Sulfonamide **B** (2.0 g, 8.9 mmol) was dissolved in dry THF (20 mL) and cooled to -78 °C under nitrogen atmosphere. *n*-BuLi in THF (2.5 M, 7.2 mL, 18.6 mmol) was added. The reaction mixture was stirred at -78 °C for 30 min, then at -20 °C for 15 min. After cooling cooled to -78 °C, dry DMF (2.3 mL, 27.5 mmol) was introduced slowly. The reaction mixture was stirred at – 78 °C for 4 h then stirred overnight at rt. The mixture was poured over ice-cold saturated NH_4Cl (10 mL) and stirred for 5 min. $NaBH_4$ (507 mg, 12.98 mmol) was added in three lots and stirring was continued for 30 min. The mixture was stirred overnight at rt. After extraction with ethyl acetate, the organic phase was dried ($MgSO_4$) and concentrated under vacuum to get a gummy mass. Purification by flash column chromatography, using a mixture of heptanes and ethyl acetate (75/25) as eluent, afforded the titled compound as a colourless solid (1.6 g, 70%). Mp 143 °C. Rf 0.45 (heptanes/ethyl acetate 50/50). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85-7.82 (m, 1H), 7.24-7.19 (m, 1H), 7.23-7.14 (m ,1H), (4.87 (s, 2H), 3.01 (s, 2H), 2.34 (s, 3H), 1.19 (s, 9H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 144.1, 141.6, 138.6, 132.4, 129.9, 129.1, 63.8, 55.5, 30.5, 21.7. IR (cm^{-1}) 3407, 3139, 2981, 1158, 1074, 1043, 983, 875, 822, 662, 594, 549. ESI^+/MS/MS m/z (%) 258.1 ($[M+H]^+$, 36), 202.1 (100), 184.1 (7). ESI^+/HRMS calcd for $C_{12}H_{19}NO_3S$ 258.1164; found 258.1175. Anal. calcd for $C_{12}H_{19}NO_3S$ C, 56.01, H, 7.44, N, 5.44, S, 12.46; found C, 56.52; H, 7.73; N, 4.96; S, 11.80.

[2-(2,5-Dimethylpyrrole-1-sulfonyl)-5-methylphenyl]methanol C

A mixture of p-toluenesulfonic acid (303 mg, 1.56 mmol) and sulfonamide **B** (1 g, 3.89 mmol) was refluxed in toluene (10 mL) using a Dean-Stark separator for 1 h. Acetonyl acetone (2.30 mL, 19.45 mmol) was added and the mixture was refluxed overnight. After cooling to rt, the toluene solution was washed with $NaHCO_3$ and water. The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was

purified by flash column chromatography using a mixture of heptanes and ethyl acetate (50/50) as eluent to yield the titled compound as a purple oil (344 mg, 32%). Rf 0.23 (ethyl acetate/heptanes 50/50). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.99 (s, 1H), 6.92(d, J = 8.0 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 5.82 (s, 2H), 4.80 (s, 2H), 2.20 (s, 3H), 2.19 (s, 6H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 144.3, 139.8, 133.4, 129.3, 128.9, 128.6, 127.3, 111.5, 61.5, 21.6, 15.7. IR (cm^{-1}) 1600, 1439, 1349, 1215, 1171, 1140, 1112, 785, 707, 675, 631, 565, 542. ESI^+/MS/MS m/z (%) 280.1 ($[M+H]^+$, 55), 262.1 (100), 244.1 (28), 216.1 (33). ESI^+/HRMS calcd for $C_{14}H_{18}NO_3S$ 280.1007; found 280.1002. Anal. calcd for $C_{14}H_{17}NO_3S$ C, 60.19, H, 6.13, N, 5.01; found, C, 60.02, H, 6.35, N, 4.98.

