Supplementary Material (ESI) for Chemical Communications

Electronic Supplementary Information

Methyl transfer reaction from monomethyltin reagent under palladium(0) catalysis: a versatile method for labelling with carbon-11

Mickaël Huiban,[a] Aline Huet,[b] Louisa Barré,[a] Franck Sobrio,*[a] Eric Fouquet,*[b] Cécile Perrio*[a,c]

[a] *Groupe de Développements Méthodologiques en Tomographie par Emission de Positons, UMR 2E FRE 2698, DRM-DSV CEA, CNRS, Université de Caen-Basse Normandie, Centre Cyceron, 15 Boulevard Henri Becquerel, BP 5229, F-14074 Caen Cedex, France*

[b] *Laboratoire de Chimie Organique et Organométallique, URA CNRS 35, Université de Bordeaux I, 351 Cours de la Libération, F-33405 Talence Cedex, France*

[c] *Laboratoire de Chimie Moléculaire et Thioorganique, UMR CNRS 6507, ENSICAEN, Université de Caen-Basse Normandie, 6 Boulevard Maréchal Juin, 14050 Caen Cedex, France*

sobrio@cyceron.fr, e.fouquet@lcoo.u-bordeaux1.fr, perrio@cyceron.fr

General. All reactions were carried out under an argon atmosphere in flame-dried glassware. THF and dioxane were distilled under argon or nitrogen from sodium/benzophenone and calcium chloride respectively. Commercially available materials were used without further purification. Tin chloride was stored under argon before use. Non radioactive reactions were monitored by gas Chromatography (GC) analysis of worked up reaction aliquots. Analytical thin-layer chromatography (TLC) and radio TLC were carried out on aluminum or plastic silica gel 60 F-254 plates (0.1 mm), with UV detection. Flash chromatography was carried out using Si 60 (40-63 μm) silica. Radioactive reactions were analysed by LC equipped with a UV detector (254 nm wavelength) and a β^+-flow detector, using a C-18 column and methanol/water (75/25) as mobile phase. ^{1}H Nuclear magnetic resonance spectra were recorded at 400 or 250 MHz and ^{13}C nuclear magnetic resonance spectra were recorded at 100.6 or 62.9 MHz. They were calibrated according to the chemical shift of tetramethysilane. Chemical shift (δ) are quoted in ppm and coupling constants (*J*) in Hz. The following abbreviations are used to denote multiplicities: s, singlet; d, doublet; dd, double-doublet; ddd: double-double-doublet; t, triplet; td, triple-doublet; m, multiplet; b, broad.

CHEMISTRY.

Synthesis of starting aryl halides 2. Aryl halides **2a-e**, **2h-i** were commercially available and used as received. Bromoquinolines **2f** and **2g** were prepared according to ref[1].

2-Bromoquinoline 2f. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.06-7.97 (m, 2H), 7.83-7.70 (m, 2H), 7.60-7.49 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 148.5, 141.8, 138.3, 130.5, 128.6, 127.7, 127.1, 126.9, 125.71.

4-Bromoquinoline 2g. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.68 (1H, d, J = 4.6 Hz), 8.20 (1H, dd, J = 8.4 and 1.1 Hz), 8.11 (1H, d, J = 8.2 Hz), 7.78 (1H, ddd, J = 8.4, 6.9 and 1.5 Hz), 7.71 (1H, d, J = 4.7 Hz), 7.66 (1H, ddd, J = 8.3, 7.0 and 1.3 Hz). ^{13}C NMR (63 MHz, $CDCl_3$) δ 150.3, 149.4, 134.6, 130.8, 130.4, 128.3, 127.3, 125.5.

