STUDIES OF THE MECHANISM OF THE IN-LOOP SYNTHESIS OF RADIOPHARMACEUTICALS

A.R. Studenov, S. Jivan, M.J. Adam, T.J. Ruth, and K.R. Buckley

UBC/TRIUMF Program on Positron Emission Tomography, 4004 Wesbrook Mall, Vancouver, BC, Canada, V6T 2A3, Studenov@triumf.ca

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Methylation with [^{11}C]CH_3I is by far the most widely used reaction in the synthesis of carbon-11 PET radiopharmaceuticals. For some radiotracers, this reaction can be conveniently conducted *in-loop* (Wilson AA, Garcia A, Jin L, Houle S. *Nucl Med Biol* 2000; **27**: 529-532). Little is known about the details of *in-loop* synthesis such as the distribution of radioactivity along the length of the tubing, the limit in the amounts of the precursor and solvent necessary for the success of the radiosynthesis and the influence of the loop material on the yield of [^{11}C]CH_3I-methylation. We studied the dynamics of radioactivity distribution in the tubing loop placed in a PET scanner using the synthesis of [^{11}C]carfentanil as a model reaction. Scanning the tubing in a TLC Linear Analyser accessed longitudinal micro distribution (20 cm segments were scanned) of the radioactivity at the end of the synthesis. The effect of differing amounts of solvent and precursor in the radiosynthesis of [^{11}C]carfentanil and [^{11}C]SCH23390 was also probed.

We found that the trapping of [^{11}C]MeI is reversible; dramatic reduction in trapping efficiency (>50%) resulted from insufficient volume of the reaction solvent or excessive [^{11}C]CH_3I delivery gas volume. Once trapped, approximately one third of the introduced [^{11}C]CH_3I was retained in the first 5-10 cm of a Tefzel loop (0.040" ID x 2.4 m long, 2.0 mL volume) loaded with 80-100 µl of DMF while the rest of the radioactivity was distributed throughout the remaining length. Uneven distribution of the radioactivity (trapped in-loop) was also confirmed by serially eluting the origin (20 cm) and the rest of the tubing (220 cm) as well as by scanning the tubing in the TLC Linear Analyser. In the case of [^{11}C]SCH23390, synthesis efficiency was found to depend on precursor to solvent concentration as opposed to precursor quantity when the effect of solvent volume on [^{11}C]MeI trapping is removed (Table 1). No decrease of [^{11}C]CH_3I-methylation yield was noticed when the amount of [^{11}C]carfentanil precursor was reduced five times (down to 0.2 mg).

Table 1. Effect of reagent quantity on [^{11}C]CH_3I trapping and yield of [^{11}C]CH_3I-methylation for *in-loop* synthesis of [^{11}C]carfentanil and [^{11}C]SCH23390.

Synthesis	Standard condition: Reaction [a]	80% reduction of precursor & solvent volume		80% reduction of precursor, unchanged solvent volume	
		Reaction [b]	[^{11}C]CH_3I trapped[c]	Reaction [b]	[^{11}C]CH_3I trapped[c]
[^{11}C]Carfentanil	70±12% [d]	75%	48%	75%	>95%
[^{11}C]SCH23390	43±4% [e]	47%	53%	20%	>95%

[a] The EOB yields of [^{11}C]CH_3I-methylation of nor precursors under "standard" conditions of 100 µl solvent and 1 mg of the precursor for [^{11}C]carfentanil and 0.5 mg precursor for [^{11}C]SCH23390, [b] conversion of trapped [^{11}C]CH_3I, [c] [^{11}C]CH_3I trapped in the loop, [d] n=6, [e] n=3

In conclusion the optimal conditions for the in-loop synthesis of radiopharmaceuticals with [^{11}C]CH_3I depend on the reaction solvent volume, gas delivery volume, and the precursor concentration.

