JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
J Label Compd Radiopharm 2004; **47**: 71–78.
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jlcr.798

Research Article

A ^{11}C-Methyl stannane (5-[^{11}C]methyl-1-aza-5-stanna-bicyclo[3.3.3]undecane) for use in palladium-mediated [^{11}C]C–C bond forming reactions with organohalides

Tobias Forngren[1], Linda Samuelsson[1] and Bengt Långström[1,2,*]
[1] *Department of Organic Chemistry, Institute of Chemistry, BMC, Uppsala University, Box 599, Uppsala S-751 24, Sweden*
[2] *Uppsala Imanet, P.O. Box 967; Uppsala SE 751 09, Sweden*

Summary

The synthesis of a ^{11}C-labelled methyl stannane, (5-[^{11}C]methyl-1-aza-5-stanna-bicyclo[3.3.3]undecane (**2**)), and its use in palladium-mediated Stille reactions to form [^{11}C]C–C bonds are described. Stannane **2** was synthesized from iodo[^{11}C]methane, 5-chloro-1-aza-5-stanna-bicyclo[3.3.3]undecane **1** and butyl lithium in 20–90% decay-corrected radiochemical yield starting from iodo[^{11}C]methane. Subsequent reaction with a series of substituted aryl and vinyl halides produced the corresponding [^{11}C]methylated products **3–5** in up to 90% decay-corrected radiochemical yield from the crude **2**. The total synthesis time, including purification, was 25–30 min from end of radionuclide production. Copyright © 2003 John Wiley & Sons, Ltd.

Key Words: iodo[^{11}C]methane; Stille reaction; palladium

Introduction

Positron emission tomography (PET) is a technique where organic molecules labelled with short-lived β^+-emitting nuclides may be used in various areas of clinical diagnosis and as tools in the drug development process.[1–5] In order to facilitate the incorporation of radionuclides into biologically interesting molecules, there is a need to improve and develop new synthetic methods. The most frequently applied radionuclides in PET are ^{11}C, ^{18}F and ^{15}O with half-lives of 20.3, 110 and 2.07 min, respectively. Owing to the short half-lives combined with the demand for radiation safety the synthetic methods have to

*Correspondence to: B. Långström, Uppsala Imanet, P.O. Box 967, Uppsala SE-751 09, Sweden. E-mail: bengt.langstrom@uppsala.imanet.se

Contract/grant sponsor: Swedish Research Council; contract/grant number: K-KU 3463

Received 28 April 2003
Revised 16 May 2003
Accepted 15 October 2003

be rapid and, if possible, suitable for automation. The short half-lives also impose requirements such as fast reactions and workup.

The Stille and Suzuki coupling reactions are widely applied in carbon–carbon bond forming reactions due to their general tolerance to many functional groups.[6] These coupling reactions have also proven to be useful in the production of PET tracers, where functionalized organostannanes and organoboranes have been reacted with iodo[^{11}C]methane to form [^{11}C]carbon–carbon coupled products.[7–11] Protection of functionalized organostannanes containing nucleophilic groups is sometimes necessary in order to prevent side-reactions with iodo[^{11}C]methane.[12] In addition, preparation and purification of highly functionalized organostannanes are sometimes difficult. Therefore, we intended to investigate an alternative route using a ^{11}C-labelled stannane and various organohalides in order to overcome some of the problems mentioned above.

