Functionalisation of ^{11}C-labelled olefins *via* a Heck coupling reaction

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A method for incorporation of ^{11}C (β^+, $t_{\frac{1}{2}}$ = 20.3 min) in internal alkenes has been developed. [β-^{11}C]Styrene and [1-^{11}C]pent-1-ene were synthesized from benzaldehyde and butyraldehyde respectively, using [^{11}C]methylenetri-*o*-tolylphosphorane in a Wittig reaction. The radiochemical yield based on analytical liquid chromatography was 85–90%. The ^{11}C-labelled olefins were further coupled with several aromatic halides in a palladium mediated cross-coupling reaction forming the compounds (*E*)-[β-^{11}C]stilbene, (*E*)-4′-amino[β-^{11}C]stilbene, (*E*)-[β-^{11}C]stilbene-2′-methanol, (*E*)-3′-ethoxycarbonyl[β-^{11}C]stilbene, (*E*)-4′-methyl[β-^{11}C]stilbene, (*E*)-1-phenyl[1-^{11}C]pent-1-ene and (*E*)-1-(4-aminophenyl)[1-^{11}C]pent-1-ene. The reaction sequence was performed without purification of the intermediate ^{11}C-labelled olefin. Radiochemical yields of the coupling products were 47–55% according to analytical liquid chromatography. The decay-corrected isolated radiochemical yield of (*E*)-[β-^{11}C]stilbene was approximately 38% and the total synthesis time was 40 min, counted from the end of radionuclide production to the isolated product. In a typical experiment starting from 4.7 GBq [^{11}C]methyl iodide, 450 MBq of (*E*)-[β-^{11}C]stilbene was obtained in a radiochemical purity higher than 95%. This method was also used for the synthesis of (*E*)-(β-^{13}C)stilbene, which was used to verify the labelling position by ^{13}C NMR.

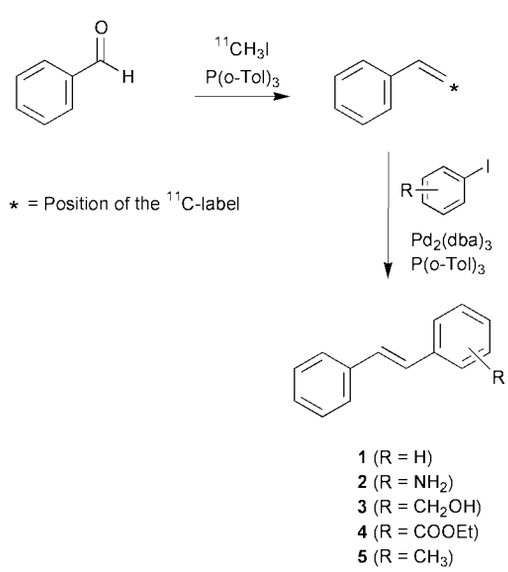
Introduction

Positron emission tomography (PET) has become an important tool for non-invasive investigations of the fate of biologically interesting compounds *in vivo*.[1] As well as the interest in PET within the field of nuclear medicine, the technology has attracted attention in the development of new drugs.[2] The radionuclides most frequently combined with PET are ^{11}C, ^{15}O and ^{18}F with half-lives of 20.3, 2.07 and 110 min, respectively. The demand for new labelled compounds is ever increasing and new routes often have to be developed to synthesise the target compounds. In order to increase the scope of synthetic possibilities new methods need to be investigated. Since the number of ^{11}C-labelled precursors will always be limited, it is important to explore the development of methods for multi-step synthesis. Synthesis time has to be kept within the time frame set by the half-life of the nuclide, which means that the reactions have to be efficient and preferably without purification in between reaction steps.

One of the most frequently used ^{11}C-labelled precursors in the production of PET tracers is [^{11}C]methyl iodide.[1] Among its applications has been the formation of [^{11}C]methylene-triphenylphosphoranes,[3] from which ^{11}C-labelled olefins have been synthesised.[4] Olefination reactions with [^{11}C]methylene-triphenylphosphoranes are general and effective reactions with few limitations regarding the aldehyde reagents.

Palladium-mediated reactions have come to play an important role in the development of carbon–[^{11}C]carbon bond formation.[5] Due to the small amount of the ^{11}C-labelled compound † the reactions are performed with an excess amount of palladium species compared to labelled compound, rather than with the catalytic amounts used under conventional reaction conditions with stable compounds. A common method for functionalising olefins is the palladium-mediated Heck reaction where a haloarene or a haloalkene is coupled with an alkene.[6] This reaction is established as an efficient and versatile method for forming carbon–carbon bonds and the tolerance of many different functional groups on the substrates makes it a suitable reaction for preparation of functionalised olefins.