HIGH YIELD REDUCTIVE *N*-ALKYLATION OF SECONDARY AMINES WITH [^{11}C]ACETONE

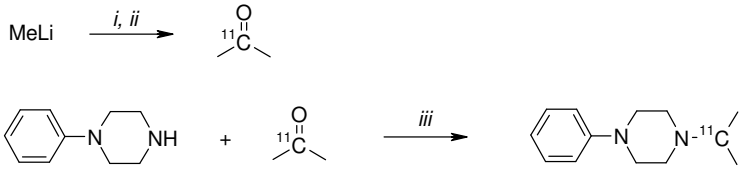
M. Van der Mey[1], N.I. Carruthers[2], J.D.M. Herscheid[1], J.A. Jablonowski[2], J.E. Leysen[3,4] and A.D. Windhorst[1]

[1]Radionuclide Center, Vrije Universiteit, De Boelelaan 1085c, 1081 HV Amsterdam, The Netherlands, mmeij@rnc.vu.nl. [2]Johnson & Johnson PRD, 3210 Merryfield Row, San Diego, CA 92121, United States. [3]Johnson & Johnson Pharmaceuticals, Turnhoutseweg 30, 2340, Beerse, Belgium. [4]Onderzoekinstituut Neurowetenschappen / Research Institute Neurosciences, Vrije Universiteit, c/o Dept. of Anatomy, Van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands

Keywords: [^{11}C]Acetone; Reductive alkylation; Reductive amination; Secondary amines

The reactions of ammonia, primary amines, or secondary amines with aldehydes or ketones in the presence of reducing agents to give primary, secondary or tertiary amines, respectively, known as reductive alkylations (of the amines) or reductive aminations (of the carbonyl compounds) are among the most useful and important tools in the synthesis of different kinds of amines. Reductive alkylations with ^{11}C-labeled carbonyl compounds such as formaldehyde, acetaldehyde and acetone have also been published. In contrast to the [^{11}C]aldehydes, reductive alkylation reactions using [^{11}C]acetone are limited to primary aliphatic amines, which generally react faster than primary aromatic and secondary aliphatic amines. Nevertheless, it would be useful to develop a labeling method for secondary amines since the R_2N-isopropyl moiety is present in many biologically active compounds.

In order to investigate the reductive alkylation of secondary amines, [^{11}C]acetone was reacted with 1-phenylpiperazine (Scheme 1). The [^{11}C]acetone, secondary amine and reducing agent were mixed without prior formation of the intermediate imine or iminium salt. Sodium cyanoborohydride and sodium triacetoxyborohydride were compared as reducing agents. In the literature the $(CH_3)_2{}^{11}C(OLi)_2$ salt, prepared by trapping of [^{11}C]CO_2 in a solution of MeLi, is usually converted to [^{11}C]acetone with water. Subsequently, the [^{11}C]acetone is distilled into the precursor solution *via* a calcium chloride column. In order to eliminate this drying procedure we examined the application of non-aqueous quenching agents. Furthermore, the influence of various parameters including solvent and temperature on the reaction outcome was studied.



Scheme 1. *Reductive alkylation of 1-phenylpiperazine with [^{11}C]acetone. Reaction conditions: (i) [^{11}C]CO_2; (ii) quenching; (iii) reductive alkylation.*

In summary, under optimized reaction conditions, the [^{11}C]acetone yield after distillation was 80% (calculated from [^{11}C]CO_2) and [^{11}C]1-isopropyl-4-phenylpiperazine was synthesized from [^{11}C]acetone and 1-phenylpiperazine in a radiochemical yield of 72% (decay corrected).

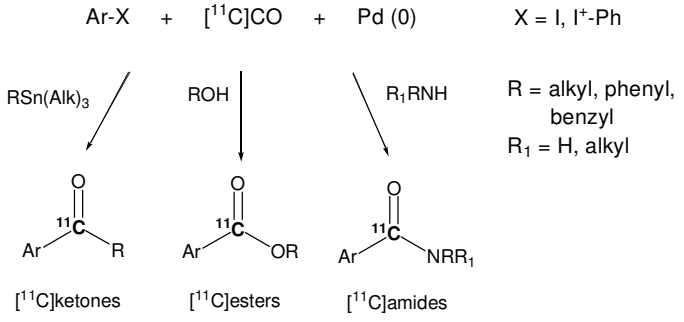
SIMPLE DEVICE FOR THE RADIOSYNTHESIS OF [CARBONYL-^{11}C]AMIDES, ESTERS AND KETONES USING CARBON-11 MONOXIDE