5-Methyl-3H-benzo[c][1,2]oxathiole-1,1-dioxide 6 [70265-10-0]

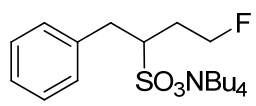
To sulfonamide **C** (83 mg, 0.297 mmol) in THF (5mL) was added slowly sodium hydride (15 mg, 0.65 mmol). The reaction mixture was stirred at rt overnight. After addition of water then extraction with DCM, the organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by flash column chromatography using a mixture of heptanes and ethyl acetate (50/50) as eluent to yield the titled compound as a white solid (40 mg, 73%). Mp 80 °C. Rf 0.81 (heptanes/ethyl acetate 50/50). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.12 (s, 1H), 5.50 (s, 2H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 145.3, 136.0, 131.4, 129.4, 123.8, 122.0, 71.3, 22.1. IR (cm^{-1}) 1328, 1194, 1153, 951, 912, 796, 741, 654, 565, 550. Anal. calcd for $C_8H_8O_3S$ C, 52.16, H, 4.38; found C, 52.60, H, 4.75. HPLC (System A) R_t 15.1 min.

3. Synthesis of the fluorosulfonates

General procedure for fluorosulfonates 7-12 and 14

The sultone (0.29 mmol) was dissolved in [d^3]-acetonitrile (1.2 mL) under nitrogen atmosphere. TBAF (1.3 eq.) was added and the reaction mixture was stirred at rt for 24 h. Progress of the reaction was followed by ^{1}H and ^{19}F NMR spectroscopy. After completion of the reaction, the solvent was evaporated to dryness to give a viscous oil.

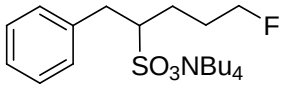
4-Fluoro-1-phenyl-butane-2-sulfonate tetrabutylammonium 7



[Texte]

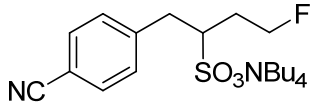
^{1}H NMR (CD_3CN, 400 MHz) δ 7.33-7.21 (m, 5H), 4.61-4.59 (m, 1H), 4.56-4.47 (m, 1H), 3.52-3.48 (m, 1H), 3.17-3.09 (m, 8H), 2.85-2.75 (m, 2H), 2.11-2.01 (m, 2H), 1.65-1.60 (m, 8H), 1.40-1.34 (m, 8H), 1.00-0.96 (m, 12H). ^{13}C NMR (CD_3CN, 100.6 MHz) δ 140.8, 129.6, 128.7, 126.4, 83.4 (d, $^{1}J_{CF}$ = 160.9 Hz), 58.7, 57.6, 37.6, 31.0 (d, $^{2}J_{CF}$ = 20.12 Hz), 23.7, 19.7, 13.3. ^{19}F NMR (CD_3CN, 376.5 MHz) δ - (216.8-217.2) (m, 1F). IR (cm^{-1}) 3406, 2961, 2875, 1464, 1200, 1176, 1033, 881, 737, 605, 547. ESI^-/MS/MS m/z (%) 231.1 ($[M]^-$, 68), 211.1 (100), 181.1 (7), 117.1 (6). ESI^-/HRMS calcd for $C_{10}H_{12}O_3FS$ 231.0491; found 231.0492. HPLC (System A) R_t 9.3 min.

5-Fluoro-1-phenyl-pentane-2-sulfonate tetrabutylammonium 8



^{1}H NMR (CD_3CN, 400 MHz) δ 7.33-7.21 (m, 5H), 4.61-4.55 (m, 1H), 4.56-4.43 (m, 1H), 3.49-3.44 (m, 1H), 3.18-3.10 (m, 8H), 2.85-2.80 (m, 1H), 2.68-2.60 (m, 1H), 2.05-1.95 (m, 2H), 1.69-1.66 (m, 2H), 1.65-1.59 (m, 8H), 1.40-1.34 (m, 8H), 1.00-0.95 (m, 12H). ^{13}C NMR (CD_3CN, 100.6 MHz) δ 140.8, 129.6, 128.7, 126.4, 83.4 (d, $^{1}J_{CF}$ = 159.5 Hz), 58.7, 57.6, 37.6 (C_5), 31.0 (d, $^{2}J_{CF}$ = 20.12 Hz), 23.9, 23.7, 19.7, 13.3. ^{19}F NMR (CD_3CN, 376.5 MHz) δ - (218.8 - 219.2) (m, 1F). IR (cm^{-1}) 3418, 2962, 2876, 1652, 1487, 1464, 1382, 1209, 1170, 1034, 881, 727, 701, 625, 530. ESI^-/MS/MS m/z (%) 245.1 ($[M]^-$, 100), 225.1 (95), 197.0 (7). ESI^-/HRMS calcd for $C_{11}H_{13}FO_3S$ 245.0648; found 245.0660. HPLC (System A) R_t 11.2 min.