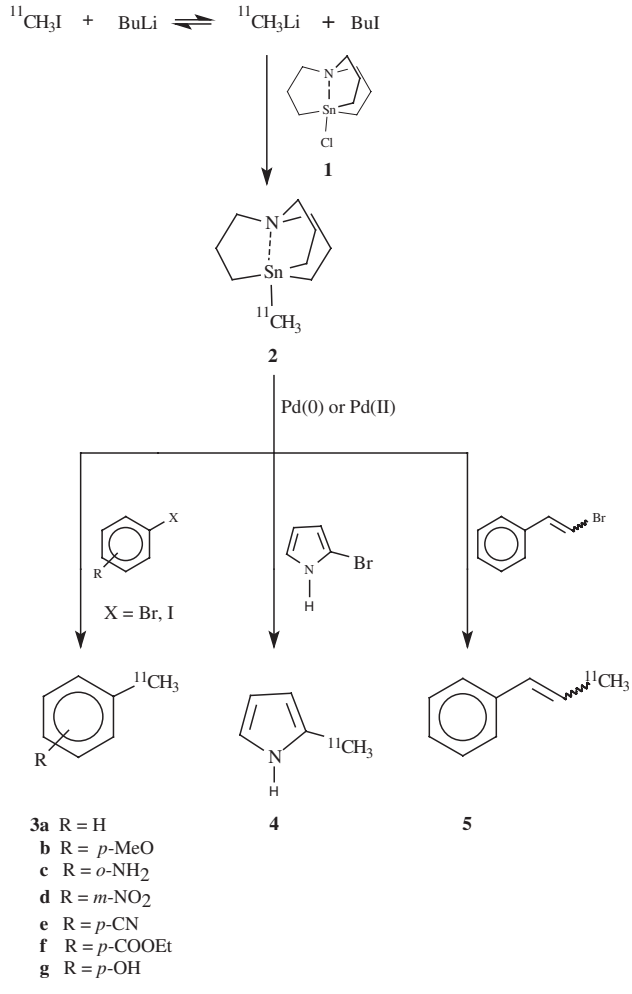
In this paper, a method for a preparation of 5-[^{11}C]methyl-1-aza-5-stanna-bicyclo[3.3.3]undecane **2** and its use in a selective and fast transfer of the [^{11}C]methyl-group in to aryl- and vinyl halides are presented (Scheme 1).

Results and discussion

Iodo[^{11}C]methane was converted to [^{11}C]methyl lithium by an exchange reaction at low temperature using butyl lithium in excess.[13] Addition of 5-chloro-1-aza-5-stanna-bicyclo[3.3.3]undecane **1**[14] to [^{11}C]methyl lithium gave the highly reactive ^{11}C-labelled organostannane **2**. Subsequent Stille-coupling reactions with various functionalized organohalides were performed in a one-pot procedure in the presence of a palladium catalyst forming products **3–5** (Scheme 1).

Stannane **2** was obtained in a variable 20–90% (average yield of 47%) decay-corrected radiochemical yield (0.2–0.9 GBq in a typical reaction) calculated from trapped iodo[^{11}C]methane. The wide range in yield when preparing **2** might be explained by the presence of proton sources in the reaction mixture resulting in the formation of [^{11}C]methane as a side-product. The amount of trapped iodo[^{11}C]methane in a typical reaction was 10–100 nmol. Traces of water and other impurities in the solvents and reagents might be the main factor for the variation in the radiochemical yield. However, no significant improvement of the radiochemical yield was observed even when using freshly distilled solvents, 24 h oven-dried glassware and carefully dried syringes.

To verify the presence of the labelled stannane **2**, a mixed ^{11}C/^{13}C-synthesis was performed using [^{11}C]- and (^{13}C)methyl iodide. The crude product was analyzed with regard to the labelling position by ^{13}C-NMR. The NMR investigation was performed after decay of ^{11}C and the peak at $\delta = -4.0$ ppm was assigned to the (^{13}C)methyl group. This was confirmed by electrospray



Scheme 1.

mass spectrometry where the ion m/z 277 was detected, which corresponds to $[M+H]^+$. In order to rule out the possibility of forming the products **3–5** from a reaction between the halides and [^{11}C]methyl lithium directly (without the participation of stannane **2**) a series of experiments were performed omitting chloride **1** or the palladium catalyst. No product was obtained in any of these control experiments. For future applications, the stannane may be useful in the synthesis of compounds with ^{11}C- or ^{18}F-labelled alkyl chains containing β-hydrogens, since the standard Stille reaction is reported to fail in these cases because of the competing β-hydrogen elimination.[6]