L. Brichard, G. Del Fiore, C. Lemaire, A. Plenevaux, A. Luxen

Cyclotron Research Center, Liege University, Sart-Tilman B30, B-4000 Liege Belgium
l.brichard@ulg.ac.be

Keywords: PET, Carbon-11 Monoxide, Palladium Catalysis, Carbonylation

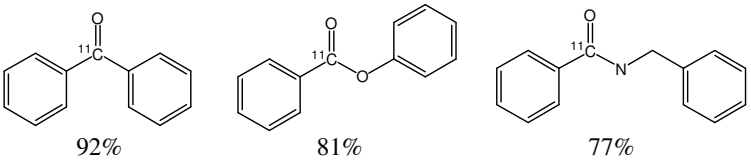
Palladium-catalyzed carbonylation reaction with [^{11}C]CO has become a versatile method for the labelling with carbon-11 (20.4 min.) of radiopharmaceuticals used in PET. Using this approach, various compounds such as amides, esters and ketones can be easily labelled on carbonyl position (Scheme 1) (1-3).



Scheme 1

A simple semi-automated system, using commercial vessel, was designed to realise, under mild conditions, all the synthesis steps: target-produced [^{11}C]CO_2 concentration, Zn reduction of [^{11}C]CO_2 into [^{11}C]CO, its trapping in the reaction vessel (a 10 ml septum-sealed glass vial), radiolabelling and subsequent disposal of unreacted [^{11}C]CO. The whole process taking about 20 minutes.

A large variety of aromatic ketones, amides and esters were produced with this device in very good radiochemical yields (some examples are shown in Scheme 2) and easily purified on HPLC. Radiochemical yields are decay-corrected and calculated by taking into account the [^{11}C]CO incorporation with respect to [^{11}C]CO production, and the radiochemical purity of the product. Depending upon the structure, [^{11}C]CO incorporation yields ranging between 80-97% were obtained.



Scheme 2

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and references cited therein.

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AN IMPROVED SYNTHESIS OF SUBSTITUTED [C-11]TOLUENES VIA SUZUKI COUPLING WITH [C-11]METHYL IODIDE

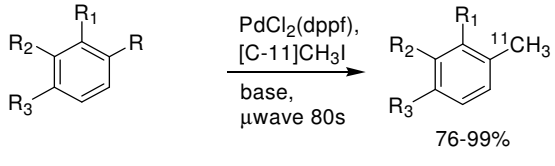
E.D. Hostetler and H.D. Burns.

Merck Research Laboratories, WP44C-2, PO Box 4, West Point, PA 19486, USA. Email: eric_hostetler@merck.com

Keywords: Carbon-11, Methyl Iodide, Suzuki Coupling, Microwave

A necessity in PET tracer discovery is integration of the radiolabel into an appropriately substituted compound. A methyl substituent on an aromatic ring is a common location for the introduction of a carbon-11 radiolabel into a potential PET tracer. Thus, [C-11]toluene derivatives are desirable C-11 labeled analogs. The most common strategy currently utilized for synthesizing [C-11]toluene derivatives is via Stille coupling of the corresponding aryl trialkyltin derivative. However, yields are often low, and most significantly, toxic tin by-products can be difficult to completely remove from the final product, which can be prohibitive for clinical studies. For these reasons, we have pursued the Suzuki coupling as an alternative route for the synthesis of [C-11]toluene derivatives. The boron-containing by-products of this reaction are considerably less toxic. Additionally, the Suzuki coupling should provide a much more robust synthetic method based on our previous success with the synthesis of [ω-^{11}C]fatty acids. (1)