1-(4-Cyanophenyl)-4-fluoro-butane-2-sulfonate tetrabutylammonium 9

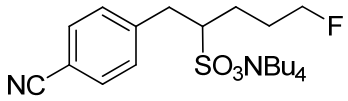


^{1}H NMR (CD_3CN, 400 MHz) δ 7.65 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 4.64-4.61 (m, 1H), 4.53-4.49 (m, 1H), 3.54-3.50 (m, 1H), 3.17-3.09 (m, 8H), 2.80-2.70 (m, 2H), 2.10-2.00 (m, 2H), 1.66-1.60 (m, 8H), 1.40-1.35 (m, 8H), 1.00-0.96 (m, 12H). ^{13}C NMR (CD_3CN, 100.6 MHz) δ 147.2, 132.4, 130.6, 118.9, 109.8, 83.3 (d, $^{1}J_{CF}$ = 160.9 Hz), 58.7, 57.1, 37.9, 31.4 (d, $^{2}J_{CF}$ = 20.12 Hz), 23.8, 19.7, 13.3. ^{19}F NMR (CD_3CN, 376.5 MHz) δ - (217.2 - 217.6) (m, 1F). IR (cm^{-1}) 3407, 2962, 2876, 1651, 1487, 1464, 1201, 1177, 1035, 881, 737, 606, 549.

[Texte]

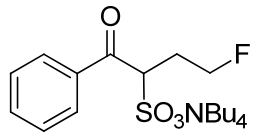
ESI$^-$/MS/MS m/z (%) 256.1 ([M]$^-$, 40), 142.1 (10), 81.0 (100). ESI$^-$/HRMS calcd for $C_{11}H_{11}NO_3FS$ 256.0444; found 256.0443. HPLC (System A) R_t 8.4 min.

1-(4-Cyanophenyl)-5-fluoro-pentane-2-sulfonate tetrabutylammonium 10



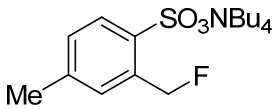
^{1}H NMR (CD_3CN, 400 MHz) δ 7.63-7.60 (m, 2H), 7.43-7.41 (m, 2H), 4.39-4.35 (m, 1H), 4.31-4.27 (m, 1H), 3.49-3.44 (m, 1H), 3.18-3.15 (m, 8H), 2.75-2.70 (m, 1H), 2.65-2.60 (m, 1H), 2.00-1.94 (m, 2H), 1.68-1.65 (m, 2H), 1.64-1.59 (m, 8H), 1.37-1.32 (m, 8H), 0.97-0.93 (m, 12H). ^{13}C NMR (CD_3CN, 100.6 MHz) δ 143.7, 132.3, 130.6, 116.5, 119.5, 86.4 (d, $^1J_{CF}$ = 160.1 Hz), 58.6, 52.6, 36.6, 29.0 (d, $^2J_{CF}$ = 20.0 Hz), 23.8, 23.7, 19.7, 13.3. ^{19}F NMR (CD_3CN, 376.5 MHz) δ - (218.7 - 219.3) (m, 1F). IR (cm^{-1}) 3416, 2960, 2875, 1654, 1485, 1460, 1207, 880, 726, 700, 623, 532. ESI$^-$/MS/MS m/z (%) 270.1 ([M]$^-$, 100), 81.0 (92). ESI$^-$/HRMS calcd for $C_{12}H_{13}FNO_3S$ 270.0600; found 270.0597. HPLC (System A) R_t 8.2 min.