It was necessary to remove the solvent used in the first step in order to proceed successfully with the Stille reaction. A stream of helium at room temperature effectively evaporated the solvents within 2 min. The palladium

Table 1. Coupling of organohalides (RHal) with 2 to yield products 3–5[a,b]

Entry	Product	Catalyst	Temp(°C)	Reaction time (min)	Yield[c,d] (%)
1a	**3a**	$Pd(PPh_3)_4$	100	2	4
b	**3a**	$Pd(PPh_3)_4$	100	2	15
c	**3a**	$Pd(allylchloride)_2$	r.t	2	-
d	**3a**	$Pd(allylchloride)_2$	50	2	15
e	**3a**	$Pd(allylchloride)_2$	100	2	85
f	**3a**	$Pd(allylchloride)_2$	120	2	>90
2a	**3b**	$Pd(allylchloride)_2$	65	2	25
b	**3b**	$Pd(allylchloride)_2$	100	2	65
3a	**3c**	$Pd(allylchloride)_2$	100	2	5
b	**3c**	$Pd(allylchloride)_2$	100	5	15
4	**3d**	$Pd(allylchloride)_2$	100	2	20
5a	**3e**	$Pd(allylchloride)_2$	50	2	-
b	**3e**	$Pd(allylchloride)_2$	100	2	29
6a	**3f**	$Pd(allylchloride)_2$,	r.t	2	-
b	**3f**	$Pd(allylchloride)_2$	100	2	32
c	**3f**	$Pd(allylchloride)_2$,	100	5	43
d	**3f**	$Pd(allylchloride)_2$	100	2	-
e	**3f**	$Pd_2(dba)_3$, $AsPh_3$,	100	2	24
f	**3f**	$Pd_2(dba)_3$, $AsPh_3$,	100	5	35
g	**3f**	$PdCl_2(CH_3CN)_2$,	100	2	7
h	**3f**	$PdCl_2(CH_3CN)_2$,	100	5	9
7	**3g**	$Pd(allylchloride)_2$,	100	2	-
8a	**4**	$Pd(allylchloride)_2$,	100	2	9
9a	**5**	$Pd(allylchloride)_2$,	100	2	30
b	**5**	$Pd(allylchloride)_2$,	100	10	47

[a]In entries 1a-f Hal = I, in all other entries Hal = Br.
[b]DMF was used as the solvent except for in entries 1a and 6d.
[c]The decay-corrected radiochemical yield was determined by analytical LC as the percentage of the total amount of radioactivity in a sample withdrawn from the reaction mixture. The yields are calculated from crude **2**.
[d]The mean values of $\geqslant 3$ experiments are reported.

catalyst together with the appropriate organohalide and solvent were then added to the reaction vial when the solvent had been removed, and the resulting mixture was then heated. In a series of reactions using aromatic, heteroaromatic and vinylic bromides and iodides with various substituents the coupling reaction with [^{11}C]methylstannane **2** was investigated by varying the temperature, the palladium catalyst and solvents (Table 1).

The temperature had a significant influence on the radiochemical yield in the coupling reaction. At room temperature, none of the model reactions tested gave products (entries 1c and 6a). When the reaction temperature was raised to 50–65°C, products were formed in moderate yields (entries 1d, 2a and 5a). Temperatures above 100°C further improved the radiochemical yield (entry 1f) but despite that, most of the reactions in this study were performed at 100°C or below in order to make a general method possible to use with compounds that may be thermo-labile. The impact of varying the palladium catalyst was

evaluated and the highest yields were achieved with allylpalladium(II) chloride dimer. The best results were obtained when DMF was used as solvent. Using THF/MeCN (50/50) as solvent gave no product or low yield (entries 1a and 6d). Iodobenzene and allylpalladium(II) chloride dimer gave the highest yield (entry 1f). The coupling-reaction of the electron-rich *o*-bromoaniline (entry 3a) gave poor yields, but when the reaction time was prolonged, substantial amounts were obtained (entry 3b). In the case of *p*-bromophenol (entry 7) no product was obtained, possibly due to either coordination of the oxygen to palladium, or abstraction of the phenolic hydrogen by residual BuLi.