Bis(*N*,*N*-bistrimethylsilylamino)stannylene[2]. *n*-Butyllithium (41.3 mL of a 2.5M hexane solution) was added dropwise to a precooled (-78°C, acetone/dry ice) solution of freshly distilled hexamethyldisilazane (21.8 mL, 1 equiv.) in anhydrous Et_2O (50 mL) and THF (30 mL). The resulting mixture was allowed to reach room temperature and stirred over a period of 1 hour. The resulting lithium amide was then added dropwise to a suspension of tin chloride(II) (10g, 1 equiv.) in anhydrous Et_2O (50 mL). The resulting reaction mixture was stirred at room temperature for additional 3 hours. The solution was transferred to a flask where the solvents were removed *in vacuo* to give an orange oil which was distilled under reduced pressure (0.1 mmHg, 110°C) to yield bis(*N*,*N*-bistrimethylsilylamino)stannylene in 89% yield (20.6 g).

Iodo-bis(*N*,*N*-bistrimethylsilylamino)methyltin 1. In a typical procedure, methyl iodide (106 μl, 2 mmol) was added at room temperature to a solution of bis(*N*,*N*-bistrimethylsilylamino)stannylene (880 mg, 2 mmol, 1 equiv.) in anhydrous THF (10 mL) under an argon atmosphere. Then was an immediate fading of the reaction mixture as indication of the tin (IV) reagent formation. The solution was allowed to stir for 5 min then was concentrated *in vacuo* to yield the monomethyltin **1** in quantitative yield. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.18 (s, $^{2}J_{Sn-H}$ = 71.7 Hz, 3H), 0.23 (s, 36H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.8 ($^{1}J_{Sn-C}$ = 560 Hz), 5.9 (12C). ^{119}Sn NMR (74.6 MHz, $CDCl_3$) δ -170.2.

General procedure for the Stille cross-coupling.

Monomethyltin reagent **1** (1.0 mmol) was prepared following the above procedure, and TBAF (3.0 mL, 3 equiv., 1M in THF) was then added *in situ* at room temperature. The reaction mixture was concentrated *in vacuo* before adding anhydrous dioxane (8 mL) and then a solution of tetrakis(triphenylphosphine) palladium (5% mol) and of the electrophile **2** (0.6 equiv) in dioxane heated at reflux for 10 min. After refluxing for 2-240 min, the reaction mixture was cooled to room temperature. Removal of solvent *in vacuo* yielded an oily residue, which was chromatographed on silica gel (eluent: petroleum ether) to furnish the cross-coupled product **3** and eventually the homocoupling product **4**. Structures of **3** and **4** were identified by NMR and GC analyses, by comparison of the data with those described in the literature, and with those of commercially available samples.

2-Methylnaphthalene 3a[3]**.** ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.86-7.77 (m, 3H), 7.66 (bs, 1H), 7.52-7.42 (m, 2H), 7.36 (dd, J = 1.7 and 8.4 Hz, 1H), 2.56 (s, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 135.8, 134.1, 132.1, 128.5, 128.1, 128.0, 127.7, 127.3, 126.3, 125.4, 22.1.

2,2'-Binaphthyl 4a[4]**.** ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.18 (s, 2H), 7.99-7.87 (m, 8H), 7.57-7.47 (m, 4H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 138.5, 133.8, 132.7, 128.6, 128.3, 127.7, 126.4, 126.2, 126.1, 125.8.

3-Methylquinoline 3b[5]**.** ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.74 (d, J = 2.1 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 7.1 Hz, 1H), 7.69 (d, J = 7.9 Hz, 1H), 7.61 (bt, J = 7.6 Hz, 1H), 7.44 (t, J = 6.2 Hz, 1H), 2.47 (s, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 152.4, 148.3, 134.6, 130.4, 129.1, 128.4, 128.1, 127.1, 126.5, 18.7.

3,3'-Bisquinoline 4b[6]**.** ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.33 (s, 2H), 8.56 (d, J = 2.2 Hz, 2H), 8.28 (d, J = 10.5 Hz, 2H), 8.01 (d, J = 10.5 Hz, 2H), 7.85 (td, J = 8.9 Hz, J = 2.2 Hz, 2H), 7.69 (t, J = 8.9 Hz, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 150.1, 149.2, 135.1, 131.5, 130.6, 130.1, 128.6, 128.3, 127.9.