4-Fluoro-1-oxo-1-phenylbutane-2-sulfonate tetrabutylammonium 11



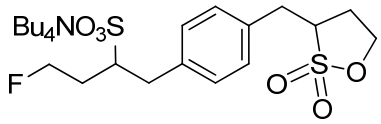
^{1}H NMR (CD_3CN, 400 MHz) δ 8.08-8.05 (m, 2H), 7.50-7.42 (m, 2H), 7.18-7.13 (m, 1H), 4.85-4.81 (m, 1H), 4.51-4.44 (m, 1H), 4.36-4.22 (m, 1H), 3.11-3.07 (m, 8H), 2.42-2.32 (m, 2H), 1.62-1.56 (m, 8H), 1.38-1.32 (m, 8H), 0.98-0.94 (m, 12H). ^{13}C NMR (CD_3CN, 100.6 MHz) δ 197, 139.0, 133.1, 129.9, 129.1, 83.7 (d, $^1J_{CF}$ = 161.9Hz), 63.3 (d, $^3J_{CF}$ = 6.0Hz), 59.2, 31.0 (d, ^2J = 23.4Hz), 24.3, 20.3, 13.7. ^{19}F NMR (CD_3CN, 376.5 MHz) δ ppm - (151.7 - 151.8) (m, 1F). IR (cm^{-1}) 3468, 2961, 2874, 1674, 1487, 1225, 1036, 981, 882, 738, 680, 592. ESI$^-$/HRMS calcd for $C_{10}H_{10}FO_4S$ 245.0289; found 245.0292. HPLC (System A) R_t 4.1 min.

2-Fluoromethyl-4-methyl-benzenesulfonate tetrabutylammonium 12



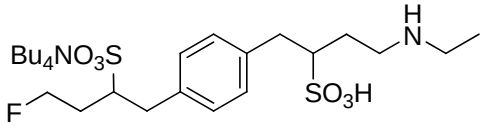
^{1}H NMR (CD_3CN, 400 MHz) δ 7.87 (d, J = 7.8 Hz, 1H), 7.49 (s, 1H), 7.26 (d, J = 7.8 Hz, 1H), 6.05 (d, J = 48.1 Hz, 2H), 3.25-3.20 (m, 8H), 2.52 (s, 3H), 1.76-1.72 (m, 8H), 1.55-1.50 (m, 8H), 1.16-1.09 (m, 12H). ^{13}C NMR (CD_3CN, 100.6 MHz) δ 143.1, 134.9, 134.5, 130.7, 129.5, 126.8, 82.1 (d, $^{1}J_{CF}$ = 155.1 Hz), 58.6, 23.5, 19.6, 13.2. ^{19}F NMR (CD_3CN, 376.5 MHz) δ ppm – 214.6 (t, J = 48.2 Hz, 1F). IR (cm^{-1}) 3427, 2961, 2876, 1653, 1487, 1463, 1381, 1195, 1087, 1021, 741, 681, 597. ESI$^-$/MS/MS m/z (%) 203.0 ([M]$^-$, 75), 183.0 (100), 135.1 (12), 119.1 (35). ESI$^-$/HRMS calcd for $C_8H_8FO_3S$ 203.0178; found 203.0172. HPLC (System A) R_t 6.7 min.

1-{4-[(2,2-Dioxido-1,2-oxathiolan-3-yl)methyl]phenyl}-4-fluorobutane-2-sulfonate tetrabutylammonium 14



^{1}H NMR (D_2O, 400 MHz) δ 7.26-7.23 (m, 4H), 4.50-4.45 (m, 1H), 4.40-4.33 (m, 2H), 4.28-4.24 (m, 1H), 3.42-3.25 (m, 4H), 3.12-3.08 (m, 8H), 2.71-2.62 (m, 2H), 2.17-1.83 (m, 4H), 1.60-1.52 (m, 8H), 1.32-1.24 (m, 8H), 0.89-0.85 (m, 12H). ^{13}C NMR (CD_3CN, 100.6 MHz) δ 138.9, 130.4, 130.1, 129.9, 83.9 (d, $^{1}J_{CF}$ = 159.0 Hz), 68.7, 68.3, 59.2, 58.2 (d, $^{3}J_{CF}$ = 6.6 Hz), 57.6, 37.9, 34.7, 31.6 (d, $^{2}J_{CF}$ = 20.0 Hz), 30.3, 24.4, 20.4, 13.8. ^{19}F NMR (D_2O, 376.5 MHz) δ - (216.0 - 216.5) (m, 1F). IR (cm^{-1}) 3449, 2961, 2875, 1514, 1468, 1382, 1340, 1197, 1168, 1031, 882, 725, 609. ESI$^-$/MS/MS m/z (%) 365.11 ([M]$^-$, 20), 284.14 (75), 192.06 (75), 182.05 (100), 172.05 (30), 167.05 (15). ESI$^-$/HRMS calcd for $C_{14}H_{18}FO_6S_2$ 365.0534; found 365.1081. HPLC (System B) R_t 2.7 min.

