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Synthesis of ^{11}C-labelled Alkyl Iodides

Using Non-thermal Plasma and Palladium-mediated Carbonylation Methods

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Abstract

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Compounds labelled with ^{11}C (β^+, $t_{1/2}$ = 20.4 min) are used in positron emission tomography (PET), which is a quantitative non-invasive molecular imaging technique. It utilizes computerized reconstruction methods to produce time-resolved images of the radioactivity distribution in living subjects.

The feasibility of preparing [^{11}C]methyl iodide from [^{11}C]methane and iodine via a single pass through a non-thermal plasma reactor was explored. [^{11}C]Methyl iodide with a specific radioactivity of 412 ± 32 GBq/μmol was obtained in 13 ± 3% decay-corrected radiochemical yield within 6 min via catalytic hydrogenation of [^{11}C]carbon dioxide (24 GBq) and subsequent iodination, induced by electron impact.

Labelled ethyl-, propyl- and butyl iodide was synthesized, within 15 min, via palladium-mediated carbonylation using [^{11}C]carbon monoxide. The carbonylation products, labelled carboxylic acids, esters and aldehydes, were reduced to their corresponding alcohols and converted to alkyl iodides. [1-^{11}C]Ethyl iodide was obtained via palladium-mediated carbonylation of methyl iodide with a decay-corrected radiochemical yield of 55 ± 5%. [1-^{11}C]Propyl iodide and [1-^{11}C]butyl iodide were synthesized via the hydroformylation of ethene and propene with decay-corrected radiochemical yields of 58 ± 4% and 34 ± 2%, respectively. [1-^{11}C]Ethyl iodide was obtained with a specific radioactivity of 84 GBq/mmol from 10 GBq of [^{11}C]carbon monoxide. [1-^{11}C]Propyl iodide was synthesized with a specific radioactivity of 270 GBq/mmol from 12 GBq and [1-^{11}C]butyl iodide with 146 GBq/mmol from 8 GBq.

Palladium-mediated hydroxycarbonylation of acetylene was used in the synthesis of [1-^{11}C]acrylic acid. The labelled carboxylic acid was converted to its acid chloride and subsequently treated with amine to yield *N*-[*carbonyl*-^{11}C]benzylacrylamide. In an alternative method, [*carbonyl*-^{11}C]acrylamides were synthesized in decay-corrected radiochemical yields up to 81% via palladium-mediated carbonylative cross-coupling of vinyl halides and amines. Starting from 10 ± 0.5 GBq of [^{11}C]carbon monoxide, *N*-[*carbonyl*-^{11}C]benzylacrylamide was obtained in 4 min with a specific radioactivity of 330 ± 4 GBq/μmol.

Keywords: isotopic labelling, carbon-11, alkyl iodides, acrylamides, specific radioactivity, carbonylation, carbon monoxide, non-thermal plasma, PET

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List of papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. **[^{11}C]Methyl iodide from [^{11}C]methane and iodine using a non thermal plasma method.** Jonas Eriksson, Johan Ulin, Bengt Långström *J Labelled Compd Radiopharm*, *In press*

II. **Synthesis of [1-^{11}C]ethyl iodide from carbon monoxide and its application in alkylation reactions.** Jonas Eriksson, Gunnar Antoni, Bengt Långström *J Labelled Compd Radiopharm* **2004**, *47*, 723-731.

III. **Synthesis of [1-^{11}C]propyl and [1-^{11}C]butyl iodide from [^{11}C]carbon monoxide and their use in alkylation reactions.** Jonas Eriksson, Gunnar Antoni, Bengt Långström *J Labelled Compd Radiopharm* **2006**, *49,* 1105-1116.

IV. **Synthesis of [^{11}C]/(^{13}C)acrylamides *via* palladium-mediated carbonylation.** Jonas Eriksson, Ola Åberg, Bengt Långström *Eur J Org Chem*, *In press*

V. **[1-^{11}C]Ethyl iodide and [1-^{11}C]propyl iodide in the synthesis of two potential NK_1-receptor ligands and initial PET-imaging.** Stina Syvänen, Jonas Eriksson, Tove Genchel, Örjan Lindhe, Gunnar Antoni, Bengt Långström, *Manuscript*

Related patent applications

Eriksson J, Långström B, Antoni G. Methods to Prepare Carbon-Isotope Organohalides with High Specific Radioactivity from Carbon-Isotope Monoxide, International patent application, publication date Sep. 29, 2005, WO2005090267

Eriksson J, Kihlberg T, Uhlin J, Långström B. Non Thermal Plasma Method to Prepare [^{11}C]Methyl iodide from [^{11}C]Methane and Iodine, US patent application, submitted on Dec. 14, 2005, US 60/750132

Kihlberg T, Långström B, Ferm T, Eriksson J. Methods and Apparatus for Production and Use of [^{11}C]Carbon Monoxide in Labeling Synthesis, International patent application, publication date Jan. 26, 2006, WO2006008603

Contents

Definitions and conventions

The following definitions and conventions are used throughout this thesis.

The term *labelled compound* refers to a mixture of an isotopically unmodified compound with one or more analogous isotopically substituted compound(s).

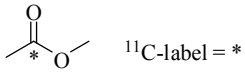
Radiochemical purity is defined as the percentage of the total radioactivity present in the specified chemical form.

Yields noted as *analytical radiochemical yields* are based on the initial amount of radioactivity at the start of the synthesis, the final amount of radioactivity in the crude reaction mixture and the radiochemical purity of the product. The yields are decay-corrected.

Yields noted as *radiochemical yields* are based on the initial amount of radioactivity at the start of the synthesis, the radioactivity of the isolated product and the radiochemical purity. The yields are decay-corrected.

The term *specific radioactivity*, expressed in Bq/mol, is defined as the radioactivity of a labelled compound divided by the molar amount of the compound.

Nomenclature of the labelled compounds:



methyl [*carbonyl*-^{11}C]acetate
or methyl [1-^{11}C]acetate

Abbreviations

AC	Alternating current
CT	Computerized tomography
DMF	*N*,*N*-Dimethylformamide
DNPH	2,4-Dinitrophenylhydrazine
eV	Electron volt
FDG	Fluoro-2-deoxy-D-glucose
HPLC	High-performance liquid chromatography
MeV	Mega electron volt
MPa	Mega Pascal
NMR	Nuclear magnetic resonance
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
PET	Positron emission tomography
p-TsOH	*p*-Toluenesulfonic acid
RCY	Radiochemical yield
RCP	Radiochemical purity
SUV	Standardized Uptake Value
THF	Tetrahydrofuran
p	Proton
α	Alpha-particle

Introduction

In this thesis two synthetic methods have been utilized for the synthesis of ^{11}C-labelled alkyl iodides. The aim was to develop reliable synthetic methods to provide the labelled compounds with high radiochemical yield and specific radioactivity. [^{11}C]Methyl iodide was synthesized using plasma chemistry (Paper I). Palladium-mediated carbonylation was used in the synthesis of [1-^{11}C]ethyl iodide (Paper II), [1-^{11}C]propyl iodide and [1-^{11}C]butyl iodide (Paper III). The alkyl iodides can be used as alkylating agents in the production of tracers for use in positron emission tomography (PET). Palladium-mediated carbonylation was also used in the synthesis of [*carbonyl*-^{11}C]acrylamides (Paper IV). [1-^{11}C]Ethyl iodide and propyl iodide were applied in the synthesis of potential NK_1-receptor ligands used in initial PET-imaging (Paper V).

Positron emission tomography

PET is a non-invasive *in vivo* molecular imaging technique based on the use of compounds labelled with short-lived positron-emitting radionuclides. The labelled compounds, called tracers, are administered in man or animal to study biochemical or physiological processes. Most endogenous substances and other biologically active compounds contain a carbon atom in a position suitable for isotopic labelling. As a consequence, ^{11}C with a half-life of 20.4 min has become a universally used radionuclide in PET-studies. The ^{11}C-radionuclide decays by the transformation of a proton into a neutron and with the emission of a positron and a neutrino, Figure 1.

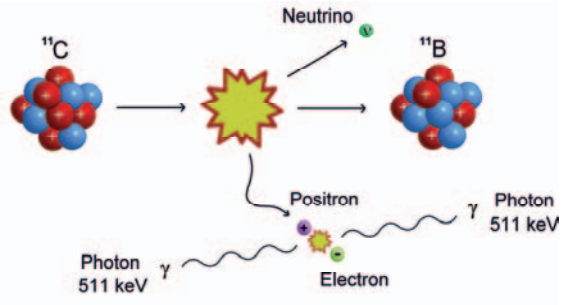


Figure 1. Radioactive decay of ^{11}C.

When the positron encounters an electron, the two particles are annihilated and converted into two photons (511 keV) travelling in opposite directions. A PET-camera detects the photons in coincidence and the collected data may be used to construct time-resolved three-dimensional images showing the distribution and concentration of the radionuclides in the subject under study. Other commonly used radionuclides in addition to ^{11}C are ^{15}O ($t_{1/2}$ = 2 min), ^{13}N ($t_{1/2}$ = 10 min), ^{68}Ga ($t_{1/2}$ = 68 min) and ^{18}F ($t_{1/2}$ = 110 min). PET is increasingly used in combination with computerized tomography (CT), a technique that provides excellent anatomical information.

PET has proved to be a useful clinical tool in oncology and neurology for the study of cancer,[1-3] epilepsy,[4] stroke, Alzheimer's[5] and Parkinson's[6] disease. In cardiology it is used for example in the evaluation of myocardial blood flow and metabolism in patients with coronary artery disease.[7]

PET is also becoming a useful tool in the development of new pharmaceutical drugs, since it can supply essential data related to pharmacokinetics and pharmacodynamics.[8] The technology can for example be used to assess whether a drug reaches the target organ at an effective concentration or to study drug interactions with enzymes and receptors. The high sensitivity of PET enables trace amounts of the labelled drug to be administered. This means that the biological system can be studied with minimal perturbation and the risks associated with toxicity compared to therapeutic doses are reduced. Hence PET may be used in an effective drug discovery process that allows rapid development from *in vitro* and *in vivo* animal studies to human investigations.[9, 10]

Strategies in ^{11}C-labelling of PET-tracers

The short half-life of the radionuclide is a factor to consider when developing methods for labelling with ^{11}C. As a rule of thumb, the labelling synthesis and purification of an ^{11}C-labelled PET-tracer should not take longer than three half-lives, i.e. about 60 min, otherwise the radioactivity and the specific radioactivity[I] of the tracer may be too low for a PET-study. Consequently, it is desirable to incorporate the radionuclide as late as possible in the synthetic sequence. The reaction time should be as short as possible, hence a sufficiently high rate of product formation is required so as to not compromise the radiochemical yield.[11]

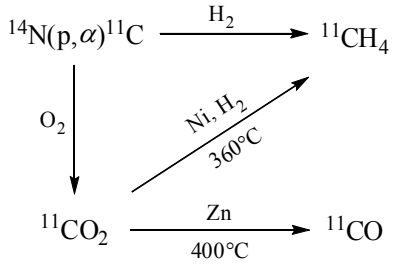
The specific radioactivity is of importance for example in receptor imaging, where the tracer should only occupy small fractions of the available receptor binding sites and yet the administered radioactivity must be sufficient to complete the PET-scan with good statistical data. All sources of isotopic dilution should be minimized in order to maximize the specific

[I] For definition refer to the Definitions paragraph.

radioactivity. Isotopic dilution may occur during the radionuclide production due to impurities in the target gas and the release of isotopically unmodified carbon from the target holder. Further isotopic dilution could occur later in the synthetic sequence, as for example in the synthesis of carboxylic acids from Grignard reagents and [^{11}C]carbon dioxide, where atmospheric carbon dioxide may participate in the reaction. Ambient atmospheric components such as carbon dioxide can to some extent be prevented from entering the reaction by using closed reaction systems. If an impurity contained in a chemical reagent contributes to the isotopic dilution, an increase in the specific radioactivity can be achieved by reducing the amount of the reagent. However, the most important factor for achieving high specific radioactivity is the choice of synthetic strategy. For example, methods that utilize ^{11}C-labelled precursors that are less common in the environment than carbon dioxide, e.g. carbon monoxide, cyanide or methane, usually give products with higher specific radioactivity than methods that utilize labelled carbon dioxide. Technical solutions may open up new labelling opportunities and allow for downscaling of the reaction volumes. An automated system would reduce the exposure of radiation to the user and potentially increase the reproducibility of the syntheses.

Production of ^{11}C and low molecular weight precursors

The most frequently used nuclear reaction for the production of ^{11}C is ^{14}N(p,α)^{11}C.[12, 13] A particle accelerator, e.g. a cyclotron, is used for the irradiation of nitrogen gas. The ^{11}C-species formed is highly reactive and by mixing small amounts of oxygen (0.05-1.0%) in the nitrogen, [^{11}C]carbon dioxide is obtained as the main labelled product, Scheme 1.[14]

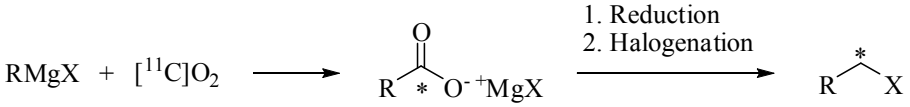


Scheme 1. [^{11}C]Methane and [^{11}C]carbon monoxide are accessible from [^{11}C]carbon dioxide *via* on-line processes.

