^{11}C-C BOND FORMATION BY PALLADIUM-MEDIATED CROSS COUPLING OF ALKENYLZIRCONOCENES WITH [^{11}C]METHYL IODIDE

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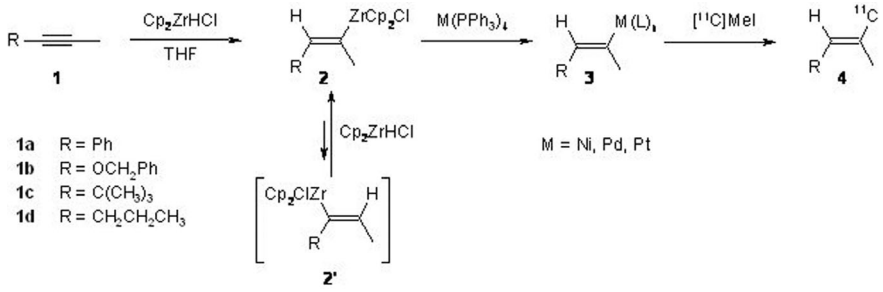
The prenyl group is known as an important structural building block in natural and medicinal products. The isotopic substitution of one of the two methyl groups with a [^{11}C]methyl group would provide an access to a large number of interesting ^{11}C-labelled compounds. Here we report a strategy for the synthesis of ^{11}C-labelled prenyl group-containing derivatives starting from methyl-substituted alkynes (**1**) via a novel ^{11}C-C bond forming reaction. A commonly employed strategy to form α,α'-disubstituted alkenes comprises the formation of alkenylzirconocenes by the syn-insertion of a C-C triple bond into the Zr-H bond of Schwartz reagent [$Cp_2Zr(H)Cl$] followed by metal-mediated C-C bond formation with electrophiles under retention of the configuration of the C-C douple bond [1,2].

In principle the formation of alkenylzirconocenes by syn-addition of Schwartz reagent onto disubstituted alkynes (**1**) leads to a mixture of regioisomers **2 and 2′**. However, treatment of an excess of Schwartz reagent favors the formation of the sterically less hindered isomer **2**. Transmetalation with transition metal complexes $M(PPh_3)_4$ and conversion with [^{11}C]MeI leads to compound **4**. Fig. 1. Reaction sequence: Hydrozirconation, transmetalation, methylation with [^{11}C]MeI.

First preliminary investigations were performed using 1-phenyl-1-propyne (**1a**) as a simple model. After treatment with 1.2 equiv. of Schwartz reagent in THF at room temperature 5 mol%



$M(PPh_3)_4$ (M = Ni, Pd, Pt) were added and [^{11}C]MeI was distilled into the solution. The mixture was heated at 60°C for 5 min. Ni or Pt complexes provided only 4% and 11% of **4a**, whereas sufficient radiochemical yields of up to 70% could be obtained when $Pd(PPh_3)_4$ was used. These reaction conditions were successfully applied to other methyl-substituted alkynes (**1b-1d**) to give the desired ^{11}C-labelled alkenes (**4b-4d**) in radiochemical yields ranging from 55-80%.

In conclusion we have developed a novel method for ^{11}C-C bond formation enabling the convenient synthesis of ^{11}C-labelled prenyl group-containing compounds.

References:
[1] Wipf, P.; Jahn, H. Tetrahedron 1996, 52, 12853-12910.
[2] Negishi, E.; van Horn, D. E. J. Am. Chem. Soc. 1977, 99, 3168-3170.

Keywords: ^{11}C-C Bond Formation, Carbon-11 Methyl Iodide, Alkenylzirconocenes

LABELLING *VIA* FREE RADICAL CARBONYLATION USING ^{11}CO

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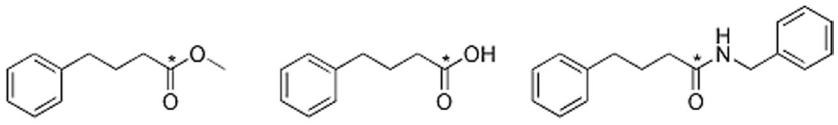
Many compounds exhibiting pharmacological effects contain aliphatic carboxy, carboxamide or ester groups. Some of the compounds may be of interest for PET provided they are easily accessible synthetically. The possibility of labeling a given tracer at the carbonyl position, as alternative to O- or N-methylation, may be useful due to metabolic properties of the tracer.[1] The use of the multistep Grignard and nitrile syntheses is limited mostly to the synthesis of carboxylic acids and also with regard to tolerable functional groups. Palladium-mediated chemistry has limited use with aliphatic halides due to facile β-elimination.