1-Methylnaphthalene 3c[7]**.** ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.07-8.03 (m, 1H), 7.92-7.89 (m, 1H), 7.76 (d, J = 7.9 Hz, 1H), 7.60-7.50 (m, 2H), 7.45-7.36 (m, 2H), 2.75 (s, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 134.4, 133.7, 132.8, 128.7, 126.7, 126.5, 126.0, 125.8, 125.7, 124.3, 19.5.

4-Nitrotoluene 3d[7]**.** ^{1}H NMR (250 MHz $CDCl_3$) δ 8.01 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 8.5 Hz, 2H), 2.26 (s, 6H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 146.2, 129.9, 123.4, 21.1.

***p*-Xylene 3e**[8]**.** ^{1}H NMR (250 MHz $CDCl_3$) δ 7.04 (s, 4H), 2.29 (s, 6H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 134.6, 128.9, 20.9.

RADIOCHEMISTRY.

Radioactive products [^{11}C]-**3a-b**,**f-i** were identified by comparison with commercially available non radioactive authentic samples **3a-b**,**f-i**.

Production of $^{11}CO_2$. [^{11}C]-CO_2 was obtained by the nuclear reaction ^{14}N (p,α) ^{11}C in a nitrogen gas target containing 0.5% oxygen, with 18 MeV protons produced by the Cyclone 18/9 IBA cyclotron at the Cyceron PET Centre.

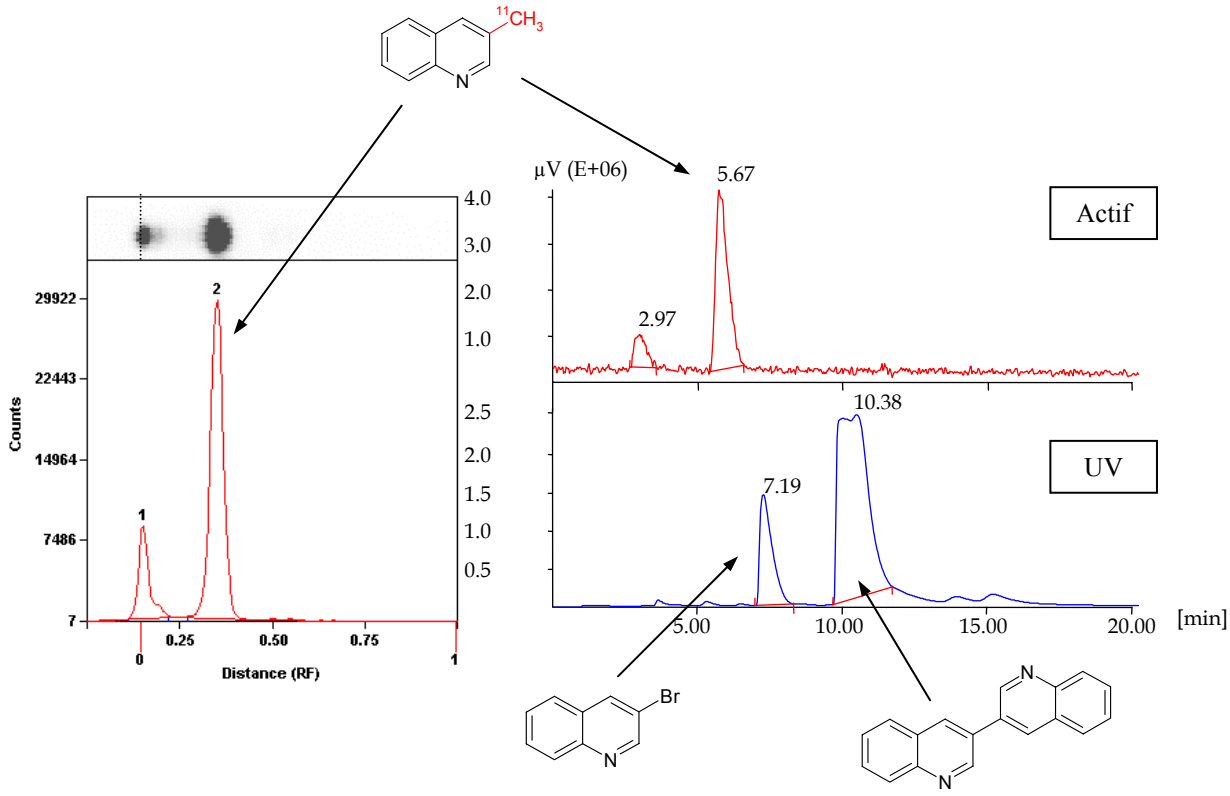
Synthesis of $^{11}CH_3I$[9]. [^{11}C]-CO_2 was converted into [^{11}C]-CH_3I via reduction with lithium aluminium hydride (0.1 M in THF, 200 µL) at room temperature, and subsequent reaction with hydriodic acid (57% in water, 1.5 mL) at 140 °C.