Compounds *p*-methoxy-[*methyl*-^{11}C]toluene (**3b**), *m*-nitro-[*methyl*-^{11}C]toluene (**3d**) and *β*-[*methyl*-^{11}C]methylstyrene (**5**) were purified and isolated using semi-preparative liquid chromatography (LC). The isolated radioactivity of these compounds corresponded to the yields obtained by analytical analysis stated in Table 1. Compounds **3b**, **3d** and **5** were obtained with a radiochemical purity $>97\%$ 30 min after end of bombardment.

Although this method may have some disadvantages (two-step reaction, dry conditions) it can be a useful complement to the traditional Stille reaction (e.g. failure in preparation of the stannane, side-reactions with [^{11}C]iodo methane). A good example is presented in ref. 12. We intend to further explore the potential of this concept by introducing longer ^{11}C- or ^{18}F-labelled alkyl groups on the stannane.

Conclusion

In this paper, the synthesis of a ^{11}C-labelled methyl stannane from [^{11}C]methyl lithium and its use in a palladium-mediated Stille reaction with various halides was reported. A general protocol was established using allylpalladium(II) chloride dimer as the catalyst in DMF at 100°C and the resulting products were [^{11}C]methylated aromatic, heteroaromatic or vinylic compounds. The method is complimentary to the reported Stille reaction when iodo[^{11}C]-methane is reacted with organostannanes.[7–11] The advantages are that the same stannane can be used in all reactions and the functionality of the substrate is not restricted by conditions for stannylation reactions.

Experimental

General

[^{11}C]Carbon dioxide was prepared by the ^{14}N(p, α)^{11}C nuclear reaction using a nitrogen gas target (AGA® Nitrogen 6.0) and 17 MeV protons produced by the Scanditronix MC 17 Cyclotron at Uppsala University PET-Center. An automated robotic system, Synthia,[14] was used for iodo[^{11}C]methane[16] production, HPLC injection and fraction collection. LC was performed at

room temperature using a Beckman 126 gradient pump equipped with a Beckman 166 UV-detector in series with a β^+-flow detector. A Beckman Ultrasphere C8 column (5 μm, 250 × 4.6 mm i.d.) was employed with the system for analytical LC and a Beckman Ultrasphere C8 column (5 μm, 250 × 10 mm i.d.) for preparative LC. The mobile phase used was 50 mM ammonium formate (40%) and acetonitrile (60%) in an isocratic program. As one part in the identification of the ^{11}C-labelled compounds, unlabelled reference substance was added in the LC runs, using UV-absorbance detection at 254 nm. The mass spectrometry (MS) analyses were performed with a Fison VG Platform spectrometer equipped with a CMA 200 autosampler using pneumatically assisted electrospray ionization (ESI+). ^{13}C-NMR spectra were recorded in benzene-*d*6 on a Varian Unity 400 (400 MHz) spectrometer at 30°C using the solvent as internal reference (δ = 128.06 ppm).

Chemicals

Iodo[^{11}C]methane was synthesized from [^{11}C]carbon dioxide according to the published procedure.[14,15] Iodo(^{13}C)methane (99% ^{13}C) was purchased from Larodan Fine Chemicals AB, Malmö, Sweden.