In the present paper a method is described where a ^{11}C-label was incorporated in aromatic and aliphatic alkene structures using the Wittig reaction. The ^{11}C-labelled olefins were then coupled with different haloarenes, mediated by a palladium catalyst, resulting in ^{11}C-labelled internal alkenes (Schemes 1 and 2).



1 (R = H)
2 (R = NH_2)
3 (R = CH_2OH)
4 (R = COOEt)
5 (R = CH_3)

Scheme 1

Results and discussion

[β-^{11}C]Styrene and [1-^{11}C]pent-1-ene were synthesised from [^{11}C]methyl iodide, benzaldehyde and butyraldehyde respectively using tri-*o*-tolylphosphine in *o*-dichlorobenzene with

† The total amount of methyl iodide is typically in the range of 10–100 nmol.

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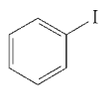
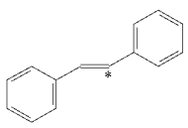
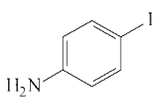
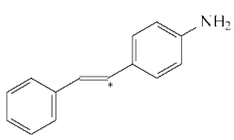
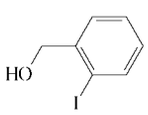
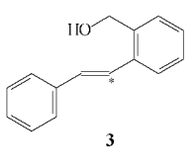
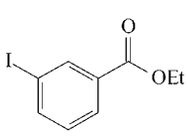
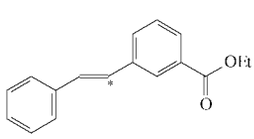
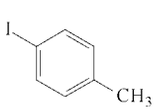
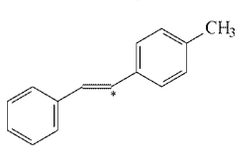
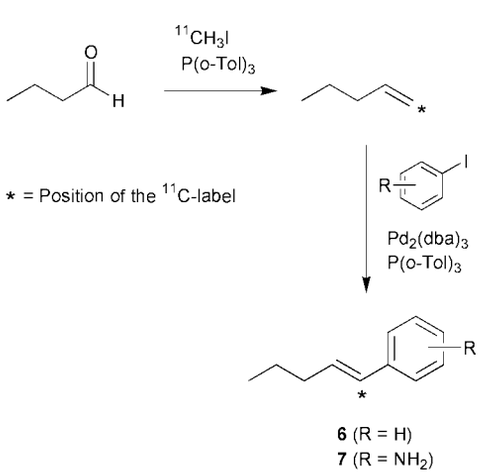
Table 1 Radiochemical yield determined by analytical LC as the percentage of the total amount of activity in samples withdrawn from the reaction mixture, $n > 5$

Entry	Halide	Radiochemical yield (%)	Unreacted [β-^{11}C]styrene (%)	Product
1		55 (38)[a]	2	 **1**
2		53 (40)[a]	0	 **2**
3		43	3	 **3**
4		49	5	 **4**
5		47 (34)[a]	1	 **5**

[a] Decay-corrected isolated radiochemical yield.



Scheme 2

epichlorohydrin as base precursor. The application of epichlorohydrin as a base precursor has been described earlier.[7] The reaction conditions were analogous to those reported previously.[3] Radiochemical yields ‡ were 85–90% in both cases and the remaining radioactivity was mainly unreacted [^{11}C]methyl iodide and [^{11}C]methyltri-*o*-tolylphosphonium salt.

The Heck reaction was performed in a one pot procedure by adding the unpurified ^{11}C-labelled olefin to a solution of palladium mediator and halide in *o*-dichlorobenzene. The palladium solution was pre-prepared and flushed with nitrogen gas. To promote the reaction the final reaction mixture was heated for five minutes. [1-^{11}C]Pent-1-ene was coupled with two aromatic halides, iodobenzene and 4-iodoaniline. Radiochemical yields ‡ of the resulting products, (*E*)-1-phenyl-[1-^{11}C]pent-1-ene (**6**) and (*E*)-1-(4-aminophenyl)[1-^{11}C]pent-1-ene (**7**) were 54 and 47%, respectively. [β-^{11}C]Styrene was coupled with five aromatic halides resulting in the ^{11}C-labelled stilbene analogues presented in Table 1. Radiochemical purity of the isolated product was more than 95% and the total synthesis time from the end of radionuclide production to the isolated product was 40 min.

‡ The radiochemical yield of the products was determined by analytical liquid chromatography (LC) as the percentage of the total amount of activity in samples withdrawn from the reaction mixture.