General procedure for ^{11}C-methyl transfer reaction. Under nitrogen, [^{11}C]-CH_3I was distilled into a solution of stannylene (6 mg, 15 µmol) in anhydrous THF (300 µL). After addition of TBAF (1M in THF, 41 µL, 45 µmol), THF was removed by heating at 120°C under nitrogen. A mixture of Pd_2dba_3 (5 mg, 5 µmol) and of the electrophile (50-75 µmol) in dioxane (250 µL) was added onto the residue and the resulting mixture was heated at 120°C for 5 min. The reaction was quenched with 100 µL of water, and analyzed by radioTLC (elution with heptane/AcOEt 70/30) and HPLC (Table 1). Radiochemical yields were calculated after HPLC purification from [^{11}C]-CH_3I and decay corrected.

Tableau 1. TLC and HPLC analyses of [^{11}C]-methylarenes [^{11}C]-**3**

Ar-X	t_R (min)	Ar-$^{11}CH_3$	t_R (min)	R_f
2a	11.0	[^{11}C]-**3a**	9.3	0.65
2b	6.2	[^{11}C]-**3b**	5.7	0.30
2f	14.3	[^{11}C]-**3f**	9.2	0.24
2g	6.7	[^{11}C]-**3g**	5.6	0.20
2h	8.4	[^{11}C]-**3h**	5.4	0.28
2i	4.7	[^{11}C]-**3i**	5.8	0.41

Example of TLC and HPLC chromatograms obtained for the synthesis of 3-[^{11}C]-methylquinoline [^{11}C]-3b



References.

(1) J. L.Butler, M.Gordon, *J. Heterocycl. Chem.*, 1975, **12**, 1015.
(2) A.Herve, A. L.Rodriguez, E. Fouquet, *J. Org. Chem.*, 2005, **70**, 1953.
(3) R. A.Aitken, C.Boeters, J. J. Morrison, *J. Chem. Soc. Perkin Trans 1*, 1997, 2625.
(4) C. F. Nising, U. K. Schmid, M. Nieger, S. Braese, *J. Org. Chem.*, 2004, **69**, 6830.
(5) H. MacNab, M. E. A. Murray, *J. Chem. Soc. Perkin Trans 1*, 1988, 333.
(6) S. Dumonchel, F. Mongin, F. Trécourt, G. Quéguiner, *Tetrahedron*, 2003, **59**, 8629. Y. Fort, S. Becker, P. Caubère, *Tetrahedron*, 1994, **50**, 11893.
(7) G. A. Molander, C.-S. Yun, M. Ribagorda, *J. Org. Chem.*, 2003, **68**, 5534.
(8) I. Perez, J. Perez Sestelo, L. A. Sarandeses, *Org. Lett.*, 1999, **1**, 1267.
(9) C. Crouzel, B. Långström, V. W. Pike, H. H. Coenen, *Appl. Radiat. Isot.*, 1987, **38**, 601.