[^{11}C]Methane is produced by proton irradiation on nitrogen gas containing hydrogen or *via* the catalytic hydrogenation of [^{11}C]carbon dioxide.[15] [^{11}C]Carbon monoxide is accessible from [^{11}C]carbon dioxide, *via* reduction over zinc at 400ºC.[15]

Common methods for the synthesis of [^{11}C]alkyl iodides

There are two frequently used production methods for [^{11}C]methyl iodide, one is based on the reduction of [^{11}C]carbon dioxide with lithium aluminium hydride and subsequent conversion to [^{11}C]methyl iodide with hydriodic acid.[16, 17] The obtained radiochemical yield is high, while the specific radioactivity suffers from isotopic dilution derived from the reaction of isotopically unmodified carbon dioxide and lithium aluminium hydride. This method has been modified for example by applying the lithium aluminium hydride suspension as a film on the inner surface of a tubing.[18] The other method, the gas-phase method, utilizes [^{11}C]methane and iodine in a reaction initiated at 720°C.[19, 20] The relatively low conversion yield of [^{11}C]methane in a single pass through the heated reactor can be increased to 60 ± 20% by trapping the formed [^{11}C]methyl iodide while recirculating the unreacted [^{11}C]methane.[21, 22] Commercially available gas-phase methyl iodide apparatus require about 12 min for a synthesis.[23] Two single pass gas-phase systems have been reported to give [^{11}C]methyl iodide in 44% and 50% radiochemical yield and with specific radioactivities of 440 GBq/μmol and 4700 GBq/μmol, respectively.[24, 25]



Scheme 2. Synthesis of ^{11}C-labelled alkyl halides from [^{11}C]carbon dioxide and a Grignard reagent.

Higher alkyl halides such as [^{11}C]ethyl iodide, [^{11}C]propyl iodide, [^{11}C]isopropyl iodide and [^{11}C]butyl iodide have been synthesized using [^{11}C]carbon dioxide and a Grignard reagent as shown in Scheme 2.[16, 26-34] Isotopic dilution originating from carbon dioxide in the environment is a potential drawback of the Grignard method. Careful preparation and handling of the Grignard reagent is required in order to maximize the specific radioactivity.

PET-tracer synthesis using ^{11}C-alkylating agents

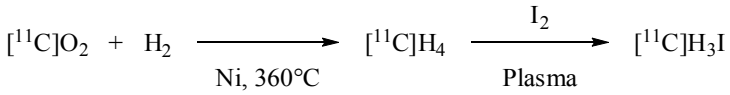
[^{11}C]Methyl iodide is predominantly used for incorporating ^{11}C *via* the alkylation of compounds containing oxygen, sulphur and nitrogen nucleophiles.[11, 35-38] Formation of carbon-carbon bonds using [^{11}C]methyl iodide is accomplished with metal-mediated reactions.[39, 40] [^{11}C]Methyl triflate, a methylating agent with a higher reactivity, is accessible from [^{11}C]methyl iodide *via* treatment with silver triflate.[41, 42] The higher labelled alkyl iodides have also been used in alkylation reactions although not as frequently as [^{11}C]methyl iodide.[16, 26, 28-32]

The alkylation of primary amines using ^{11}C-labelled alkyl halides typically proceeds without the formation of tertiary amines or quaternary ammonium salts. The labelled alkyl halides are obtained in minute amounts, usually under 100 nmol. Hence, by using amine in large excess, e.g. 100-1000 times, mono alkylation can be achieved. The use of reagents in large excess, compared to the labelled precursor, can also speed up the reaction and increase the yield.

A library of ^{11}C-labelled alkyl iodides, e.g. methyl, ethyl, propyl, isopropyl, butyl iodide, can be utilized in alkylation reactions to label a series of analogues, each representing an incremental change in physical properties. The labelled alkyl halides can thus be used for tuning the properties of a tracer, for example the brain penetration may be increased by changing the lipophilicity of the tracer molecule.[34, 43, 44] The passage through the cell membrane that separates the brain from the vascular space, the blood-brain barrier, can occur *via* diffusion or *via* carrier-mediated and receptor-mediated transport.[45] Consequently, the alkyl chain length of analogous compounds can influence the brain penetration due to a change in diffusion rate. The octanol-water partition coefficient (log P_{oct}), is a measurement of the lipophilicity and may be used as a rough prediction whether a compound is able to diffuse through the lipophilic blood-brain barrier. In some cases it may also predict the relative biological activity for homologous compounds which structurally only differ in alkyl chain lengths.[46]

Synthesis of [^{11}C]methyl iodide

A method for the preparation of [^{11}C]methyl iodide from [^{11}C]methane and iodine *via* electron impact using non-thermal plasma was developed based on the chemistry presented in Scheme 3.



Scheme 3. [^{11}C]Methyl iodide was prepared from [^{11}C]carbon dioxide *via* nickel catalyzed reduction and iodination initiated by electron impact.

Non-thermal plasma

Progress has been made in developing methods for the conversion of methane to low molecular weight hydrocarbons *via* electron impact using non-thermal plasma.[47-49]

Non-thermal plasma has non-equilibrium properties. While the gas temperature in the plasma may be close to room temperature, the free electrons can reach energies up to 10 eV.[50] The electrons are accelerated in an electric field and collisions with molecules initiate chemical reactions. To reach the same electron energy with plasma in equilibrium (thermal plasma), the temperature of the gas needs to be high. In thermal plasma the energy is divided equally between electrons, ions and neutral particles. This may lead to a breakdown of thermally unstable reactants or products. Although the gas temperature is low in non-thermal plasma, a mixture of radicals, excited species and ions are formed, often resulting in low product selectivity. This problem may be overcome by selecting appropriate reagents and reaction conditions.

Okumoto *et al.* demonstrated that methane in the presence of iodine was converted to methyl iodide with 95% selectivity in a single pass through a dielectric barrier discharge plasma reactor.[51] These findings inspired us to explore the possibility to convert [^{11}C]methane to [^{11}C]methyl iodide by use of non-thermal plasma in search for a method that would give higher yield and specific radioactivity than the current gas-phase methods. There are examples in the literature of non-thermal plasma being used specifically in

labelling reactions with ^{11}C, however, the full potential of the technique in this context has not yet been explored.[52, 53]

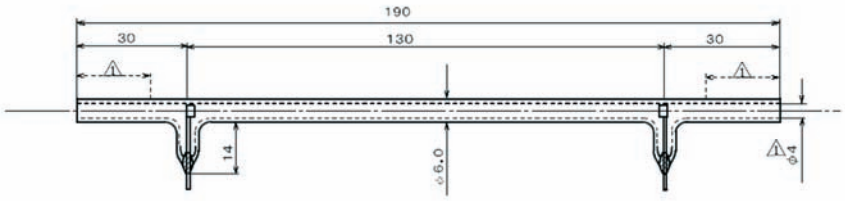


Figure 2. Glow discharge plasma reactor (mm). The electrodes were made of tungsten and the reactor body from quarts glass.

In our experiments glow discharge plasma was utilized. This type of non-thermal plasma is generated by applying a high voltage to electrodes in a gas at low pressure.[50] The plasma was sustained with 400 V AC and the power consumption was lower than 6 W. The reduced pressure enables homogenous excitation of the gas volume in the reactor, which then emits light. The reactor, depicted in Figure 2, generated small amounts of heat and the plasma could instantly be turned on or off.

[^{11}C]Methyl iodide

Hydrogen and nickel were used in the catalytic hydrogenation of [^{11}C]carbon dioxide, the conversion yield was approximately 90%. The formed [^{11}C]methane was converted to [^{11}C]methyl iodide in the system by a single pass through the non-thermal plasma reactor (Paper I). The set-up used in the experiments consisted of two reactors see Figure 3. [^{11}C]Carbon dioxide was trapped in the reduction reactor (A1) containing molecular sieves (4Å 60/80) and nickel powder. The reactor was flushed with hydrogen gas before it was closed and heated to 360ºC to facilitate the reduction of [^{11}C]carbon dioxide to [^{11}C]methane.[19] Unreacted [^{11}C]carbon dioxide was removed by an Ascarite trap (A2) and residual hydrogen was removed using palladium on aluminium oxide (A3). Water from the reaction of oxygen and palladium-hydride was removed on a column containing phosphorous pentoxide (A4). The [^{11}C]methane was transferred in a carrier gas to the plasma reactor (A7) by passing through the iodine feed (A6), thus mixing with the iodine before entering the plasma reactor. The produced [^{11}C]methyl iodide was collected in the CH_3I-Trap (A8) before being transferred to the reaction vial (A10). The high energy electrons in the plasma initiated the reaction which converted [^{11}C]methane to [^{11}C]methyl iodide, the mechanism of this reaction has not yet been studied. However, we assumed that free radicals of iodine were formed in the plasma which subsequently reacted with

[^{11}C]methane. It was not clear if the electron energy was high enough to directly ionize methane.

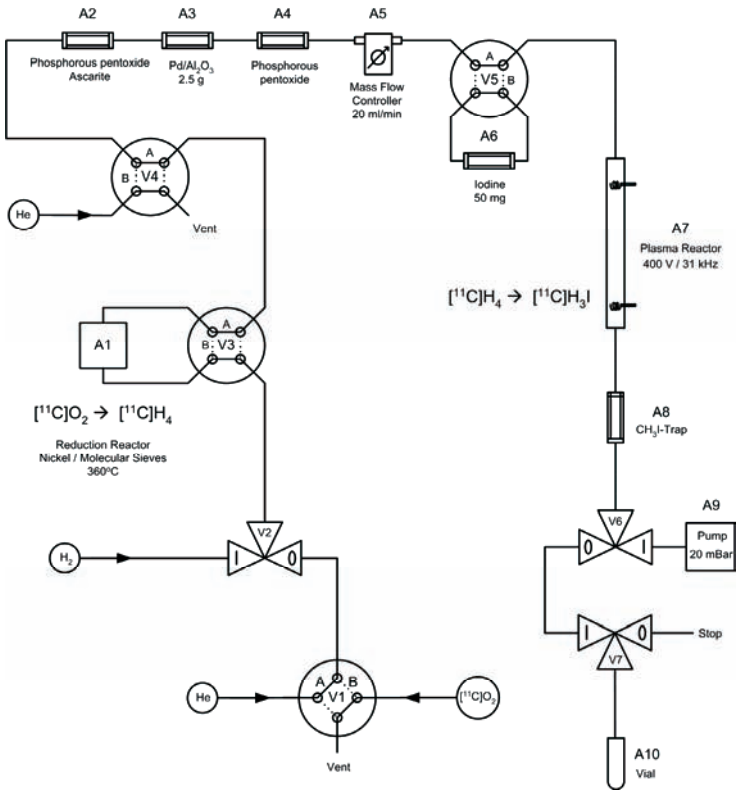


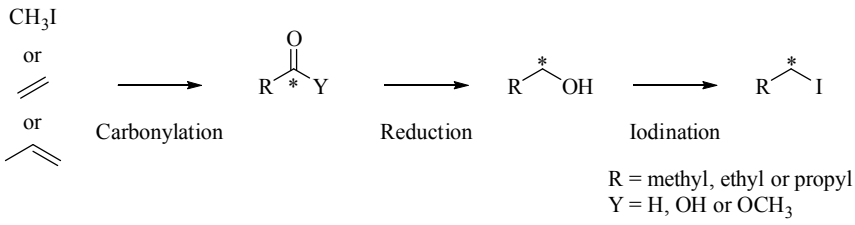
Figure 3. The experimental set-up used in the study.

Both neon and helium were utilized as carrier gases, with best results obtained using helium with the vacuum pump operated at 20 mbar and the mass flow through the plasma reactor regulated to 20 ml/min. When using these conditions [^{11}C]methyl iodide was obtained with a decay-corrected radiochemical yield of 13 ± 3% (number of experiments, n=12) based on the amount of [^{11}C]carbon dioxide at start of synthesis, the radiochemical purity was 64 ± 7% (n=5). By installing a column with phosphorous pentoxide before the vial (A10), the radiochemical purity was increased to 88 ± 7% (n=6). The procedure to convert [^{11}C]carbon dioxide and transfer the formed [^{11}C]methyl iodide to the vial required less than 6 min. A small amount of iodine was consumed in the system, 50 mg being sufficient for over 30 experiments.

[^{11}C]Methyl iodide with a specific radioactivity of 412 ± 32 GBq/μmol (n=2) was obtained from 24 GBq of [^{11}C]carbon dioxide. 2.0 ± 0.1 GBq of product was trapped in acetonitrile at -20ºC, the amount was 4.9 ± 0.6 nmol as determined by analytical HPLC.