Recently we showed the application of photoinitiated free radical carbonylation using [^{11}C]carbon monoxide to the rapid labeling synthesis.[2] To extend further the scope of the radical-mediated carbonylation thermally initiated systems were explored.

The results of the preliminary experiments are summarized in the table:



1 2 3

compound	solvent	convn of ^{11}CO (%)	yield (%)[a]
1	THF / methanol	39	26
2	THF / water	48	28
3	THF	30	19

[a]decay-corrected radiochemical yield

The labeling syntheses were performed in an microautoclave at 40 MPa, with a temperature gradient 30 to 100°C for 6 min. Tris(trimethylsilyl)silane in combination with AIBN were used for the generation of radicals. Stannyl compounds, which were reported as superior radical mediators for this transformation,[3] were avoided due to their toxicity and difficulties with purification. Markedly, under the employed conditions amines, water and alcohols showed more uniform reactivity without addition of bases. In contrast, at photoinitiation conditions amines are more reactive, but to achieve good yields of acids and esters it was necessary to use hydroxide and alkoxides.

These preliminary data are encouraging and the method will be explored further. Thermally initiated free radical carbonylation should be advantageous in situations where photoirradiation may cause isomerizaton or undesirable side reactions. The further advantage is possibility to perform labeling synthesis on the equipment regularly used for palladium carbonylations.

[1] As in the case of WAY-100635: Pike, V. W.; McCarron, J. A.; Lammertsma, A. A.; Osman, S.; Hume, S. P.; Sargent, P. A.; Bench, C. J.; Cliffe, I. A.; Fletcher, A.; Grasby, P. M. *Eur. J. Pharmacol.* **1996,** R5-R7.

[2] Itsenko, O.; Kihlberg, T.; Långström, B. *J. Org. Chem.* **2004,** 4356-4360.

[3] (a) Ryu, I. *Chem.Soc. Rev*. **2001**, 30, 16-25. (b) Ryu, I.; Nagahara, K.; Kambe, Sonoda, N.; Kreimerman, S.; Komatsu, M. *Chem. Commun*. **1998**, 1953-1954.

Keywords: Carbon-11 Carbon Monoxide, Radical Carbonylation, Acids, Esters, Amides

SYNTHESIS OF [^{11}C]OXAZOLIDONE IN AN ISOCYANATE INTERMEDIATE RHODIUM-MEDIATED CARBONYLATION REACTION USING [^{11}C]CARBON MONOXIDE

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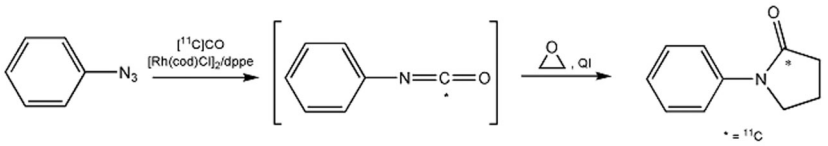
The increasing need of pharmaceutically interesting tracers for PET investigation has resulted in the demand of new synthetic strategies for labelling with ^{11}C ($t_{1/2}$=20.3 min). From that perspective, the synthesis of [^{11}C]isocyanate from [^{11}C]carbon monoxide was explored due to their big potential as intermediates in a wide event of reactions[1]. A rhodium-mediated carbonylation reaction starting from azide compound and [^{11}C]carbon monoxide was successfully set up for the synthesis of diphenyl[^{11}C]urea and ethyl phenyl[^{11}C]carbamate[2]. To form the [^{11}C]isocyanate, it was assumed that the nitrene produced as a reaction intermediate from azide compounds, would react with [^{11}C]carbon monoxide in the presence of a transition metal complex such as Rh complex to form the [^{11}C]isocyanate or a [^{11}C]isocyanate-coordinated Rh complex as a possible intermediate. The latter complex would be expected to have a similar reactivity to isocyanates. [^{11}C]Oxazolidone was synthesized using a similar procedure, phenyl azide was mixed in dioxane together with the complex formed *in situ* by the mixture of Chloro(1,5-cyclooctadiene)rhodium(I) dimer ([Rh(cod)Cl]$_2$) and 1,2-bis(diphenylphosphino)ethane (dppe), in the presence of [^{11}C]carbon monoxide. The [2+2] cycloaddition could proceed by introducing ethylene oxide into the reaction mixture.