In accordance with our expectations, the Suzuki coupling has proved to be a versatile method for the synthesis of a variety of functionalized aromatics. Both electron-rich and electron-poor aryl boronates couple with [C-11]methyl iodide quickly and with high efficiency. A wide variety of functional groups are tolerated, including esters, nitriles and halides. The effectiveness of the Suzuki coupling is not diminished by ortho substituents. Additionally, both aryl boronic esters and acids couple with high efficiency. The implementation of aryl boronic esters as precursors for the Suzuki coupling provides for a broader range of available precursors, allowing the synthesis of highly functionalized boronate precursors not accessible via the traditional metallation route used to synthesize aryl boronic acids. (2) Product yields are highest with the use of a microwave cavity, heating at 45 watts for less than two minutes. The microwave cavity has been incorporated into the platform of a Gilson SK233 liquid handler, which facilitates the automated synthesis and purification. Thermal heating also provides good product yields.



R = BPin or $B(OH)_2$
$R_{2,3}$ = H, R_1 = Br, CHO, NO_2
$R_{1,2}$ = H, R_3 = NHAc, OH, CO_2Me
R_1 = H, $R_{2,3}$ = OCH_3

In conclusion, the Suzuki coupling provides a robust, non-toxic alternative to the Stille coupling for the synthesis of functionalized [C-11]toluene derivatives from [C-11]methyl iodide.

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EXPERIENCE FROM TWO SYSTEMS FOR RECIRCULATING PRODUCTION OF [^{11}C]METHYL IODIDE FROM TARGET PRODUCED [^{11}C]METHANE

K. Någren[1], P. Truong[2], S. Helin[1], A. Amir[2] and C. Halldin[2]

[1]Radiopharmaceutical Chemistry Laboratory, Turku PET Centre, P.O. Box 52, FIN-20521 Turku, Finland, kjell.nagren@utu.fi [2]Karolinska Institutet, Department of Clinical Neurosciences, Psychiatry Section - Karolinska Hospital, S-17176 Stockholm, Sweden

Keywords: [^{11}C]methyl iodide, [^{11}C]methyl triflate, [^{11}C]methane, recirculation, [^{11}C]FLB 457

The original system for recirculating production of [^{11}C]methyl iodide was using [^{11}C]methane that was prepared from target produced [^{11}C]carbon dioxide (1). Recently, single pass production of [^{11}C]methyl iodide from target produced [^{11}C]methane with improved specific radioactivity (SRA) has been reported (2). This improvement of SRA was due to the direct in target production of [^{11}C]methane, the use of a single pass production method or a combination of both.

We have constructed two new systems (A and B) for the conversion of target produced [^{11}C]methane to [^{11}C]methyl iodide using recirculation and compared these two systems with two old systems using target produced [^{11}C]carbon dioxide, either via the LiAlH4/HI system (C) or a GEMS post target [^{11}C]methane/recirculating iodination system (D). SRA was measured on final [^{11}C]FLB 457 preparations (3). For the picomolar affinity radioligand [^{11}C]FLB 457 a SRA of 150 GBq/ mol is minimum if 200 MBq is injected into a human subject (4).

Systems A and C uses 5-40 min 10 A irradiations, whereas systems B and D uses 2-40 min irradiations at 10-60 A. The two new systems A and B uses a Valco 6-way/2 position valve to either load/unload or to recirculate the ^{11}C-gases, and two separate Porapak N traps for [^{11}C]methane and [^{11}C]methyl iodide. In the comparison of systems A and C, very similar total synthesis times and radiochemical yields (RCY) of final ^{11}C products were found. But the improvement of SRA for system A was nearly three-fold (200-400 versus 70-140 GBq/ mol). In the comparison of systems B and D, synthesis times where reduced by 5-10 min for B with similar RCY. The improvement of SRA for system B was in a similar order as reported above for system A. The replacement of 3 three-way valves (1) with the Valco 6-way/2 position valve facilitated automation. For heating of the Porapak N columns either air flow or RT water ([^{11}C]methane) and either an oven or heating bath ([^{11}C]methyl iodide) were used. At higher beam currents (20-60 A) the yield of [^{11}C]methane has been found to be dependent on hydrogen content in the target gas (5). We have compared 5% and 10% hydrogen in nitrogen as target gases. A 30-40% increase in amount of [^{11}C]methane produced was obtained after switching to 10% hydrogen.