Synthesis of higher [^{11}C]alkyl iodides

To overcome the limitations of Grignard reagents with respect to specific radioactivity, palladium-mediated carbonylation was explored for the synthesis of carboxylic acids and aldehydes followed by reduction and iodination to give the labelled alkyl iodides as shown in Scheme 4.

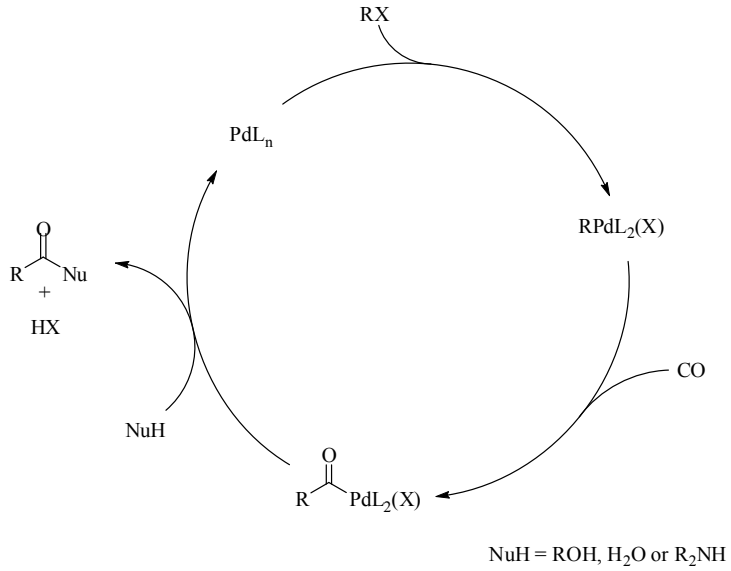


Scheme 4. Synthesis of labelled alkyl iodides via carbonylation.

Carbonylation using palladium

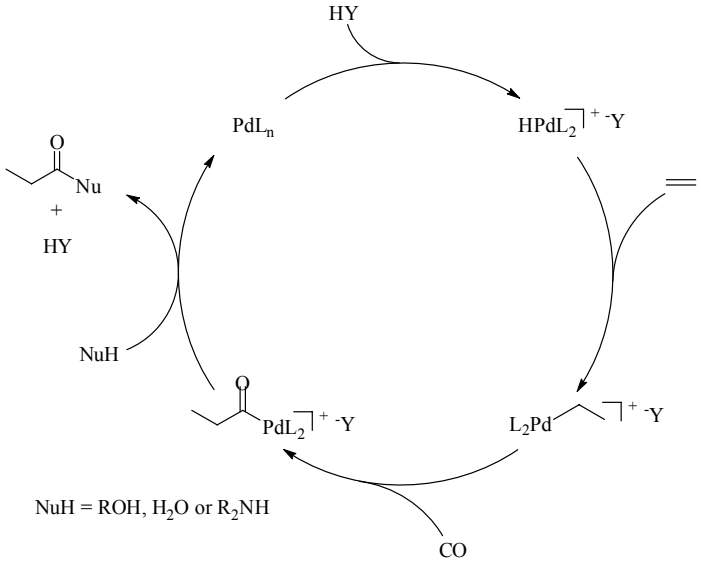
Palladium complexes have been used extensively in organic chemistry for the synthesis of carbonyl compounds *via* incorporation of carbon monoxide.[54, 55] Carboxylic acids, esters and amides are some of the products accessible *via* palladium-catalyzed carbonylation of olefins,[56, 57] alkynes[58, 59] and organic halides[60] using carbon monoxide at atmospheric pressure.

The catalytic cycle of palladium-catalyzed carbonylation of organohalides consists of three steps, Scheme 5.[54, 61, 62] The first step is the oxidative addition of the organohalide to Pd^0, carbon monoxide is then inserted into the carbon-palladium bond. In the last step, the reductive elimination, the product is cleaved off *via* nucleophilic attack on the carbonyl carbon. Commonly used nucleophiles are amines, alcohols and water. Olefin hydroxycarbonylation performed in an acidic medium starts with the formation of a palladium-hydride complex, as shown in Scheme 6, followed by the insertion of an alkene into the Pd-H bond.[63] Migratory insertion of carbon monoxide into the palladium-alkyl bond forms a palladium-acyl complex that, upon nucleophilic attack, is cleaved and a carbonyl compound is produced.



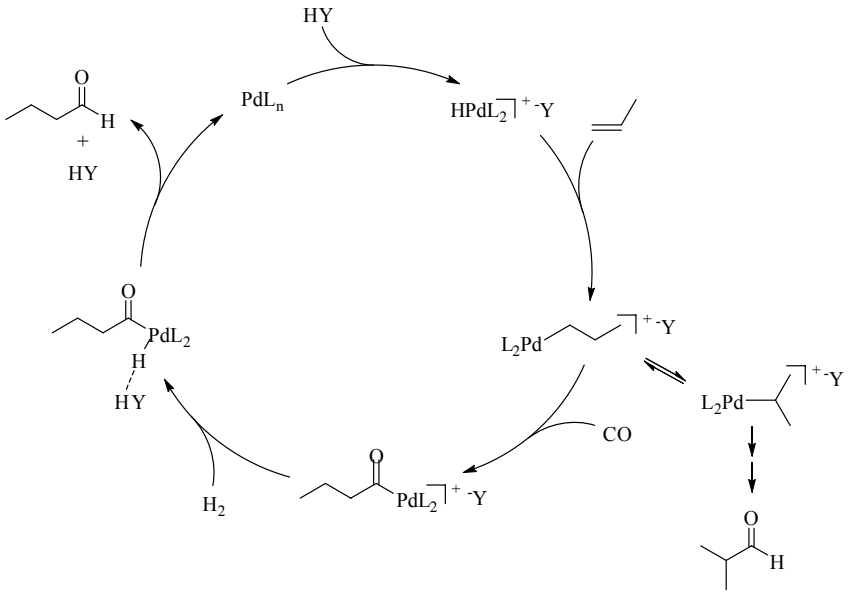
Scheme 5. Mechanism of palladium-catalyzed carbonylation of organohalides.

Transition-metal mediated carbonylation of olefins and acetylenes using [^{11}C]carbon monoxide have previously not been reported. Alkynes follow a similar mechanistic pathway in carbonylation reactions as olefins. However, the reactivity of alkynes is usually higher while the selectivity is often lower when compared to the olefins.



Scheme 6. Mechanism of palladium-catalyzed carbonylation of ethene.

Hydroformylation involves the addition of carbon monoxide and hydrogen to an alkene to form an aldehyde.[64] A mechanism for the hydroformylation of propene is shown in Scheme 7.



Scheme 7. Mechanism of palladium-catalyzed hydroformylation of propene. Carbonylation of α-olefins often yields a mixture of branched and linear products.

The use of palladium in the carbonylation of organohalides has successfully been adopted in labelling reactions using a few nmol of [^{11}C]carbon monoxide.[65-71] There are some central questions in carbonylation with [^{11}C]carbon monoxide which differ from the general scheme of transition metal catalyzed carbonylation. In conventional carbonylation the conversion yields of the substrates are optimized and the catalyst load is reduced to a minimum while in labelling the conversion of [^{11}C]carbon monoxide is optimized. Due to the low concentration of [^{11}C]carbon monoxide, approximately 25 nmol, an excess of the catalyst and the substrates is always used. The excess of palladium complex in relation to [^{11}C]carbon monoxide is believed to omit the possibility of repetitive turns in the catalytic cycle, hence the process is referred to as being *mediated* rather than *catalyzed* by the transition metal complex.

Despite the fact that carbon monoxide has been frequently used in general organic chemistry for a long time, the use of [^{11}C]carbon monoxide has been limited. This can be explained by the need in ^{11}C-labelling chemistry to use small amounts of the labelled precursor. The low concentrations of [^{11}C]carbon monoxide does not only affect the stoichiometry but also has an impact on its physical handling. Methods that bubble [^{11}C]carbon monoxide

through the reaction mixture are not efficient due to the low solubility of carbon monoxide in most solvents.[72] This problem may partly be solved by use of systems that circulate the [^{11}C]carbon monoxide in the reaction mixture.[65, 73] A method that has been shown to give carbonylation products in high radiochemical yields was developed by Kihlberg *et al*. This method was based on the confinement of [^{11}C]carbon monoxide and the carbonylation reagents in a small volume under high pressure, Figure 4.[66, 74]

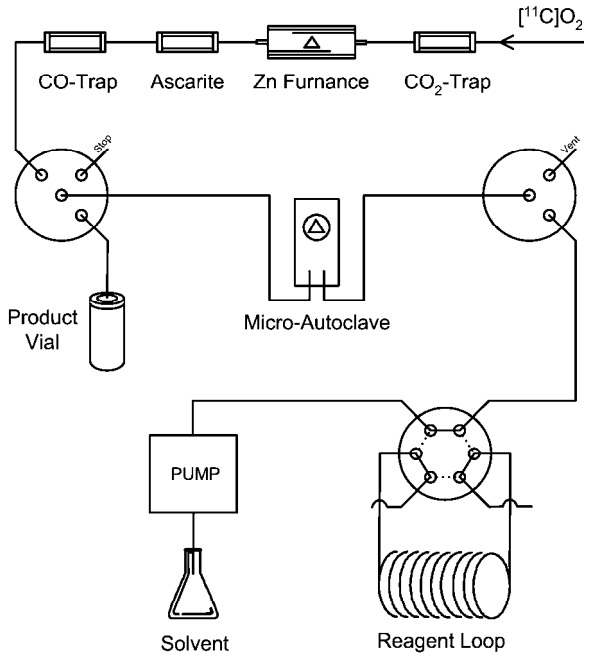
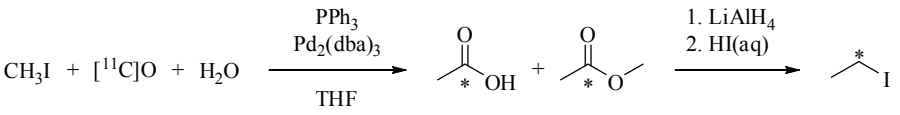


Figure 4. Schematic drawing of the experimental set-up used in the carbonylation reactions.

By use of the experimental set-up shown in Figure 4 [^{11}C]carbon dioxide is converted to [^{11}C]carbon monoxide. The gas volume containing the [^{11}C]carbon monoxide is reduced to a few μl at the CO-Trap before it is transferred to the micro-autoclave by an induced pressure difference in the system. Liquid reagents are transferred into the micro-autoclave at a high pressure resulting in the compression of the gas volume containing the [^{11}C]carbon monoxide from 200 μl to approximately 1 μl. The high pressure improves the solubility of [^{11}C]carbon monoxide, thus increasing the efficiency of the carbonylation reaction. The autoclave allows the use of an elevated reaction temperature beyond the boiling point of the reaction medium. The carbonylation reactions described in this thesis were carried out using this method, a detailed description of the functions of the apparatus can be found in patent literature and in Paper III.[74]

[1-^{11}C]Ethyl iodide

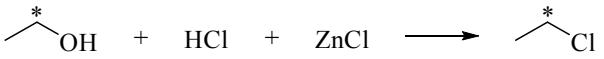
[1-^{11}C]Ethyl iodide was synthesized *via* carbonylation of methyl iodide followed by reduction with lithium aluminium hydride and iodination with hydriodic acid (Paper II). The active palladium complex used as the catalyst in the carbonylation reaction was generated from $Pd_2(dba)_3$ and triphenyl phosphine. $Pd_2(dba)_3$ and triphenylphosphine was used because of excellent shelf life and stability compared to some active Pd^0-complexes, e.g. tetrakis(triphenylphosphine)palladium(0).



Scheme 8. Synthesis of [1-^{11}C]ethyl iodide from [^{11}C]carbon monoxide.

A mixture of [1-^{11}C]acetic acid and methyl [1-^{11}C]acetate was obtained in the carbonylation reaction, Scheme 8. The labelled ester was assumed to originate from the alkylation of [1-^{11}C]acetic acid with methyl iodide. The [1-^{11}C]acid derivatives were reduced to [1-^{11}C]ethoxide by treatment with lithium aluminium hydride and the conversion of [1-^{11}C]ethoxide to [1-^{11}C]ethyl iodide was carried out with hydriodic acid. To achieve a good conversion of [1-^{11}C]ethoxide to [1-^{11}C]ethyl iodide it was important to thoroughly remove the tetrahydrofuran from the reaction mixture prior to the addition of the hydriodic acid. After the reaction was completed, the labelled ethyl iodide was carried in a stream of nitrogen to a reaction vessel where it was trapped in DMF. The transfer separated the labelled organohalide from non-volatile by-products. The radiochemical yield of [1-^{11}C]ethyl iodide trapped in DMF was 55 ± 5% based on [^{11}C]carbon monoxide. [1-^{11}C]Ethyl iodide accounted for 85 ± 5% of the transferred radioactivity and the only radiolabelled by-product detected was [^{11}C]methyl iodide. The position of the label was confirmed by ^{13}C-labelling and ^{13}C-NMR analysis.