Tetrabutylammonium iodide (QI) was mixed to a solution of ethylene oxide in DMF. The resulting mixture was added to a solution containing the azide and the Rh complex, and finally the resulting mixture was added to the [^{11}C]carbon monoxide reactor[3]. The reaction was carried at 190 °C for 5 min.

Using this method, [^{11}C]oxazolidone was synthesized in 93 % analytical radiochemical yield and 94 % trapping efficiency.

References

1. Ulrich H., *Chemistry and Technology of Isocyanates*, John Wiley & Sons, 1996.
2. Doi H., Barletta J., Suzuki M., Noyori R., Watanabe Y. and Långström B., *Org. Biomol. Chem.* 2004; 2; 3063-3066.
3. Kilhberg T; Långström B; *Method and apparatus for production and use of [^{11}C]carbon monoxide in labeling synthesis*, International PCT-pending patent. Application number: PCT/SE02/01222.

Acknowledgement: International pending patent. Application number: PH0389-3.

Keywords: [^{11}C]oxazolidone, [^{11}C]carbon Monoxide, Isocyanate

A NEW CARBON-11 LABELLING METHOD USING [^{11}C]-MONOORGANOTIN REAGENT

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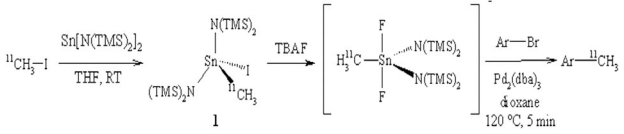
The palladium mediated Stille reaction using [^{11}C]-iodomethane has proved to be an important route for the development of radiotracers[1]. However, preparation of an aryltrialkylstannane as starting material is not always straightforward and difficulties for toxic tin by-product elimination might be encountered. For these reasons, the use of original [^{11}C]-methylstannane[2] and the Suzuki reaction[3] have been proposed as attractive alternative approaches.

Monoorganotins have been showed to be very reactive in Stille coupling reaction, allowing the transfer of allyl, alkyl, aryl, vinyl, alcynyl and benzyl groups onto an aryl or vinyl moiety[4]. They are less toxic than di-, tri- and tetra-alkylstannane[5] and inorganic by-products after hydrolysis can be easily removed. Since such a reagent is readily prepared from Lappert's stannylene[6] ($Sn[N(TMS)_2]_2$) and an alkyl/aryl halide, we anticipated the possibility of synthesizing [^{11}C]-monomethyltin reagent **1** from [^{11}C]-iodomethane (Fig. 1), and developing the rapid transfer of the ^{11}C- methyl group onto aromatic or heteroaromatic structures. 2-Bromonaphthalene and several bromoquinolines were chosen as model compounds.

The strategy we developed was as follows. [^{11}C]-Iodomethane was distilled into a solution of Lappert's stannylene in THF. Formation of the intermediate **1** was complete and immediate. After addition of tetrabutylammonium fluoride (TBAF) and evaporation of THF, the aromatic halide and Pd_2dba_3 in dioxane were added, and the mixture was heated for 5 min at 120 °C. Yields for the ^{11}C-methyl transfer were established by radioTLC and ranged from about 40-80% depending of the aromatic substrate (Fig. 2).

In conclusion, this new ^{11}C-labelling reaction was found efficient and fast. Its scope for the ^{11}C-labelling of polyfunctional molecules have been examined[7].