In summary, direct production of [^{11}C]methane in target significantly improves SRA and reduces total synthesis time for ^{11}C-radiopharmaceuticals. An interesting observation is that the rise in SRA using [^{11}C]methane targets was slow, and optimal SRA was not expected to reach optimal until several hundreds of irradiations have been carried out. For both systems (especially B) SRA is still rising, so the reported values are sub-optimal.

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A NEW METHOD FOR TRAPPING [^{11}C]CARBON MONOXIDE AND ITS APPLICATION FOR THE SYNTHESIS OF PET RADIOPHARMACEUTICALS

H. Audrain[1], L. Martarello[2], A. Gee[2] and D. Bender[1]

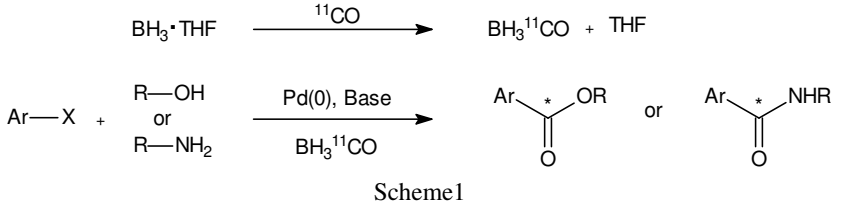
1: PET Center, Aarhus University Hospital, Nørrebrogade 44, DK-8000 Aarhus C, Denmark, e-mail: helene@pet.auh.dk
2: GlaxoSmithKline, Addenbrooke's Centre for Clinical Investigations, Addenbrooke's Hospital, Cambridge CB2 2GG, UK

Keywords: PET; radiolabelling; carbon-11; carbon monoxide; carbonylation

Introduction: Carbonyl groups are found in numerous of compounds possessing biological activity. The labelling of group functionalities like esters, amides, or carbamates with [^{11}C]CO would allow the evaluation of many new potential radiopharmaceuticals for the identification and characterization of drug binding sites in the brain, thanks to positron emission tomography (PET).

Only few research groups have succeeded in routinely using [^{11}C]CO for the production of PET radiopharmaceuticals, as it is the case with $^{11}CH_3I$ for the methylation of alcohols or amines. This limited use is due to the difficulty of trapping [^{11}C]CO in a small volume of organic solvent, and to its low reactivity. By recirculating [^{11}C]CO through the reaction media, or concentrating and enclosing [^{11}C]CO in a microautoclave at high pressure, carbonyl groups can be incorporated into organic molecules (1). In any case these techniques require a high degree of automation. We present here a new method for the trapping of [^{11}C]CO based on the formation of a [^{11}C][H_3BCO] complex and its behavior in a palladium coupling reaction. The [H_3BCO] complex is already known to be an *in situ* CO source in aqueous solution and a standard reagent in technicium chemistry (2).

Chemistry: [^{11}C]CO, prepared by reduction of [^{11}C]CO_2 on zinc, is first trapped in molecular sieves in liquid nitrogen and then released with a flow of nitrogen, and carried into a solution of BH_3•THF. The [^{11}C][H_3BCO] complex thus formed is carried by the flow of nitrogen and is directly bubbled into the reaction flask containing an aryl halide, a nucleophile (alcohol or amine), a base and a palladium(0) catalyst. Subsequently, the coupling reaction takes place at elevated temperature: esters or amides are then obtained (scheme 1).



Scheme1

Results and discussion: The use of BH_3•THF drastically increased the trapping efficiency of [^{11}C]CO in a solution containing $Pd(PPh_3)_4$, compared to the trapping done without the use of BH_3•THF. More over, it was possible to use the [^{11}C][H_3BCO] for carbonylation reactions avoiding autoclaving process. Applying this new technique, it was possible to make some standard coupling reactions, like the formation of phthalide from 2-bromobenzyl alcohol.

Conclusion: The simple approach described above allows the realization of carbonylation reactions catalyzed by palladium at ambient pressure. Since very little automation is demanded, the method can potentially make [^{11}C]CO chemistry more accessible in a routine way.

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