The [1-^{11}C]ethanol was also utilized in the synthesis of [1-^{11}C]ethyl chloride by treatment with hydrochloric acid and $ZnCl_2$. [1-^{11}C]Ethyl chloride and [1-^{14}C]ethyl chloride were used for determining the kinetic isotope effect of the ethyl chloride–cyanide ion S_N2 reaction.[75, 76]



Scheme 9. Synthesis of [1-^{11}C]ethyl chloride from [^{11}C]ethanol.

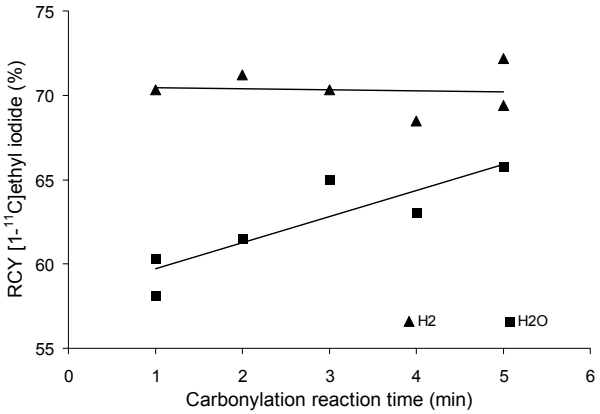
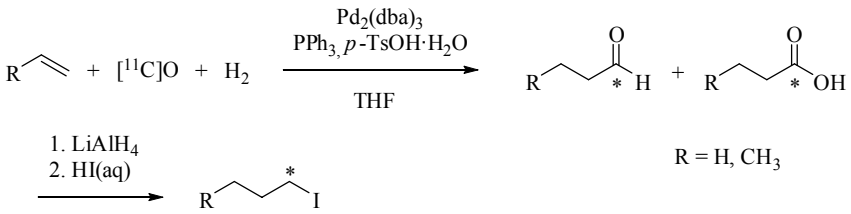


Figure 5. The impact on the radiochemical yield of [1-^{11}C]ethyl iodide when using different reaction times and either hydrogen or water in the carbonylation reaction.

Later experiments indicated that the use of hydrogen instead of water in the carbonylation reaction increased the radiochemical yield of the final product [1-^{11}C]ethyl iodide, Figure 5.

[1-^{11}C]Propyl iodide and [1-^{11}C]butyl iodide

In order to extend the labelling methodology to include higher labelled organoiodides than [1-^{11}C]ethyl iodide, routes to prepare [1-^{11}C]propyl iodide and [1-^{11}C]butyl iodide with high specific radioactivity from [^{11}C]carbon monoxide were investigated (Paper III). The first attempt to synthesize [1-^{11}C]propyl iodide *via* [1-^{11}C]propionic acid involved a minor modification of the carbonylation reaction described in the synthesis of [1-^{11}C]ethyl iodide. Methyl iodide was simply replaced with ethyl iodide in an effort to obtain [1-^{11}C]propionic acid. However, no desired product was obtained, probably due to rapid *β*-hydrogen elimination of the ethyl-palladium complex.[77] The second approach was olefin carbonylation. While olefin carbonylation has attracted much interest in the literature owing to its many applications,[55] no such reactions have previously been reported utilizing [^{11}C]carbon monoxide. Olefins form alkyl-palladium complexes *via* insertion into palladium-hydride bonds. While the complex formed using ethene or propene is still susceptible for *β*-hydrogen elimination, the elimination only leads to regeneration of the starting material. Since the olefin is not consumed by this side reaction it remains available for repeated reactions until the alkyl-palladium is trapped by insertion of carbon monoxide.



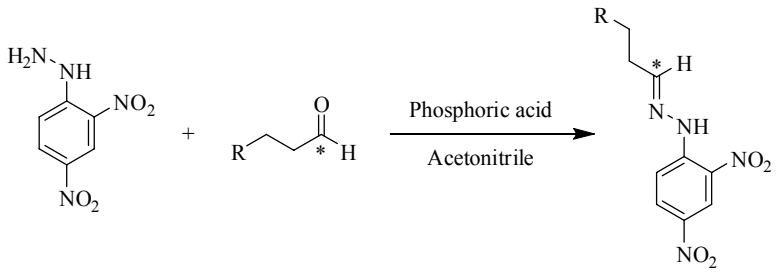
Scheme 10. Synthesis of [1-^{11}C]propyl iodide and [1-^{11}C]butyl iodide from [^{11}C]carbon monoxide.

The active palladium-hydride complex was generated in THF by treatment of $Pd_2(dba)_3$ with triphenylphosphine and *p*-TsOH monohydrate. The synthetic approach to [1-^{11}C]propyl and [1-^{11}C]butyl iodide is shown in Scheme 10. Hydrogen gas was used as a hydride source in the carbonylation reaction yielding labelled aldehyde; hence the reaction is referred to as hydroformylation. However, labelled carboxylic acid was also obtained most likely due to the presence of water, e.g. from the acid monohydrate.

The radiochemical yield of [1-^{11}C]propyl iodide was 58 ± 4% based on the amount [^{11}C]carbon monoxide in the autoclave at the start of the synthesis. [1-^{11}C]Propyl iodide accounted for 93 ± 4% of the transferred radioactivity. [1-^{11}C]Butyl iodide was obtained in 34 ± 2% yield and with a radiochemical purity of 79 ± 9%. The labelled propyl and butyl iodides were synthesized and transferred to DMF within 15 min. The only labelled by-product found was [^{11}C]methyl iodide.

A change from *p*-TsOH monohydrate to methyl sulfonic acid gave similar results. No desired product was obtained when hydrogen was used without sulfonic acid present. Acidic conditions without the addition of hydrogen resulted in the formation of labelled carboxylic acid but no aldehyde was obtained. These observations indicated that the aldehyde was formed *via* the insertion of the olefin into the palladium-hydride, generated by *p*-TsOH, followed by the insertion of [^{11}C]carbon monoxide into the palladium-carbon bond and finally by the reductive elimination induced by hydrogen. No branched product was obtained in the hydroformylation of propene, more than 95% selectivity towards the linear product using this catalytic system has recently been reported using high concentrations of carbon monoxide.[78]

The formylation reactions proceeded readily at a broad range of temperatures from room temperature to 70ºC, 60ºC was used throughout the experiments. The highest radiochemical yield for the formylation of ethene was obtained with 28 μmol of the olefin while the amount of propene used in the synthesis of [1-^{11}C]butyl iodide was 170 μmol, an equimolar amount of olefin and hydrogen was used. The identity of the labelled aldehydes were confirmed with analytical HPLC after derivatization with 2,4-dinitrophenylhydrazine as shown in Scheme 11.[79]



Scheme 11. Derivatization of the labelled aldehydes with DNPH.

The radiochemical purity of the propyl hydrazine derivative was 47% while the butyl derivative was obtained with a purity of 28%.

By-product formation and the water-gas shift reaction

[^{11}C]Methyl iodide was formed as a by-product in the synthesis of [1-^{11}C]ethyl iodide, [1-^{11}C]propyl iodide and [1-^{11}C]butyl iodide. The probable source was [^{11}C]carbon dioxide *via* the reduction with lithium aluminium hydride and the subsequent iodination with hydriodic acid. Since an ascarite column efficiently removed unreacted [^{11}C]carbon dioxide after the on-line reduction with zinc, the [^{11}C]carbon dioxide was assumed to derive from the reoxidation of [^{11}C]carbon monoxide in the micro-autoclave. Oxidation of [^{11}C]carbon monoxide may occur in the presence of Pd^{II} *via* the water-gas shift reaction, Scheme 12.[80-82]

$$[^{11}C]O + H_2O + L_2X_2Pd^{II} \longrightarrow [^{11}C]O_2 + 2\,HX + L_2Pd^0$$

Scheme 12. Pd^{II} induced water-gas shift reaction.

It is also possible that [^{11}C]carbon monoxide is oxidized to [^{11}C]carbon dioxide in the heterogeneous reaction with molecular oxygen on the surface of the micro-autoclave, Scheme 13.[83]

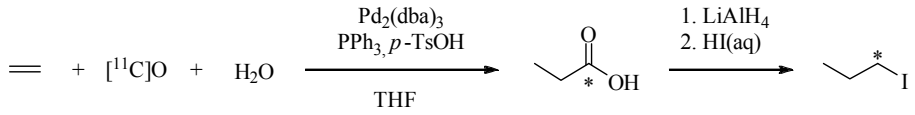
$$[^{11}C]O + \tfrac{1}{2}\,O_2 \xrightarrow{M} [^{11}C]O_2$$

Scheme 13. Catalytic oxidation of [^{11}C]carbon monoxide at metal surface.

Experiments were carried out to probe whether [^{11}C]carbon dioxide could be generated from [^{11}C]carbon monoxide in the micro-autoclave. A solution of THF and [^{11}C]carbon monoxide was heated in the micro-autoclave. This solution was then transferred to a vial containing an aqueous solution of sodium hydroxide to convert [^{11}C]carbon dioxide, if present, to carbonate. The radioactivity was measured and the solution was degassed to remove

[^{11}C]carbon monoxide. The amount of trapped radioactivity was then measured again. The solution was finally acidified to convert the [^{11}C]carbonate back to [^{11}C]carbon dioxide. After degassing the radioactivity was measured to confirm that the radioactivity was removed. With only THF and [^{11}C]carbon monoxide transferred to the micro-autoclave, the amount of trapped radioactivity in the hydroxide solution was 5-10%. Saturation of the THF with oxygen increased the amount of radioactivity trapped in the hydroxide solution to approximately 95%, experiments where Pd^{II} and water was added gave 70% trapping. These results support the hypothesis that [^{11}C]carbon monoxide may be oxidized to [^{11}C]carbon dioxide in the micro-autoclave, which then explains why [^{11}C]methyl iodide is formed as a by-product in the synthesis of the higher labelled alkyl halides.

Zudin *et al.* reported inhibition of the water-gas shift reaction at acidic conditions by the addition of hydrogen.[84] Accordingly, when water was used instead of hydrogen in the synthesis of [1-^{11}C]propyl iodide, as shown in Scheme 14, the radiochemical purity was significantly decreased from 93% to 75%. The radiochemical yield of [1-^{11}C]propyl iodide decreased moderately from 58% to 52% while the radiochemical yield of [^{11}C]methyl iodide increased from 4% to 13%.



Scheme 14. Synthesis of [1-^{11}C]propyl iodide from [^{11}C]carbon monoxide, ethene and water.

Contrary to when hydrogen was used, there was a strong temperature dependence with a maximum radiochemical yield of [1-^{11}C]propyl iodide at 70°C. The fact that the reaction did not occur readily at room temperature suggested a kinetically less favourable reductive elimination step. While an increase in the temperature was thought to favour the reductive elimination step, an increase in temperature was also likely to favour the β-hydrogen elimination of the palladium-ethyl complex. Only a small quantity of water was used in the experiments since the amount of lithium aluminium hydride used in the next reaction step needed to be increased proportionally.

Alkylation reactions

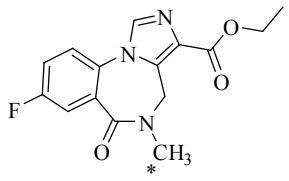


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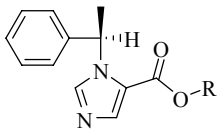
Figure 6. [*N-methyl*-^{11}C]Flumazenil

Flumazenil is a benzodiazepine antagonist and of interest as a PET-tracer for the study of epilepsy.[85, 86] [*N-methyl*-^{11}C]Flumazenil **(1)** was synthesized *via* methylation of *N*-desmethyl flumazenil utilizing [^{11}C]methyl iodide produced from [^{11}C]methane and iodide in the non-thermal plasma reactor. After preparative HPLC-purification, [^{11}C]flumazenil was obtained in 12% radiochemical yield based on [^{11}C]carbon dioxide.



2. R = [^{11}C]H_2CH_3
3. R = [^{11}C]$H_2CH_2CH_3$
4. R = [^{11}C]$H_2CH_2CH_2CH_3$

Figure 7. (*R*)-[*O-ethyl*-1-^{11}C]etomidate **(2)** and analogues.

Etomidate is a short acting intravenous anaesthetic agent used for the induction of general anaesthesia. It is of interest as a PET-tracer due to its selective interaction with the enzyme 11β-hydroxylase mainly found in the adrenal glands.[26] [1-^{11}C]Ethyl iodide, [1-^{11}C]propyl iodide and [1-^{11}C]butyl iodide were used in the labelling of etomidate and two analogues, Figure 7. Purified (*R*)-[*O-ethyl*-1-^{11}C]etomidate **(2)** was obtained within 40 min with a radiochemical yield of 45% from 2.5 GBq of [^{11}C]carbon monoxide. When starting with 10 GBq of [^{11}C]carbon monoxide, labelled etomidate was obtained with a specific radioactivity of 36 GBq/μmol. The propyl and butyl

analogues, **(3)** and **(4)** were isolated within 30 min with radiochemical yields of 37% and 27% respectively.

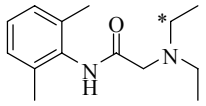


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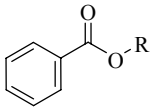
Figure 8. [*N-ethyl*-1-^{11}C]Lidocaine.