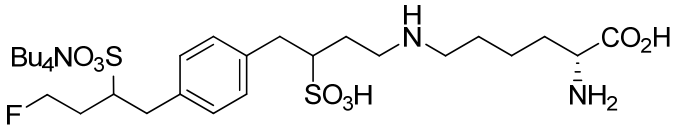
1-{4-[4-(Ethylamino)-2-sulfobutyl]phenyl}-4-fluorobutane-2-sulfonate tetrabutylammonium 15



To a solution of **14** (186mg, 0.3mmol) in acetonitrile (1.5mL) was added ethylamine (70% water 24µL, 0.3mmol). The reaction mixture was stirred at room temperature for 24h and evaporated under reduced pressure to give **15** (214mg) as a viscous oil. ^{1}H NMR (D_2O, 400

MHz) δ 7.47-7.38 (m, 4H), 4.67-4.62 (m, 1H), 4.56-4.50 (m, 2H), 4.45-4.41 (m, 1H), 3.53-3.42 (m, 3H), 3.21-3.17 (m, 8H), 3.04-3.00 (m, 1H), 2.91-2.79 (m, 3H), 2.33-2.22 (m, 2H), 2.12-1.99 (m, 3H), 1.69-1.61 (m, 8H), 1.42-1.35 (m, 8H), 1.32-1.19 (m, 3H), 0.98-0.95 (m, 12H). ^{13}C NMR (CD_3CN, 100.6 MHz) δ 137.7, 137.0, 128.9, 128.7, 82.7 (d, $^{1}J_{CF}$ = 159Hz), 57.9, 57.8, 56.8 (d, $^{3}J_{CF}$ = 6.1Hz), 45.3, 41.7, 36.6, 36.1, 32.1, 30.3 (d, $^{2}J_{CF}$ = 20.2Hz), 23.0, 19.9, 12.6, 11.0. ^{19}F NMR (CD_3CN, 376.5 MHz) δ - (216.0 - 216.4) (m, 1F). IR (cm^{-1}) 3462, 2961, 2875, 1635, 1514, 1468, 1382, 1197, 1167, 1031, 883, 725, 607. ESI$^-$/HRMS calcd for $C_{16}H_{25}FNO_6S_2$ 410.1113; found 410.1116. HPLC (System B) R_t 12.0 min.

1-(4-{4-[(5-amino-5-carboxypentyl)amino]-2-sulfobutyl}phenyl)-4-fluorobutane-2-sulfonate tetrabutylammonium 16



^{1}H NMR (D_2O, 400 MHz) δ 7.23 (m, 4H), 4.50-4.44 (m, 1H), 4.39-4.32 (m, 2H), 4.27-4.22 (m, 1H), 3.67-3.64 (m, 1H), 3.32-3.26 (m, 2H), 3.20-3.16 (m, 8H), 2.96-2.92 (m, 2H), 2.70-2.64 (m, 2H), 2.17-2.05 (m, 2H), 1.94-1.79 (m, 4H), 1.74-1.71 (m, 4H), 1.68-1.60 (m, 8H), 1.54-1.44 (m, 2H), 1.39-1.34 (m, 8H), 0.97-0.94 (m, 12H). ^{13}C NMR (D_2O, 100.6 MHz) δ 174.7, 136.9, 136.8, 129.5, 129.4, 82.6 (d, $^{1}J_{CF}$ = 160 Hz), 76.6, 58.2, 58.1, 57.7 (d, $^{3}J_{CF}$ = 5.2Hz), 54.5, 39.1, 38.9, 35.8, 32.5, 29.9 (d, $^{2}J_{CF}$ = 20.4Hz), 29.8, 26.4, 23.1, 21.4, 19.1, 12.8. ^{19}F NMR (D_2O, 376.5 MHz) δ - (216.7 - 217.0) (m, 1F). IR (cm^{-1}) 3521, 2961, 2874, 1584, 1515, 1496, 1381, 1315, 1196, 1168, 1031, 882, 805, 723, 607, 547. ESI$^-$/HRMS calcd for $C_{20}H_{32}FN_2O_8S_2$ 511.1590; found 511.1597. HPLC (System B) R_t 15.4 min.