Allylpalladium(II) chloride dimer, bis(acetonitrile)dichloropalladium(0), tris(dibenzylideneacetone)dipalladium(0), triphenylarsine, butyl lithium (2.5 M in hexanes), *N,N*-dimethylformamide (99.8%) were purchased from Aldrich and were used without further purification. Tetrakis(triphenylphosphine)palladium(0) was purchased from Lancaster, acetonitrile (HPLC grade) from Riedel-de Haën and ammonium formate solution (50 mM, pH 3.5) from Apoteket Produktion & Laboratorier, Göteborg, Sweden. Tetrahydrofurane (>99.5%) and diethylether (>99.5%) were purchased from Merck and were distilled under nitrogen from sodium and benzophenone prior to use. All halides and reference compounds were obtained from commercial sources and used as supplied.

*Synthesis of 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane (**1**)*

5-Chloro-1-aza-5-stanna-bicyclo[3.3.3]undecane **1** was synthesized and purified as described by Vedejs *et al.*[16] We found this method being very unreliable, giving yields ranging from 0 to 43%. Identification and characterization was performed by ^{1}H- and ^{13}C-NMR and was compared with literature values,[17] and by electrospray MS on the protonated molecule $[M+H]^+$ using a mobile phase of acetonitrile-50 mM formic acid at a flow rate of 20 μl/min. The most abundant isotopic peak was detected at *m*/*z* 296 and the isotopic pattern was consistent with that expected from a compound containing Sn and Cl isotopes.

*Synthesis of 5-[^{11}C]methyl-1-aza-5-stanna-bicyclo[3.3.3]undecane (**2**)*

The iodo[^{11}C]methane, produced from [^{11}C]carbon dioxide by the automated synthesis system Synthia,[14] was passed through a phosphorus pentoxide drying tower and trapped in freshly distilled ether (100 µl) in a 3 ml septum-equipped glass vessel placed in a dry ice-ethanol bath (−72°C). BuLi (2.5 M in hexane, 4.0 µl, 10 µmol) was added to the trapped iodo[^{11}C]methane and kept at −72°C for 2 min. A solution of 5-chloro-1-aza-5-stanna-bicyclo[3.3.3]undecane **1** (1.5 mg, 5.1 µmol) in THF (70 µl) was added to the [^{11}C]methyl lithium solution and was kept at room temperature for 2 min. A stream of helium gas on top of the solvent surface was used to evaporate the solvents and dry the crude product. Compound **2** was used without further purification in the Stille-coupling reaction. Attempts to isolate compound **2** by LC for further characterization by analytical LC, ESI–MS and TLC failed.

*Synthesis of 5-(^{13}C)methyl-1-aza-5-stanna-bicyclo[3.3.3]undecane (^{13}C)–(**2**)*

Iodo[^{11}C]methane was dried by passage through a phosphorous pentoxide tower and was trapped in freshly distilled ether (200 µl) in a 3 ml septum equipped vial at –72°C (dry ice-ethanol). The radioactivity was measured in an ion chamber and the vial was placed in the cooling bath again. Iodo(^{13}C)-methane (20% v/v in octane, 5.0 µl, 16 µmol) was added followed by BuLi (1.6 M in hexane, 20 µl, 32 µmol) and the mixture was left in the cooling bath for 3 min. A solution of 5-chloro-1-aza-5-stanna-bicyclo[3.3.3]undecane (**1**) (7.0 mg, 24 µmol) in dry THF (200 µl) was added and the resulting solution was kept at −72°C for 1 min and then at room temperature for 5 min. A stream of helium on top of the surface evaporated the solvent and the remaining radioactivity was measured. After decay of the ^{11}C, the residue was dissolved in benzene-d_6 (0.7 ml), the resulting solution was filtered and a ^{13}C-NMR spectrum was acquired at 30°C. A peak was detected at $\delta = -4.0$ ppm using the solvent as reference. This is consistent with the shift reported for the corresponding ^{12}C-compound.[16] Unfortunately, the amount of ((^{13}C)-**2**) was too small to determine the ^{13}C-^{119}Sn coupling constant. The crude product was also analyzed by electrospray MS using direct inlet. The mobile phase used was acetonitrile-50 mM formic acid (95:5, v/v) at a flow rate of 20 µl/min. The ion m/z 277 was detected, which corresponds to $[M+H]^+$. The isotopic pattern was consistent with that expected.