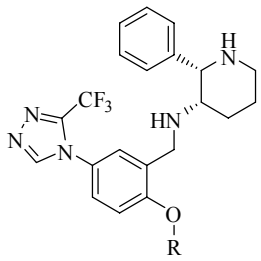
Lidocaine is used as an antiarrhythmic drug and as a local anaesthetic. [*N-ethyl*-1-^{11}C]Lidocaine[16] **(5)** was synthesized and isolated within 40 min with a radiochemical yield of 25% based on [^{11}C]carbon monoxide.



6. R = [^{11}C]$H_2CH_2CH_3$
7. R = [^{11}C]$H_2CH_2CH_2CH_3$

Figure 9. [1-^{11}C]Propyl benzoate and [1-^{11}C]butyl benzoate

Isolated [*O-propyl*-1-^{11}C]propyl benzoate **(6)** was obtained within 30 min with a radiochemical yield of 52% based on [^{11}C]carbon monoxide. When starting with 12 GBq of [^{11}C]carbon monoxide, [*O-propyl*-1-^{11}C]propyl benzoate was isolated with a specific radioactivity of 162 GBq/μmol. Starting from 8 GBq of [^{11}C]carbon monoxide, [*O-butyl*-1-^{11}C]butyl benzoate **(7)** was isolated with a specific radioactivity of 88 GBq/μmol within 30 min, the radiochemical yield was 26% based on [^{11}C]carbon monoxide.



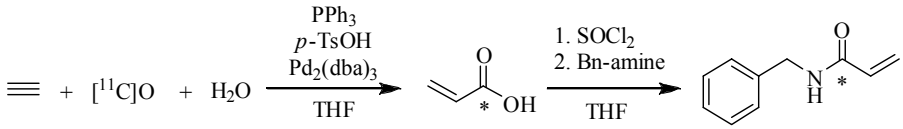
GR205171. R = CH_3
8. R = [^{11}C]H_2CH_3
9. R = [^{11}C]$H_2CH_2CH_3$

Figure 10. Labelled analogues of the NK_1-receptor antagonist GR205171.

Analogues of the NK_1-receptor antagonist GR205171 were synthesized *via* alkylation of desmethyl GR205171 with [1-^{11}C]ethyl iodide and [1-^{11}C]propyl iodide,[87] caesium carbonate was used as base.[88] The reaction was carried out without protective groups on the secondary amines. The selectivity for *O*-alkylation over *N*-alkylation was 1:7 for both compounds, hence the radiochemical yield was poor, 5.1 ± 0.6% **(8)** and 4.7 ± 0.8% **(9)** based on [^{11}C]carbon monoxide. However, the amount of radioactivity obtained was sufficient for PET-scans in rhesus monkey, see Paper V. The use of tetrabutylammonium hydroxide as base resulted in a lower radiochemical yield due to hydrolysis of the labelled alkyl halides and reduced selectivity for *O*-alkylation.

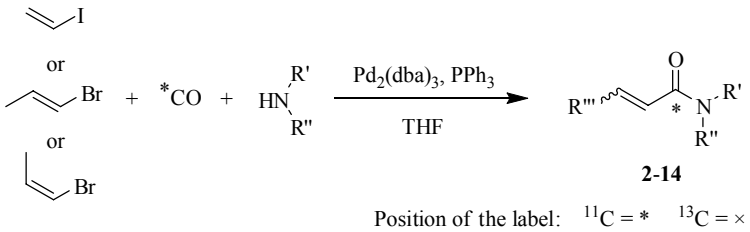
Synthesis of [^{11}C]/(^{13}C)acrylamides

The successful synthesis of labelled alkyl iodides from olefins gave the incentive to explore the use of acetylene in the production of [1-^{11}C]allyl iodide. [1-^{11}C]Acrylic acid was obtained in approximately 60% analytical radiochemical yield *via* carbonylation of acetylene. However, the conversion to [1-^{11}C]allyl iodide was not successful. Instead, effort was concentrated on the synthesis of [*carbonyl*-^{11}C]acrylamides according to the route shown in Scheme 15 (Paper IV). The acrylamide functionality is found in several biomedically interesting compounds.[89-93]



Scheme 15. *N*-Benzyl[*carbonyl*-^{11}C]acrylamide via hydroxycarbonylation of acetylene.

The [1-^{11}C]acrylic acid **(1)** was converted to its acid chloride using thionylchloride, treatment with benzylamine (82 μmol) gave *N*-benzyl[*carbonyl*-^{11}C]acrylamide **(2)** in 51 ± 4% analytical radiochemical yield based on [^{11}C]carbon monoxide (n=2). A second approach to synthesize ^{11}C-labelled acrylamides from vinyl halides and amines was explored according to Scheme 16.



Scheme 16. One-pot synthesis of [*carbonyl*-^{11}C]acrylamides from [^{11}C]carbon monoxide.

The active palladium catalyst complex was generated from palladium $Pd_2(dba)_3$ and triphenylphosphine in THF. Amine was added and the resulting solution was transferred to the micro-autoclave containing [^{11}C]carbon monoxide. The reagents were kept in the micro-autoclave at 110ºC for 4 min.

A significantly higher radiochemical yield of *N*-benzyl[*carbonyl*-^{11}C]acrylamide was achieved compared to the results obtained with the first approach using acetylene. At the same time the amine concentration was decreased to 1/20.

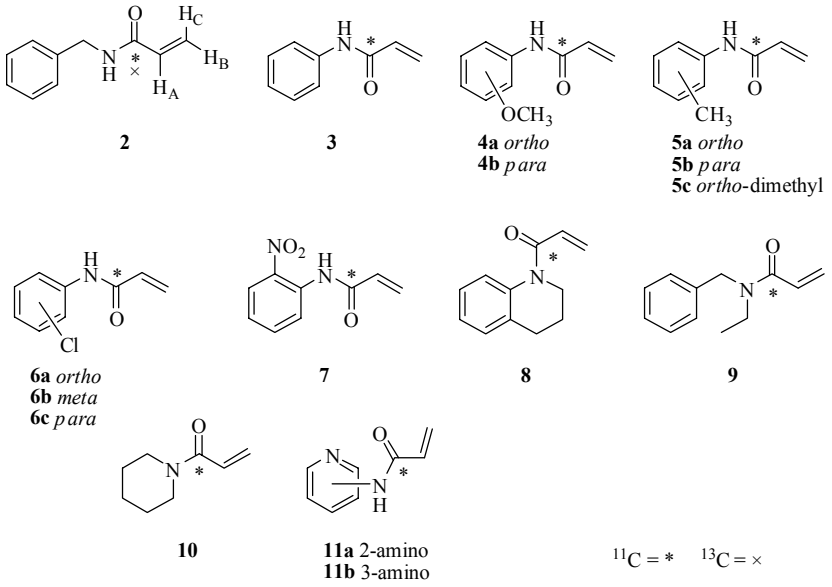


Figure 11. Products obtained from the aminocarbonylation of vinyl iodide.

In Figure 11 the labelled acrylamides are shown, the amines used in the aminocarbonylation ranged from activated and deactivated anilines to highly nucleophilic amines. The nucleophilicity of the amines corresponded well with the outcome of the reactions. The steric hindrance of *o*-substituents lowered the yield compared to *m*- and *p*-substituted anilines as illustrated in the synthesis of the mono- and disubstituted *N*-(methylphenyl)-acrylamides **(5a) – (5c)**, Table 1.

Table 1. Synthesis of [*carbonyl*-^{11}C]acrylamides *via* carbonylation of vinyl iodide.

Product	Nucleophile	μmol	*T* (°C)	[^{11}C]O conversion[a,b] (%)	Anal. RCY[b,c] (%)	RCY[b,d,e] (%)
2	Benzylamine	4.3	110	94 ± 2 (7)	87 ± 9 (5)	81 ± 3 (4)
3	Aniline	4.3	110	91 ± 5 (2)	84 ± 6 (2)	74 ± 6 (2)
4a	2-Methoxyaniline	4.3	110	-	-	71 ± 4 (2)
4b	4-Methoxyaniline	4.3	110	95 ± 2 (2)	86 ± 3 (2)	72 ± 2 (2)
5a	2-Methylaniline	4.3	110	94 ± 2 (2)	81 ± 2 (2)	65 ± 4 (2)
5b	4-Methylaniline	4.3	110	94 ± 1 (2)	89 ± 1 (2)	72 ± 2 (2)
5c	2,6-Dimethylaniline	4.3	110	92 ± 1 (3)	62 ± 4 (3)	52 ± 2 (2)
6a	2-Chloroaniline	4.3	110	81	21	-
6a	2-Chloroaniline	4.3	145	90	26	19
6a	2-Chloroaniline	19	145	85 ± 1 (2)	58 ± 4 (2)	51 ± 1 (2)
6b	3-Chloroaniline	4.3	110	95 ± 1 (3)	79 ± 6 (3)	63 ± 1 (3)
6c	4-Chloroaniline	4.3	25	88	55	49
6c	4-Chloroaniline	4.3	110	96 ± 3 (3)	82 ± 2 (3)	73 ± 1 (2)
7	2-Nitroaniline	4.3	110	90	0	0
7	2-Nitroaniline	22	150	81	0	0
8	1,2,3,4-Tetrahydro-quinoline	5.3	110	94 ± 3 (2)	77 ± 5 (2)	66 ± 4 (2)
9	*N*,*N*-Benzyl-ethylamine	4.3	110	92 ± 1 (2)	83 ± 1 (2)	75 ± 1 (2)
10	Piperidine	4.3	110	90 ± 1 (2)	86 ± 1 (2)	76 ± 1 (2)
11a	2-Aminopyridine	4.3	110	86 ± 4 (3)	48 ± 3 (3)	46 ± 2 (2)
11b	3-Aminopyridine	4.3	110	94 ± 1 (3)	74 ± 1 (3)	70 ± 1 (2)

[a] Decay-corrected conversion yield of [^{11}C]carbon monoxide to non-volatile products remaining in the reaction mixture after removal of solvent. [b] The number in brackets is the number of experiments. [c] Decay-corrected analytical radiochemical yield determined from the conversion yield and the radiochemical purity assessed with analytical HPLC. [d] Decay-corrected radiochemical yield based on the initial amount of radioactivity at the start of the synthesis and the radioactivity of the isolated product. The radioactivity of the crude product was measured after transfer from the micro-autoclave to an evacuated vial. The radioactive residues left in the micro-autoclave were estimated to be less than 1%. Hence, the amount of initial radioactivity could be determined. [e] Radiochemical purity was >97% in all experiments.

For all entries the amount of amine used was 4.3 μmol except for the weakly deactivated and sterically hindered *o*-chloroaniline, which gave **6a** in moderate yield using 19 μmol. It was noted that the reaction of *p*-chloroaniline proceeded even at room temperature although with lower radiochemical yield. The aminocarbonylation of *o*-nitroaniline did not give the desired product even though the temperature and concentration of the nucleophile was increased. The reaction with 2-aminopyridine gave a significantly lower yield than the less deactivated 3-aminopyridine in the synthesis of **(11a)** and **(11b)** respectively. [1-^{11}C]Acrylic acid was formed in the competing hydroxycarbonylation of vinyl iodide when the less reactive amines were used, probably due to minute amounts of water.

The aminocarbonylation of (*E*)-bromopropene and (*Z*)-bromopropene gave the compounds in Figure 12. The radiochemical yields are listed in Table 2. The same reaction time and temperature were used as for the aminocarbonylation of vinyl iodide.

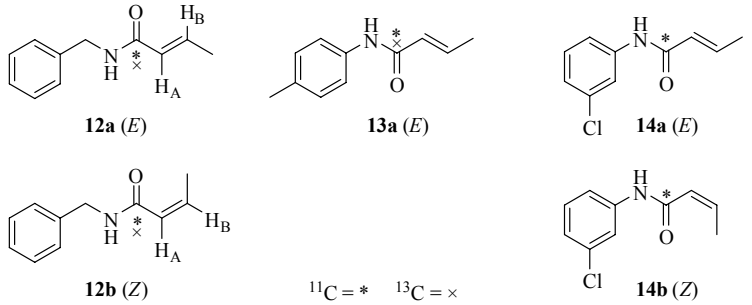
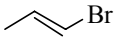
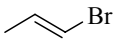
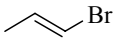


Figure 12. Products obtained via aminocarbonylation of (*Z*) and (*E*)-bromopropene.

The formation of products **(12) – (14)** proceeded with retention of configuration of the C=C double bond.[94] When reacted with a strong nucleophile such as benzylamine, both (*E*)-bromopropene and (*Z*)-bromopropene gave products in good radiochemical yields. When reacted with the less activated 3-chloroaniline the yields were lower although **(14a)** was obtained in significantly higher amounts compared to **(14b)**.

Table 2. Synthesis of [*carbonyl*-^{11}C]acrylamides via aminocarbonylation of (*E*)- and (*Z*)-bromopropene.