4. Radiochemistry

Preparation of nucleophilic [^{18}F]fluoride ion ([^{18}F]KF/K222). [^{18}F]F^- was separated from ^{18}O-enriched water using ion exchange resin (QMA light, Waters, ABX) eluted with aqueous potassium carbonate K_2CO_3 (36 mM, 500 µL). The [^{18}F]-fluoride solution was collected into a conical Reactivial® containing Kryptofix 2.2.2 (22-24 mg) and K_2CO_3 (4.5-5.5 mg), and dissolved in acetonitrile. The water was removed azeotropically with acetonitrile (4×1 mL)

under a stream of nitrogen affording a dry residue of $[K/K_{222}]^+ {}^{18}F^-$. Between 500 µCi (18.5 MBq) and 2 mCi (72 MBq) of dried $[K/K_{222}]^+ {}^{18}F^-$ were obtained in 20 to 25 min.

Preparation of [^{18}F]TBAF. [^{18}F]F^- was separated from ^{18}O-enriched water using ion exchange resin (QMA light, Waters, ABX) eluted with aqueous tetra-*n*-butylammonium bicarbonate nBu$_4$NHCO$_3$ (70 mM, 200 µL) and acetonitrile (800 µL). The [^{18}F]-fluoride solution was collected into a conical Reactivial®. The water was removed azeotropically with acetonitrile (3×1 mL) under a stream of nitrogen affording a dry residue of [^{18}F]TBAF. Between 1 mCi (37 MBq) and 2 mCi (72 MBq) of dried [^{18}F]TBAF were obtained in 20 to 25 min.

General procedure for the fluorination reaction with [^{18}F]KF/K222. Sultone (4-6 mg) in acetonitrile (500µL) was added to the dried [^{18}F]KF/K222 complex and the sealed reaction vial was heated at 20 °C, 50 °C or 110 °C for 15 min. Aliquots (50 µL) were taken at 2, 5, 10 and 15 min, dissolved in 50 µL of an aqueous solution of TFA (0.1% in water) and analysed by HPLC. The radioactive fractions were collected and the radioactivity was counted.

Radiosynthesis of [^{18}F]15 and [^{18}F]16 from [^{18}F]TBAF

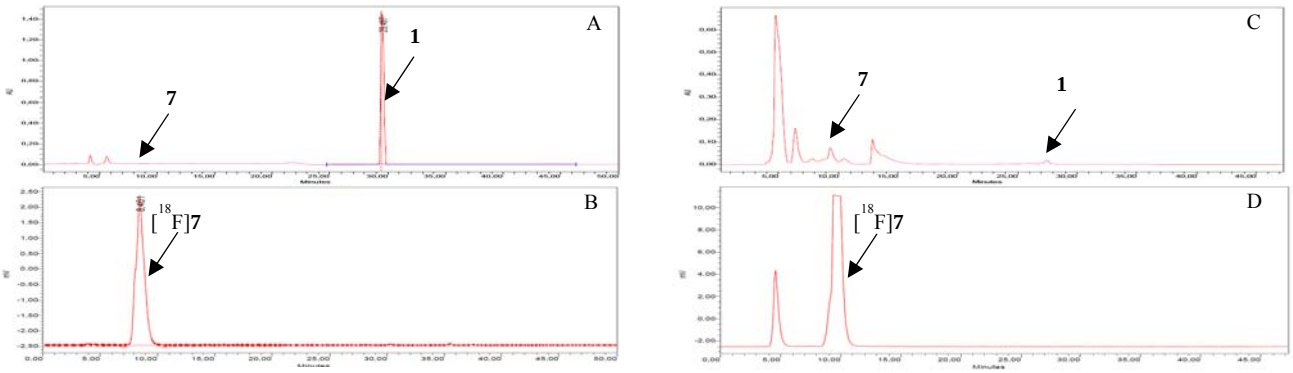
Without SPE purification. The disultone **13** (5 mg) in acetonitrile (300 µL) was added to dried [^{18}F]TBAF and the sealed reaction vial was heated at 75 °C for 15 min. Ethylamine (70% in water, 50 µL) or lysine (6 mg) in water (100 µL) was added and the sealed reaction vial was heated at 110 °C for 15 min. For each step, aliquots (20 µL) were analysed by HPLC. The radioactive fractions were collected and the radioactivity was counted.