1. for example Karimi F., Langström B. *J. Label. Compd. Radiopharm.*, **2002**, *45*, 423-434.
2. Forngren T., Samuelsson L., Langström B. *J. Label. Compd. Radiopharm.*, **2004**, *47*, 71-78.
3. Hostetler E. D., Burns H. D. *J. Label. Compd. Radiopharm.*, **2003**, *46*, S1-S403.
4. Fouquet E., Pereyre M.,. Rodriguez A. L, *Synlett*, **1998,** 1323 and *J. Org. Chem*., **1997,** *62*, 5242-5243.
5. Smith P. J. in *Health and safety aspect of tin chemicals, Chemistry of Tin*, **1998,** Ed. PJ Smith, Chap 11.
6. Lappert M. F., Misra M. C., Onyszchuk M., Rowe R. S.,. Power P. P,. Slade M. J. *J. Organomet. Chem.,* **1987,** 330.
7. Bourdier T., Huiban M., Sobrio F., Perrio C., Barré L., *Tetra- or mono-organotin reagents in the stille reaction for the labelling of E potential radiotracers with carbon-11:comparative study*, 16th ISRC, Iowa City, **2005**.



ArBr	$^{11}CH_3$ - Incorporation	ArBr	$^{11}CH_3$ - Incorporation
	41 % ± 3		69 % ± 2
	77 % ± 2		63 % ± 14
	78 % ± 5		65 % ± 12

Keywords: Carbon-11, Monoorganotin, Stille Coupling Reaction

PRELIMINARY STUDIES OF CONDUCTING HIGH LEVEL PRODUCTION RADIOSYNTHESES USING MICROFLUIDIC DEVICES

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Current automated systems are needlessly large relative to the very small amounts of reagents and radioactivity used. Consequently, microfluidic devices (MFD) can be used to conduct radiosyntheses on a scale more amenable for radiotracer production. Our group and other workers in the field have recently reported that enhanced reaction rates can be achieved using MFD under experimental conditions (1, 2, 3, 4). This work examined the feasibility of conducting radiosynthesis of 2-deoxy-2-[F-18]fluoro-D-glucose ([F-18]FDG) at a high level of radioactivity using an MFD system incorporated in an automated synthesis system. The preparation of [F-18]FDG was based on the stereo specific synthesis of nucleophilic fluorination employing 1,3,4,6-tetra-O-acetyl-2-O-trifluoromenthanesulfonyl-β-D-mannopyranose (triflate) as a precursor (5) followed by basic hydrolysis to remove the acetyl groups of the protected form (6).

A fully automated [F-18]fluoridation synthesis system was developed for use with the MFD. The system was controlled via a laptop integrated to a PLC (Beckhoff). The automated synthesis system consisted of a drying vessel for use in the conventional drying of [F-18]fluoride and three pumps for introducing reagents into the MFD. The pumps were used to transfer reagents at a flow rate of 50 μL/min. A single MFD was used to perform the two-stage [F-18]fluoridation and deprotection steps for the synthesis of 2-[F-18]FDG. The MFD was interfaced to the system via fused silica capillaries. Localised heating (70 °C) of the MFD for the [F-18]fluoridation step was achieved via a novel electrode etched on a glass substrate. The electrode MFD was positioned to the underside of the two-stage MFD and powered from a high voltage supply.

Starting radioactivity of non-carrier added [F-18]fluoride was 1Ci. The system used a conventional drying method where aliquots of acetonitrile were added from a reservoir and concentrated to dryness. The anhydrous [F-18]fluoride was resuspended in 500μL acetonitrile and transferred back into the reservoir. Two additional reservoirs were filled with 500μL triflate solution and 0.5M NaOH during the set-up steps. All three lines from the reservoirs to the MFD were primed with the respective reagents. [F-18]Fluoridation was achieved by diffusive mixing of the dry [F-18]fluoride solution and the triflate solution at 70 °C in ~ 6s. The deprotection step was performed at room temperature via the reaction between TA-[F-18]FDG and 0.5M NaOH in ~ 3s. 2-[F-18]FDG was recovered from the MFD and analysed by radio-HPLC.

Non-optimised radiochemical yields for high level production were 15% - 20%. Reaction times for radiosynthesis on the MFD were <20 seconds. Work is in progress to optimise the reaction parameters, rate of synthesis and product yield. These results have shown that high level production 2-[F-18]FDG can be conducted on an MFD. No significant product change was observed when comparing results obtained with high and low levels of starting radioactivity.