Product	Substrate	Nucleophile	*μ*mol	*T* (°C)	[^{11}C]O conversion[a] (%)	Anal. RCY[a] (%)	RCY[a] (%)
12a (*E*)		Benzylamine	4.3	110	82 ± 5 (2)	76 ± 5 (2)	72 ± 5 (2)
12b (*Z*)		Benzylamine	4.3	110	84 ± 2 (2)	73 ± 1 (2)	67 ± 1 (2)
13a (*E*)		4-Methylaniline	4.3	110	88 ± 3 (2)	81 ± 4 (2)	67 ± 3 (2)
14a (*E*)		3-Chloroaniline	4.3	110	85 ± 4 (2)	56 ± 6 (2)	41 ± 5 (2)
14b (*Z*)		3-Chloroaniline	4.3	110	76 ± 1 (2)	18 ± 2 (2)	16 ± 2 (2)

[a] For explanations see Table 1.

The compounds **(2)**, **(12a)**, **(12b)** and **(13a)** were co-labelled with ^{11}C and ^{13}C. By adding (^{13}C)carbon monoxide the total amount of carbon monoxide was scaled up from approximately 25 nmol to 44 *μ*mol. Consequently, the reaction time was prolonged and the amount of vinyl halide and benzylamine was increased. The co-labelling enabled confirmation of the labelled position by ^{13}C-NMR analysis, Figure 13.

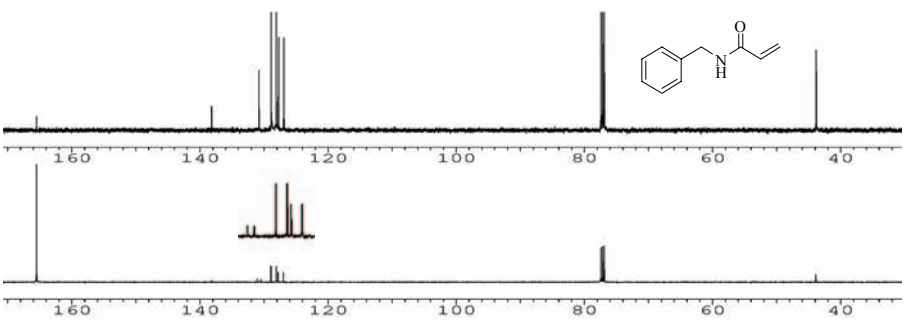


Figure 13. ^{13}C-NMR. Above: Isotopically unmodified reference compound. Below: *N*-benzyl(*carbonyl*-^{13}C)acrylamide **(2)** with a strong carbonyl signal and signal splitting of the carbon adjacent to the carbonyl carbon.

Compound **(14b)** was synthesized from the moderately basic 3-chloroaniline using carrier added [^{11}C]carbon monoxide. Triethylamine was needed in order to obtain enough amount of product for the characterization by ^{1}H-NMR analysis. The introduction of base reduced the number of radio-labelled products to a single product.

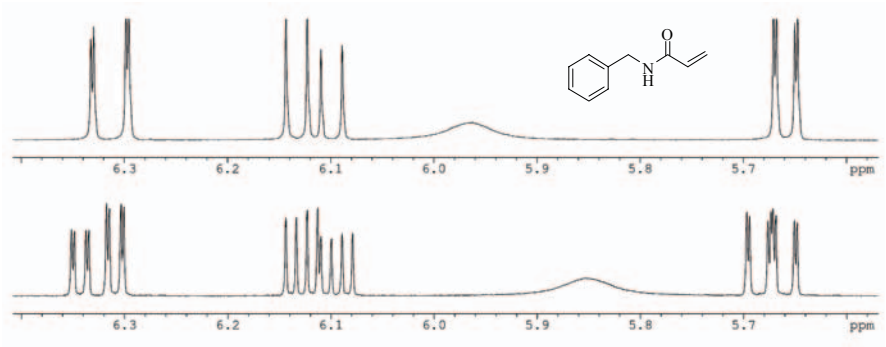


Figure 14. ^{1}H-NMR. Above: Isotopically unmodified reference compound. Below: *N*-benzyl(*carbonyl*-^{13}C)acrylamide **(2)** with additional $^{2}J_{C,H}$, $^{3}J_{C,H}$ and $^{4}J_{C,H}$ couplings.

When assessing the specific radioactivity, cyclotron bombardments of 10 μAh were made resulting in 10 ± 0.5 GBq of [^{11}C]carbon monoxide (n=2). After 20 min *N*-benzyl[*carbonyl*-^{11}C]acrylamide **(2)** was isolated with a radioactivity of 4.2 ± 0.3 GBq. The amount of product was 22 ± 1 nmol and the specific radioactivity was 330 ± 4 GBq/μmol at end of synthesis.

Specific radioactivity

High specific radioactivity of the labelled compound is desirable in PET-applications to avoid perturbation of the biological system under study. Aside from the time factor, which obviously is important for the specific radioactivity, the amount of radioactive material produced using the cyclotron influences the specific radioactivity of the final product. As shown in Figure 15, the specific radioactivity of (*R*)-[*O-ethyl*-1-^{11}C]etomidate was approximately proportional to the initial radioactivity used in the [1-^{11}C]ethyl iodide synthesis. However, this linearity breaks down when the radionuclide production approaches steady-state.

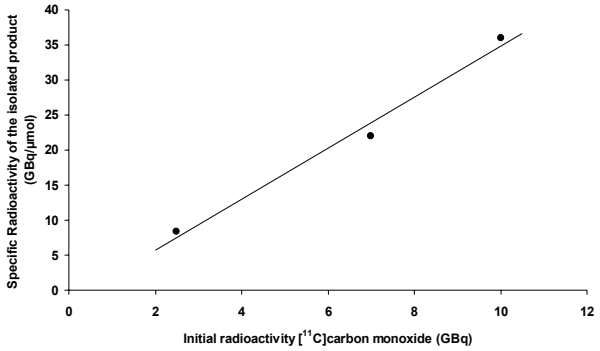


Figure 15. Specific radioactivity of isolated (*R*)-[*O-ethyl*-1-^{11}C]etomidate 40 min after start of synthesis plotted against the initial radioactivity of [^{11}C]carbon monoxide.

The specific radioactivities of the labelled alkyl iodides are listed in Table 3. These values are decay-corrected to the time when the alkyl iodides had been transferred to the reaction vial and were ready to be used in the alkylation reaction. When comparing the specific radioactivity obtained for [1-^{11}C]ethyl iodide, [1-^{11}C]propyl iodide and [1-^{11}C]butyl iodide, the values differ quite significantly from each other. The low value for [1-^{11}C]ethyl iodide can be explained by the fact that commercially available solutions of THF may contain up to 10 ppm acetic acid, resulting in up to 25 nmol of isotopically unmodified ethyl iodide. The higher specific radioactivity of [1-^{11}C]propyl iodide compared to [1-^{11}C]butyl iodide may be explained by ring opening of THF supported by the following observation; the temperature

Table 3. Specific radioactivity.

Alkyl iodide	Initial Radioactivity (GBq)	Synthesis time (min)	RCY (%)	Specific Radioactivity (GBq/μmol)	Paper
[^{11}C]Methyl iodide	24	6	13 ± 3	412 ± 32 (3)	I
[1-^{11}C]Etyl iodide	10	15	55 ± 5	87 ± 3[a] (2)	II
[1-^{11}C]Propyl iodide[b]	12.2	15	58 ± 4	270 ± 33[a] (3)	III
[1-^{11}C]Butyl iodide[b]	8.1	15	34 ± 2	146 ± 20[a] (3)	III
[1-^{11}C]Butyl iodide[c]	4.6	15	29 ± 2	43 ± 18[a] (3)	III
N-benzyl[*carbonyl*-^{11}C] acrylamide	10 ± 0.5	4	81 ± 3	330 ± 4 (2)	IV

[a] Value that was obtained from the analysis of the corresponding alkylated compound. [b] Evaporation of THF at 60°C prior to the addition of the hydriodic acid. [c] Evaporation of THF at 120°C prior to the addition of the hydriodic acid.

used in the evaporation of the THF prior to the addition of hydriodic acid influenced the specific radioactivity for [1-^{11}C]butyl iodide but not for [1-^{11}C]propyl iodide, Table 3. Heating the vial at 120°C rather than 60°C during the evaporation resulted in a significant increase of the amount of butyl iodide while there was a small change in the radiochemical yield, there is no clear explanation for this. However, it may indicate that excessive heating of minute amounts of THF in the presence of the lithium/aluminium salt may have resulted in ring opening of THF and formation of butoxide. The treatment of the alkoxide with hydriodic acid would then give butyl iodide. Conventional ether cleavage of THF by hydriodic acid may be a less likely source of the isotopic dilution since it should have resulted in the formation of 1,4-diiodobutane.[95]

Another factor that may affect the specific radioactivity of the higher alkyl iodides is the radiochemical yield of the reactions. However, this is true only if the isotopically modified product and the isotopically unmodified product originate from different chemical routes. For example in the case of [1-^{11}C]ethyl iodide; the radiochemical yield of the carbonylation reaction will influence the specific radioactivity if the isotopic dilution mainly originates from the isotopically unmodified acetic acid present as an impurity in the THF.

The specific radioactivity obtained for [1-^{11}C]ethyl iodide synthesized *via* carbonylation using [^{11}C]carbon monoxide was similar to the results reported using highly optimized Grignard methods; alkylated compounds synthesized using [1-^{11}C]ethyl iodide have been reported with specific radioactivities of up to 41 GB/μmol.[28, 33, 34, 96] The specific radioactivities of [1-^{11}C]propyl and [1-^{11}C]butyl iodide are significantly improved compared to previously reported results for higher alkyl iodides. Products obtained *via* alkylation with [1-^{11}C]propyl iodide or [2-^{11}C]isopropyl iodide have been reported with values up to 66 GBq/μmol.[33, 34]

The use of [^{11}C]alkyl iodides in the preparation of PET-tracers

The following examples demonstrate the use of ^{11}C-labelled alkyl iodides as building blocks in the synthesis of PET-tracers. Methyl-, ethyl- and propyl analogues were synthesized and used in PET-imaging in guinea pig, cynomolgus- and rhesus monkey.

Potential NK_1-receptor radioligands

There is a growing interest in the development of drugs for the Neurokinin-1 (NK_1) receptor system. The possible therapeutic areas of NK_1-receptor antagonists are not fully defined yet, but their potential as drugs is explored in a range of disorders, including emesis, pain, inflammation, depression and other psychiatric diseases.[87, 97-99] Previous studies has shown that the PET-radioligands [*O-methyl*-^{11}C]GR205171 and [^{18}F]SPA-RQ bind selectively to NK_1-receptors.[100-102] These two compounds are based on the same pharmacophore and display a very high affinity for the NK_1-receptor, hence they can be used for visualisation of the receptor system. However, due to slow dissociation from the receptor the compounds can not be used for detecting changes in Substance P levels. The latter is required when a new drug candidate's ability to enhance endogenous Substance P levels are investigated. It has been demonstrated that small changes in the structure of a receptor ligand can lead to changes in affinity and also in the ability to penetrate the blood-brain barrier.[34, 43] Thus, the aim of the study was to synthesize ethyl- and propyl analogues of [*O-methyl*-^{11}C]GR205171, Figure 10, and to compare the binding characteristics in guinea pig and rhesus monkey (Paper V).

The uptake of [*O-methyl*-1-^{11}C]GR205171 and the two analogues in guinea pig striatum was low. The maximum SUV-values in striatum were less than 1 at the end of the study. PET images obtained from the studies in two rhesus monkeys are shown in Figure 16. [*O-methyl*-^{11}C]GR205171 and the two analogues were transported into the brain in a much higher extent than in the guinea pigs. The SUV values for [*O-methyl*-^{11}C]GR205171 did not decline during the 90 min scan indicating that the binding was

irreversible during the investigation time. This was in accordance with earlier reported results.[100]

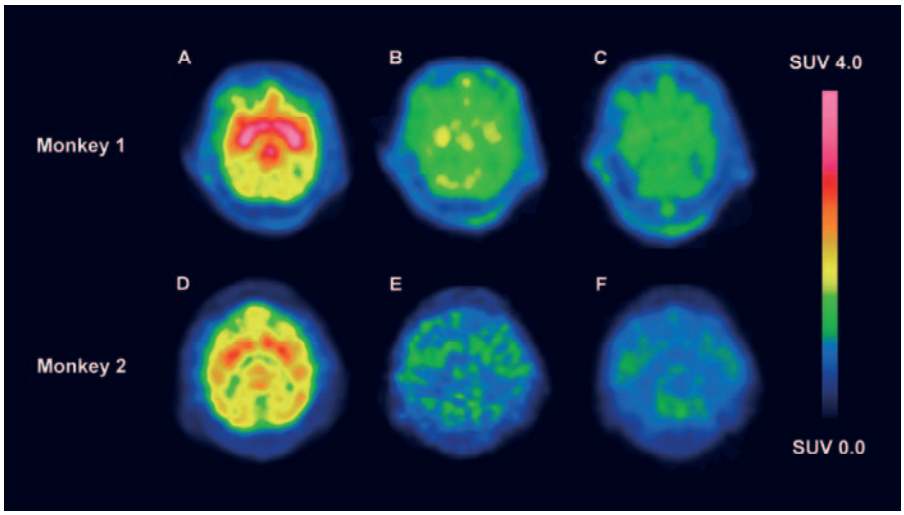


Figure 16. PET-images over the transaxial rhesus monkey brain at the level of striatum. A. [*O-methyl*-^{11}C]GR205171, B. Ethyl-analogue, C. Ethyl-analogue after predosing with GR205171, D. [*O-methyl*-^{11}C]GR205171, E. Propyl-analogue, F. Propyl-analogue after predosing with GR205171.