With SPE purification. The disultone **13** (5 mg) in acetonitrile (300 µL) was added to dried [^{18}F]TBAF and the sealed reaction vial was heated at 75 °C for 15 min. After cooling to room temperature then addition of water (100 µL), the solution was adsorbed on a C-18 cartridge (Sep-pak plus®, Waters). The radioactive fraction recovered after elution with a mixture of water and acetonitrile (60/40, 1 mL) was added to lysine (6 mg) in water (100 µL). The final mixture was heated at 110 °C for 15 min. Water (2 mL) was added and the solution was passed through a C-18 cartridge (Sep-Pak plus, Waters). For each step, aliquots (20 µL) were analysed by HPLC. The radioactive fractions as well as the final solution were collected and the radioactivity was counted.

[Texte]

5. HPLC Chromatograms

Radiosynthesis of fluorosulfonate [^{18}F]7 (taken as representative)

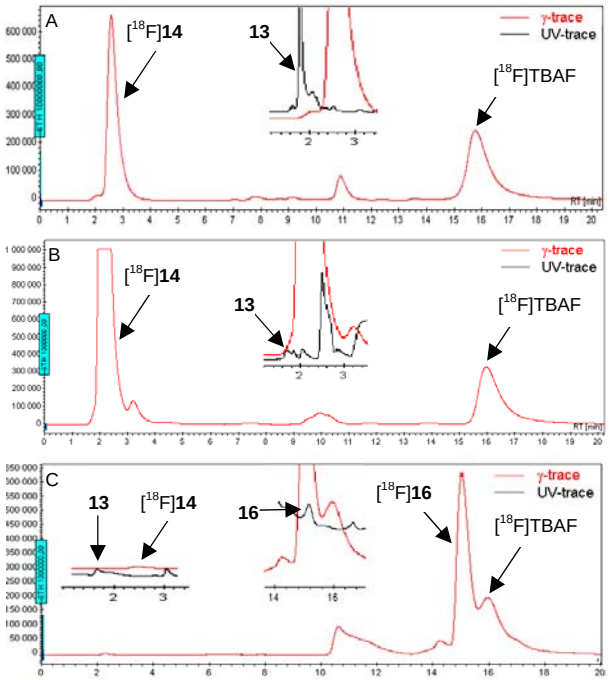


A, C : UV trace; B and D : γ-trace

A and B : injection of an aliquot containing 0.5 mg of sultone **1** before SPE

C and D : injection of the overall final volume after SPE

Radiosynthesis of the fluoro-bis-sulfonate [^{18}F]16 from bis-sultone 13



A: after radiofluorination and before SPE

B: after radiofluorination then SPE

C: after radiofluorination, SPE then amination with lysine

[Texte]

6. References

1 M. B. Smith and J. Wolinsky, *J. Org. Chem*., 1981, **46**, 101.

2 E. L. Margelefsky, R. K. Zeidan, V. Dufaud and M. E. Davis, *J. Amer. Chem. Soc*., 2007, **129**, 13691.

3 S. K. Singh, P. G. Reddy, K. S. Rao, B. B. Lohray, P. Misra, S. A. Rajjak, Y. K. Rao, and A. Venkateswarlu, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 499.

4 S. K. Singh, S. Shivaramakrishna, V. Saibaba, K. S. Rao, K. R. Ganesh, R. Vasudev, P. P. Kumar, J. M. Babu, K. Vyas, Y. K. Rao and J. Iqbal, *Eur. J. Med. Chem.*, 2007, **42**, 456.