*General procedure for the synthesis of the coupling products (**3–5**)*

A solution of the palladium catalyst (1.6 mg, 4.4 µmol) and the organohalide (10 µmol) in 200 µl solvent was added to the dry reaction-vial containing crude **2**. The reaction mixture was kept at the desired temperature for 2, 5 or 10 min. A sample was withdrawn from reaction mixture and injected on the analytical

LC-system or the reaction mixture was injected onto the semi-preparative LC-system for purification and isolation. The labelled products were identified by co-elution of their stable ^{12}C-derivatives using UV-absorbance detection in series with β^+ detection.

Acknowledgements

Dr Margareta Björkman is gratefully acknowledged for her contribution to this work. Financial support was provided by the Swedish Research Council grant K-KU 3463.

References

1. Wagner Jr HN, Szabo Z, Buchanan JW (eds). *Principles of Nuclear Medicine* (2nd ed). W.B. Saunders Company: Philadelphia, USA, 1995.
2. Phelps ME, *Neurochem Res*. 1991; **16**: 929.
3. Långström B, Hartvig P. In *Radiopharmaceuticals*: *Chemistry and Pharmacology*, Nunn, AD (ed.). Mercel Dekker Inc.; New York, USA, 1992; 221–266.
4. Comar D (ed.). *PET for Drug Development and Evaluation*. Kluwer Academic Publishers: Dordrecht, The Netherlands, 1995.
5. Bergström M, Grahnén A, Långström B. *Eur J Clin Pharmacol* 2003; **59**: 357–366.
6. Stille JK, *Angew Chem Int Ed Engl* 1986; **25**: 508–524.
7. Andersson Y, Cheng A, Långström B. *Acta Chem Scand* 1995; **49**: 683–688.
8. Björkman M, Andersson Y, Doi H, Kato K, Suzuki M, Noyori R, Watanabe Y, Långström B. *Acta Chem Scand* 1998; **52**: 635–640.
9. Suzuki M, Doi H, Björkman M, Långström B, Watanabe Y, Noyori R. *Chem Eur J* 1997; **3**(12): 2039–2042.
10. Karimi F, Långström B, *J Label Compd Radiopharm* 2002; **45**(5): 423–434.
11. Sandell J, Yu M, Emond P, Garreau L, Chalon S, Någren K, Guilloteau D, Halldin C, *Bioorg Med Chem Lett* 2002: **12**(24); 3611–3613
12. Lange O, Forngren T, Sandell J, Dollé F, Långström B, Halldin C. *J Label Compd Radiopharm* 2003; **46**(1): 55–65.
13. Reiffers S, Vaalburg W, Wiegman T, Wynberg H, Woldring MG. *J Appl Radiat Isot* 1980; **31**: 535; Långström B, *PhD Thesis*, Uppsala University, Sweden, 1980.
14. Bjurling P, Reineck R, Westerberg G, Schultz J, Gee A, Sutcliffe J, Långström B. *Proceedings of the Sixth Workshop on Targetry and Target Chemistry*, Vancouver, 1995; 282–285.
15. Långström B, Antoni G, Gullberg P, Halldin C, Malmborg P, Någren K, Rimland A, Svärd H. *J Nucl Med* 1987; **28**: 1037–1040.
16. Vedejs E, Haight AF, Moss WO. *J Am Chem Soc* 1992; **114**: 6556–6558.
17. Mügge C, Pepermans H, Gielen M, Willem R, Tzschach A, Jurkschat KZ. *Anorg Allg Chem* 1988; **567**: 122–130.