The ethyl-analogue showed binding in the striatum with a maximum SUV value of 2.7 at 5 min after administration, but the ratio between specific and unspecific binding was smaller than with [*O-methyl*-^{11}C]GR205171. The SUV value decreased during the rest of the scan with a half-life around 60 min. The striatum could not be visualised with the ethyl analogue after predosing with GR205171 (0.5 mg/kg). With the more lipophilic propyl-analogue the striatum could not be distinguished in the images either with or without predosing. The conclusion was that the propyl-analogue could not be used for detecting changes in NK_1-ligand levels, while further studies are needed for the ethyl-analogue.

Potential tracers for imaging of the adrenal cortex

[*O-methyl*-^{11}C]Metomidate and [*O-ethyl*-1-^{11}C]etomidate were used in whole-body PET-imaging of cynomolgus monkeys. The compounds were synthesized *via* alkylation with [^{11}C]methyl iodide and [1-^{11}C]ethyl iodide, respectively. The [1-^{11}C]ethyl iodide was obtained using the carbonylation method and gave [*O-ethyl*-1-^{11}C]etomidate with a specific radioactivity of 38 GBq/μmol.

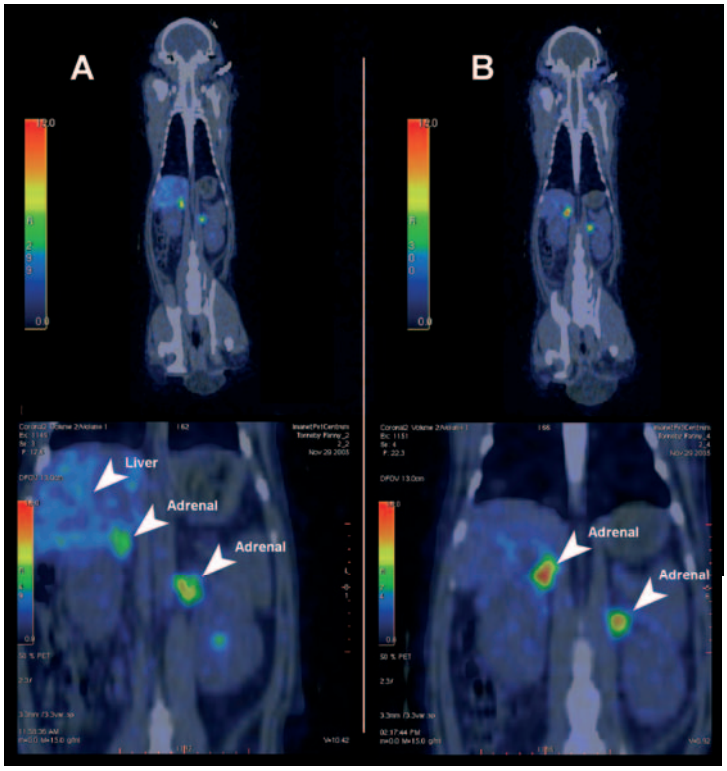


Figure 17. PET/CT imaging of cynomolgus monkey after administration of (A) [*O-methyl*-^{11}C]metomidate and (B) [*O-ethyl*-1-^{11}C]etomidate.

To be able to differentiate between the liver and the adrenal a high uptake in the adrenal and lower uptake in the liver was desired. This was observed with [*O-ethyl*-1-^{11}C]etomidate, see Figure 17 and Table 4. The adrenal-to-liver ratio for [*O-methyl*-^{11}C]metomidate and [*O-ethyl*-1-^{11}C]etomidate was 2.0 and 4.5, respectively. The data was obtained using [*O-ethyl*-1-^{11}C]etomidate with six times higher specific radioactivity than a previous study by Bergström *et al*.[26] The previous study reported adrenal-to-liver ratios of 1.3 and 1.8 in rhesus for the respective compound.

Table 4. SUV 1 hour post injection in cynomolgus monkey.

Organ	[^{11}C]metomidate	[^{11}C]etomidate
Adrenal	10.7	13.7
Liver	5.4	3.0
Gall Bladder	5.0	6.6
Urine	25	16

Conclusions

A series of ^{11}C-labelled alkyl iodides ranging from [^{11}C]methyl iodide to [1-^{11}C]butyl iodide were synthesized using novel methods.

It was demonstrated that [^{11}C]methyl iodide could be synthesized from [^{11}C]methane and iodine by use of non-thermal plasma. A minute amount of iodine was needed for the reaction hence the iodine contamination in the reactor system was negligible. The reactor generated small amounts of heat and the plasma could instantly be turned on or off. The single pass procedure was reliable and fast. While the radiochemical yield was lower compared to other more developed methods, the results are encouraging and may also illustrate some of the potential of using non-thermal plasma methods in ^{11}C-labelling chemistry.

Carbonylation methods were used in the synthesis of labelled alkyl iodides from [^{11}C]carbon monoxide. [1-^{11}C]Ethyl iodide, [1-^{11}C]propyl iodide and [1-^{11}C]butyl iodide were synthesized with very competitive levels of specific radioactivity. [1-^{11}C]Propyl iodide was obtained with the highest specific radioactivity (270 ± 33 GBq/μmol), followed by [1-^{11}C]butyl iodide(146 ± 20 GBq/μmol) and [1-^{11}C]ethyl iodide (87 ± 3 GBq/μmol).

The labelled alkyl iodides were useful alkylating agents in the synthesis of esters, amines and ethers. In addition to the utility of the alkyl halides, the experiments proved olefins to be viable substrates in palladium-mediated carbonylation using [^{11}C]carbon monoxide. Hydroformylation was shown to give better results than hydroxycarbonylation.

Successful carbonylation of acetylene further expanded the scope of palladium-mediated carbonylation in ^{11}C-labelling. Originally the work with acetylene was aimed at the synthesis of [1-^{11}C]allyl iodide. However, when the conversion of [1-^{11}C]acrylic acid failed, the interest turned to the synthesis of amides with vinylic functionality. *N*-Benzyl[*carbonyl*-^{11}C]acrylamide was synthesized in good yield from [1-^{11}C]acrylic acid *via* the conversion to its acid chloride and subsequent treatment with benzylamine. Significant improvements were achieved when the [*carbonyl*-^{11}C]acrylamide was synthesized *via* the Pd^0-mediated aminocarbonylation of vinyl iodide. Several ^{11}C-labelled acrylamides were synthesized using vinyl iodide, (*E*)- and (*Z*)-bromopropene and various amines. The one-pot synthesis gave products with high radiochemical yields and high specific radioactivity.

Svensk populärvetenskaplig sammanfattning

I denna avhandling presenteras nya syntesmetoder för ^{11}C-märkning av spårsubstanser för användning i positronemissiontomografi (PET).

En PET-spårsubstans innehåller en positronemitterande radionuklid. De mest använda radionukliderna vid PET-undersökningar är ^{11}C, ^{18}F, ^{15}O och ^{68}Ga, samtliga positronstrålare med kort halveringstid. Särskilt intressant är ^{11}C, med med en halveringstid på 20,4 min, eftersom kol är vanligt förekommande i kroppsegna substanser och läkemedel. Vid en PET-undersökning administreras vanligen spårmolekylen intravenöst till patienten. Spårmolekylens utbredning och koncentration i kroppen kan bestämmas genom att radioaktiviteten registreras med en s.k. PET-kamera. Detta resulterar i data som sedan kan sammanställas till en serie tidsupplösta bilder. Olika biologiska skeenden kan avbildas beroende på vilken PET-spårsubstans som valts, t.ex. metabolism i cancertumörer och interaktioner med olika proteiner t.ex. receptorer eller enzymer. Genom att använda sig av skräddarsydda spårsubstanser för användning inom t.ex. kardiologi, neurologi och onkologi kan information erhållas som underlättar diagnos och val av behandling. PET används också allt mer inom läkemedelsforskningen. Det är därför viktigt att utveckla nya syntesmetoder för att kunna öka antalet möjliga PET-spårsubstanser.

Ett effektivt sätt att möjliggöra ^{11}C-märkning av ett stort antal substanser är att syntetisera radioaktiva molekylära ”byggstenar” inmärkta med ^{11}C. PET-spårsubstansen syntetiseras därefter genom att koppla ihop den radioaktiva byggstenen med ett strukturelement som innehåller en lämplig funktionell grupp, t.ex. amin, alkohol eller karboxylsyra. Genom att använda olika radioaktiva byggstenar till samma strukturelement och vice versa ges möjlighet att modifiera PET-spårsubstansens biologiska funktion. I avhandlingen presenteras metoder för syntes av ^{11}C-märkta byggstenar med varierande längd på kolkedjan.

När ^{11}C används vid PET-undersökningar är mängden radioaktivitet som erhålls vid syntesen av spårsubstansen viktig. Om för lite radioaktivitet administreras vid undersökningen så fås PET-bilder av dålig kvalitet. Högt radiokemiskt utbyte är därför önskvärt. För att få bästa upplösning och känslighet med PET-kameran krävs även att spårsubstansen har hög specifik radioaktivitet. Detta innebär att mängden radioaktiv substans ska vara så hög

som möjligt samtidigt som mängden substans som saknar radioaktiv atom minimeras. Detta kan bland annat uppnås genom att välja kemikalier vilka inte bidrar till en isotoputspädning, genom att utföra syntesen i mycket liten skala och att minimera syntestiden.

Kolmonoxid och metan märkt med ^{11}C kan användas som radioaktivt startmaterial. Det minskar betydligt risken för isotoputspädning jämfört med de gängse metoderna som använder ^{11}C-koldioxid som till skillnad mot kolmonoxid och metan finns i hög koncentration i atmosfären. Kolmonoxid märkt med ^{11}C inkorporeras i strukturelement genom palladiumkatalyserad karbonylering. Genom vidare kemiska modifikationer kan märkta alkyljodider erhållas och dessa kan användas som byggstenar vid syntesen av PET-spårsubstanser. En ny metod för syntes av metyljodid märkt med ^{11}C presenteras också. [^{11}C]Metyljodid är i dag den mest använda byggsten för syntes av PET-spårsubstanser märkta med ^{11}C. Vidare presenteras en metod för att syntetisera akrylamider märkta med ^{11}C i karbonylpositionen.

In vivo studier med PET har genomförts med fokus på avbildning av binjure samt neurokinin-1-(NK_1)-receptorn.

Utveckling av teknisk apparatur har varit en del av arbetet som en konsekvens av att ^{11}C är radioaktiv. Synteserna kräver en hög grad av automatisering pga strålskyddsbehov och hanteringen av små mängderna reagens, både gasformiga och i lösning.

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References

1. Czernin J., Phelps M. E. *Annu Rev Med* **2002**, *53*, 89-112.
2. Gambhir S. S. *Nat Rev Cancer* **2002**, *2*, 683-693.
3. Jerusalem G., Hustinx R., Beguin Y., Fillet G. *Eur J Cancer* **2003**, *39*, 1525-1534.
4. Henry T. R., Heertum R. L. *Semin Nucl Med* **2003**, *33*, 88-104.
5. Klunk W. E., Engler H., Nordberg A., Wang Y., Blomqvist G., Holt D. P., Bergström M., Savitcheva I., Huang G.-F., Estrada S., Ausén B., Debnath M. L., Barletta J., Price J. C., Sandell J., Lopresti B. J., Wall A., Koivisto P., Antoni G., Mathis C. A., Långström B. *Ann Neurol* **2004**, *55*, 306-319.
6. Burn D. J., O'Brien J. T. *Mov Disord* **2003**, *18*, S88-95.
7. Jadvar H., Strauss H. W., Segall G. M. *Radiographics* **1999**, *19*, 915-926.
8. Bergström M., Långström B. *Prog Drug Res* **2005**, *62*, 279-317.
9. Bergström M., Grahnén A., Långström B. *Eur J Clin Pharmacol* **2003**, *59*, 357-366.
10. Lappin G., Garner C. *Nat Rev Drug Discovery* **2003**, *2*, 233-240.
11. Långström B., Kihlberg T., Bergström M., Antoni G., Björkman M., Forngren B. H., Forngren T., Hartvig P., Markides K., Yngve U., Ögren M. *Acta Chem Scand* **1999**, *53*, 651-669.
12. Bida G. T., Ruth T. J., Wolf A. P. *Radiochim Acta* **1980**, 181-185.
13. Casella V., Christman D. R., Ido T., Wolf A. P. *Radiochim Acta* **1978**, *25*, 17-20.
14. Ache H. J., Wolf A. P. *J Phys Chem* **1968**, *72*, 1988-1993.
15. Christman D. R., Finn R. D., Karlstrom K. I., Wolf A. P. *Appl Radiat Isot* **1975**, *26*, 435-442.
16. Långström B., Antoni G., Gullberg P., Halldin C., Malmborg P., Någren K., Rimland A., Svärd H. *J Nucl Med* **1987**, *28*, 1037-1040.
17. Comar D., Cartron J. C., Maziere M., Marazano C. *Eur J Nucl Med Mol* **1976**, *1*, 11-14.
18. Suzuki K., Yoshida Y., Ogawa M., Kovacs Z., Szelecsenyi F. *J Labelled Compd Radiopharm* **2003**, *46*, S241.
19. Larsen P., Ulin J., Dahlström K., Jensen M. *Appl Radiat Isot* **1997**, *48*, 153-157.
20. Larsen P., Orbe M., Dahlström K., Ulin J. Production of 11C-methyl iodide. 1999. US patent No. US60008421.
21. Ametamey S., Vollenweider F. X., Patt J., Bourquin D., Hasler F., Beer H. F., Schubiger P. A. *J Labelled Compd Radiopharm* **1998**, *41*, 585-594.
22. Fallis S., McCarthy T. J., Welch M. J. *Proceedings of the Seventh International Workshop on Targetry and Target Chemistry, Heidelberg, Germany* **1997**, 128-129.
23. www.GE.com.
24. Link J. M., Krohn K. A., Clark J. C. *Nucl Med Biol* **1997**, *24* 93–97.
25. Noguchi J., Suzuki K. *Nucl Med Biol* **2003**, *30*, 335–343.