References

1. Brady F., Luthra S. K., Gillies J. M. and Jeffery N. T. (2003) WO 03/078358
2. Jeffery N.T., Luthra S. K., Manz A., DeMello A., Wooton R and Brady F. (2004) Proceedings of the SNM 51st Annual Meeting, 51P
3. Gillies J. M., Chimon G. N., Smethurst G. J., Perrie W. and Zweit J. (2004) Proceedings of the SNM 51st Annual Meeting, 109P
4. Lu S., Watts P., Chin F.T., Hong J., Musachio J.L., Briard E., Pike V.W. (2004) Lab Chip, 4: 523-525
5. Hamacher K., Coenen H. H. and Stocklin G. J (1986) Nucl Med, 27: 235-238
6. Füchtner F., Steinbach J., Mäding P. and Johannsen B. (1996) Appl Radiat Isot, 47: 61-66

Keywords: Microfluidics, Automation, FDG

MICRO-FLUIDIC RADIOCHEMISTRY FOR PET AND SPECT TRACER DEVELOPMENT

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Nanotechnology, the miniaturization of macroscale processes and devices, offers distinct advantages to PET radiochemistry. In particular, the intrinsic reduction in resources and logistics required for PET radiochemical preparations.

Microfluidic, technologies are capable of controlling and transferring tiny quantities of liquids which allow chemical and biochemical assays to be integrated and carried out on a small scale. Such technologies could potentially have advantages over current methods of radiochemical synthesis.

The design and fabrication of a simple microfluidic reactor, to generate adequate mixing and transfer of reactants was carried out in house. The microreactor was constructed from 3 layers of thermally bonded soda-lime glass (15 x 15 x 1 mm) using standard photolithographic techniques. The microreactor disc was 10 mm in diameter and 0.1 mm deep. The middle and bottom plates were etched using 50% HF solution to give the mixing discs. The top plate had three 1 mm holes drilled to form the inlets. This gave a total internal volume of 16.0uL. The central mixing disc was connected via 0.1 mm channels to the three inlets. The inlets were connected, via fused silica capillaries, to external reagent reservoirs (PEEK HPLC loops, 200uL) linked to a nitrogen gas manifold (51.4 ccmin-1 flowrate). This generated a back pressure of $6.0x10^4$ Nm^{-2} which was enough to drive the contents of the three reagent reservoirs through the microreactor at a flowrate of 250 $uLmin^{-1}$. The bottom and reactor plates were then aligned and a 1mm diameter hole 5 mm deep drilled horizontally into the interface between the bottom and reactor plates to act as placement for the outlet.

Here we present preliminary data on a number of applications of a microfabricated system to radiosynthesis. To provide proof of principle, we have investigated the radiolabelling of small and large molecules using a microfabricated device. These applications involved the radiolabelling of the SPECT imaging agents hydroxyl diphosphinate (HDP) Oxidronate and macroaggregated albumen (MAA) with ^{99m}Tc, radioiodination of the apoptosis marker Annexin-V, the nucleosides ^{124}I-5-deoxyuridine (IUdR) and [^{124}I]5-iodo-1-(2-deoxy-2-fluoro-b-D-arabinofuranosyl)uracil (FIAU) using Iodine-124, and the radiosynthesis of 2-deoxy-2-[^{18}F]fluoro-D-glucose from a mannose triflate precursor with fluorine-18 and hence provide a test bed for microfluidic reactions.

We demonstrate the rapid radioiodination of the protein Annexin V (40% radiochemical yield within 1 min), the direct radioiodination of the nucleoside ^{124}I-5-deoxyuridine (30% radiochemical yield within 10 seconds) and [^{124}I]5-iodo-1-(2-deoxy-2-fluoro-b-D-arabinofuranosyl)uracil (70% radiochemical yield in 10 seconds), both at ambient temperature. Rapid radiofluorination of 2-deoxy-2-[^{18}F]fluoro-D-glucose (60% radiochemical yield) was achieved within 4 seconds using a polymer micro-reactor. Chromatographic analysis showed that the labelling efficiency of the microfluidic chip is comparable to conventional radiolabelling reactions.

Taken together, these preliminary results demonstrate the feasibility of microfluidic radiochemistry, and the preliminary data presented here indicate similar reaction yields of the two methods. Further studies based on modelling and experimental validation are necessary for optimisation of the device.

Keywords: Microfabrication, Nanotechnology, Radiosynthesis