26. Bergström M., Bonasera T. A., Lu L., Bergström E., Backlin C., Juhlin C., Långström B. *J Nucl Med* **1998**, *39*, 982–989.
27. Ishiwata K., Ishii S. I., Shinoda M., Maekawa S., Senda M. *Appl Radiat Isot* **1999**, *50*, 693-697.
28. Halldin C., Farde L., Högberg T., Hall H., Sedvall G. *Appl Radiat Isot* **1990**, *41*, 669-674.
29. Antoni G., Långström B. *Appl Radiat Isot* **1987**, *38*, 655-659.
30. Fasth K. J., Antoni G., Långström B. *Appl Radiat Isot* **1990**, *41*, 611-613.
31. Antoni G., Långström B. *Acta Chem Scand B* **1987**, *41*, 511-517.
32. Antoni G., Långström B. *J Labelled Compd Radiopharm* **1987**, *24*, 125-143.
33. Zhang M. R., Ogawa M., Maeda J., Ito T., Noguchi J., Kumata K., Okauchi T., Suhara T., Suzuki K. *J Med Chem* **2006**, *49*, 2735-2742.
34. Nishiyama S., Tsukada H., Sato K., Kakiuchi T., Ohba H., Harada N., Takahashi K. *Synapse* **2001**, *40*, 159-169.
35. Långström B., Lundqvist H. *Int J Appl Radiat Isot* **1976**, *27*, 357–363.
36. Dannals R. F., Ravert H. T., Wilson A. A., Wagner H. N. *Int J Appl Radiat Isot* **1986**, *37*, 433-434.
37. Crouzel C., Långström B., Pike V. W., Coenen H. H. *Int J Appl Radiat Isot* **1987**, *38*, 601–604.
38. Welch M. J., Redvanly C. Handbook of Radiopharmaceuticals Radiochemistry and Applications. John Wiley and Sons Ltd; 2003.
39. Björkman M., Doi H., Resul B., Suzuki M., Noyori R., Watanabe Y., Långström B. *J Labelled Compd Radiopharm* **2000**, *43*, 1327-1334.
40. Bolton R. *J Labelled Compd Radiopharm* **2001**, *44*, 701-736.
41. Jewett D. M. *Appl Radiat Isot* **1992**, *43*, 1383-1385.
42. Lundkvist C., Sandell J., Nagren K., Pike V. W., Halldin C. *J Labelled Compd Radiopharm* **1998**, *41*, 545-556.
43. Wagner H. N., Burns H. D., Dannals R. F., Wong D. F., Långström B., Duelfer T., Frost J. J., Ravert H. T., Links J. M., Rosenbloom S. B., Lukas S. E., Kramer A. V., Kuhar M. J. *Science* **1983**, *221*, 1264-1266.
44. Mach R. H., Jackson J. R., Luedtke R. R., Ivins K. J., Molinoff P. B., Ehrenkaufer R. L. *J Med Chem* **1992**, *35*, 423-430.
45. Begley D. J. *Acta Paediatr* **2003**, *92*, 83-91.
46. Habgood M. D., Liu ZD, Dehkordi L. S, Khodr H. H, Abbott J, R.C. H. *Biochem Pharmacol* **1999**, *57*, 1305-1310.
47. Liu C. J., Xu G. H., Wang T. *Fuel Process Technol* **1999**, *58*, 119-134.
48. Eliasson B., Liu C., Kogelschatz U. *Ind Eng Chem Res* **2000**, *39*, 1221-1227.
49. Okumoto M., Kim H. H., Takashima K., Katsura S., Mizuno A. *IEEE Trans Ind Appl* **2001**, *37*, 1618-1624.
50. Eliasson B., Kogelschatz U. *IEEE Trans Plasma Sci* **1991**, *19*, 1063-1077.
51. Okumoto M., Mizuno A. *Catal Today* **2001**, *71*, 211-217.
52. Crouzel C., Sejourne C., Comar D. *Int J Appl Radiat Isot* **1979**, *30*, 566-568.
53. Niisawa K., Ogawa K., Saito T., Taki K., Karasawa T., Nozaki T. *Int J Appl Radiat Isot* **1984**, *35*, 29-33.
54. Yamamoto A., Kayaki Y., Nagayama K., Shimizu I. *Synlett* **2000**, 925-937.
55. Beller M., Cornils B., Frohning C. D., Kohlpaintner C. W. *J Mol Catal A: Chem* **1995**, *104*, 17-85.
56. Drent E., Budzelaar P. H. *Chem Rev* **1996**, *96*, 663-682.
57. Benedek C., Toros S., Heil B. *J Organomet Chem* **1999**, *586*, 85-93.

58. Li J., Jiang H., Feng A., Jia L. *J Org Chem* **1999**, *64*, 5984-5987.
59. Scrivanti A., Beghetto V., Zanato M., Matteoli U. *J Mol Catal A: Chem* **2000**, *160*, 331-336.
60. Jiang H., Xu Y., Liao S., Yu D., Chen H., Li X. *J Mol Catal A: Chem* **1998**, *130*, 79-84.
61. Schoenberg A., Bartoletti I., Heck R. F. *J Org Chem* **1974**, *39*, 3318-3326.
62. Schoenberg A., Heck R. F. *J Org Chem* **1974**, *39*, 3327-3331.
63. del Rió I., Claver C., van Leeuwen P. *Eur J Inorg Chem* **2001**, 2719-2738.
64. Konya D., Leñero K. Q. A., Drent E. *Organometallics* **2006**, *25*, 3166-3174.
65. Lidström P., Kihlberg T., Långström B. *J Chem Soc, Perkin Trans 1* **1997**, 2701-2706.
66. Kihlberg T., Långström B. *J Org Chem* **1999**, *64*, 9201-9205.
67. Karimi F., Kihlberg T., Långström B. *J Chem Soc, Perkin Trans 1* **2001**, 1528-1531.
68. Doi H., Barletta J., Suzuki M., Noyori R., Watanabe Y., Långström B. *Org Biomol Chem* **2004**, *2*, 3063-3066.
69. Rahman O., Kihlberg T., Långström B. *Org Biomol Chem* **2004**, *2*, 1612-1616.
70. Itsenko O., Långström B. *J Org Chem* **2005**, *70*, 2244-2249.
71. Karimi F., Barletta J., Långström B. *Eur J Org Chem* **2005**, 2374-2378.
72. Andersson Y., Långström B. *J Chem Soc, Perkin Trans 1* **1995**, *4*, 287-289.
73. Brichard L., Del Fiore C., Lemaire A., Plenevaux A., Luxen A. *J Labelled Compd Radiopharm* **2003**, *46*, S74.
74. Kihlberg T., Långström B., Ferm T., Eriksson J. *Methods and Apparatus for Production and Use of [11C]Carbon Monoxide in Labeling Synthesis, International patent application, publication date Jan 26, 2006, WO2006008603*.
75. Fang Y. R., Gao Y., Ryberg P., Eriksson J., Kolodziejska-Huben M., Dybala-Defratyka A., Madhavan S., Danielsson R., Paneth P., Matsson O. *Chem Eur J* **2003**, *9*, 2696-2709.
76. Fang Y. R., Macmillar S., Eriksson J., Kolodziejska-Huben M., Dybala-Defratyka A., Paneth P., Matsson O., Westaway K. C. *J Org Chem* **2006**, *71*, 4742-4747.
77. Crabtree R. H. The Organometallic Chemistry of the Transition Metals, 4th Ed. Wiley-Interscience, New York; 2005, p.55-56.
78. Chepaikin E. G., Bezruchenko A. P., Suerbaev K. A., Shalmagambetov K. M. *Petrol Chem* **2006**, *46*, 117-121.
79. Lipari F., Swarin S. J. *J Chromatogr* **1982**, *247*, 297-306.
80. James D. E., Stille J. K. *J Am Chem Soc* **1976**, *98*, 1810-1823.
81. Robertson R. A. M., Cole-Hamilton D. J. *Coord Chem Rev* **2002**, *225*, 67-90.
82. Chiusoli G. P., Costa M., Cucchia L., Gabriele B., Salerno G., Veltri L., Statement V. P. *J Mol Catal A: Chem* **1999**, *143*, 297-310.
83. Hahn J. R., Ho W. *Phys Rev Lett* **2001**, *87*, 166102.
84. Zudin V. N., Chinakov V. D., Nekipelov V. M., Rogov V. A., Likholobov V. A., Yermakov Y. U. I. *J Mol Catal* **1989**, *52*, 27-48.
85. Maziere M., Hantraye P., Prenant C., Sastre J., Comar D. *Int J Appl Radiat Isot* **1984**, *10*, 973-976.
86. Samson Y., Hantraye P., Baron J. C., Soussaline F., Comar D., Maziere M. *Eur J Pharmacol* **1985**, *110*, 247-251.
87. Gardner C. J., Armour D. R., Beattie D. T., Gale J. D., Hawcock A. B., Kilpatrick G. J., Twissell D. J., Ward P. *Regul Pept* **1996**, *65*, 45-53.

88. Salvatore R. N., Nagle A. S., Schmidt S. E., Jung K. W. *Org Lett* **1999**, *1*, 1893-1896.
89. Smaill J. B., Rewcastle G. W., Loo J. A., Greis K. D., Chan O. H., Reyner E. L., Lipka E., Showalter H. D., Vincent P. W., Elliott W. L. *J Med Chem* **2000**, *43*, 1380–1397.
90. Ben-David I., Rozen Y., Ortu G., Mishani E. *Appl Radiat Isot* **2003**, *58*, 209-217.
91. Mishani E., Abourbeh G., Rozen Y., Jacobson O., Laky D., Ben David I., Levitzki A., Shaul M. *Nucl Med Biol* **2004**, *31*, 469-476.
92. Wu Y. J., He H., Sun L. Q., L'Heureux A., Chen J., Dextraze P., Starrett Jr J. E., Boissard C. G., Gribkoff V. K., Natale J. *J Med Chem* **2004**, *47*, 2887-2896.
93. Morin M. J. *Oncogene* **2000**, *19*, 6574 - 6583.
94. Nicholas P. P. *J Org Chem* **1987**, *52*, 5266-5272.
95. Burwell R. L. *Chem Rev* **1954**, *54*, 615-685.
96. Dence S. S., Welch M. J. *Proceedings of the Seventh International Workshop on Targetry and Target Chemistry, Heidelberg, Germany* **1997**, 133.
97. Rupniak N. M. *Can J Physiol Pharmacol* **2002**, *80*, 489-494.
98. Hokfelt T., Pernow B., Wahren J. *J Intern Med* **2001**, *249*, 27-40.
99. Rupniak N. M., Kramer M. S. *Trends Pharmacol Sci* **1999**, *20*, 485-490.
100. Bergström M., Fasth K. J., Kilpatrick G., Ward P., Cable K. M., Wipperman M. D., Sutherland D. R., Långström B. *Neuropharmacology* **2000**, *39*, 664-670.
101. Solin O., Eskola O., Hamill T. G., Bergman J., Lehikoinen P., Gronroos T., Forsback S., Haaparanta M., Viljanen T., Ryan C. *Mol Imaging Biol* **2004**, *6*, 373-384.
102. Hietala J., Nyman M. J., Eskola O., Laakso A., Grönroos T., Oikonen V., Bergman J., Haaparanta M., Forsback S., Marjamäki P. *Mol Imaging Biol* **2005**, *7*, 262-272.

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