Aryl exchange between palladium and phosphine

In the beginning of the investigation, triphenylphosphine was used to form the phosphonium ylide in the Wittig reaction. It was then revealed that the triphenylphosphine was also acting as a ligand to palladium and causing an aryl exchange between palladium and the phosphine to take place in the Heck reaction. This was evident since the same product, (*E*)-[^{11}C]stilbene, was formed in the Heck reaction with [^{11}C]styrene, regardless of which aromatic halide was added to the reaction mixture. The aryl exchange has been reported to take place between phosphorus bound aryl and palladium bound aryl[8,9] or alkyl[10] groups within a palladium complex, (Fig. 1).

A suggested mechanism for this process involves the formation of a phosphonium salt from the oxidatively added moiety together with one of the phosphine ligands, *via* a reductive elimination. If the salt is oxidatively added to the palladium again a different carbon–phosphorus bond may be broken.[9,11]

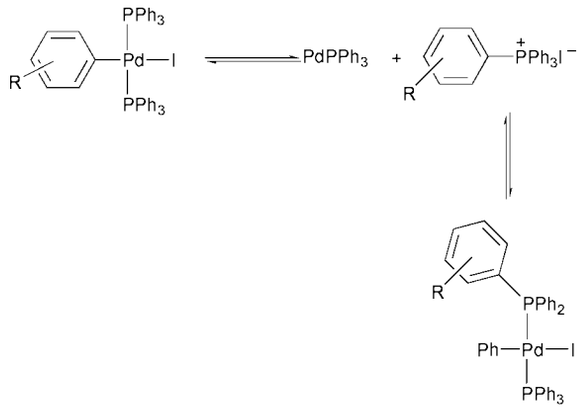


Fig. 1

It was confusing to see the aryl exchange in this reaction since tri-*o*-tolylphosphine was used as a ligand to palladium and the aryl exchange has been reported to be suppressed by this palladium complex.[9] The complex has also been reported to give good results in Heck reactions[12] and the formation of tetraarylphosphonium salts, which has been reported to be a problem in Heck reactions with electron rich aryl halides, can also be suppressed by this ligand.[13] However, the products formed after the aryl exchange did not originate from a palladium complex with tri-*o*-tolylphosphine but from a complex with triphenylphosphine as the ligand. This indicated that there was triphenylphosphine remaining from the Wittig reaction that was acting as ligand to palladium and causing the exchange to take place. To avoid the exchange, triphenylphosphine had to be excluded from the reaction mixture before the Heck reaction was performed. In order to simplify automation and minimise the loss of radioactivity due to transfers, a one pot system is preferred in most labelling syntheses with short-lived radionuclides. The automation of labelling synthesis is important in order to ensure radiation protection for the chemists and also to ensure the pharmaceutical integrity of the labelled compound. Instead of purifying the intermediate olefin, the triphenylphosphine in the Wittig reaction was exchanged for tri-*o*-tolylphosphine. Tri-*o*-tolylphosphine worked equally well as a Wittig reagent and no other modifications to the method reported earlier[3] were needed. A method using polymer-bound triphenylphosphine for the synthesis of [^{11}C]methylenetriphenylphosphoranes has been developed[14] and this approach was also investigated. In this method the polymer was removed from the reaction solution by filtration using a syringe filter unit. The major drawback using the polymer-bound triphenylphosphine was that one third of the radioactivity was lost after filtering of the polymer matrix from the reaction solution. Washing of the filter and the polymer did not improve this result.

o-Dichlorobenzene is a medium polar solvent suitable for the Wittig reaction. *o*-Dibromobenzene has also been reported as a good solvent for Wittig reactions with [^{11}C]methyl iodide,[14] but this solvent could be implemented in the Heck reaction. For the Heck reaction a more polar solvent than *o*-dichlorobenzene is usually preferred,[15] but since a polar solvent also enhances the ligand interchange,[9] *o*-dichlorobenzene seemed to be a good compromise. Microwave heating of the reaction mixture was investigated since high temperatures are required for the coupling reaction to take place, and improved results have been reported using this method.[16] In this case however, conventional heating was equally efficient and offered a more convenient way of handling the radioactive reaction mixture. As more than one equivalent of the palladium catalyst was used compared to the ^{11}C-labelled olefin, formed in the Wittig reaction, no base was used to regenerate the active palladium species.

Characterisation

After each LC-analysis a GM-tube was used to establish that there was no residual radioactivity on the LC-column, in the form of uneluted ^{11}C-labelled by-products.

The identities of **1**, **2**, **3**, **4**, **5** and **6** were verified using two different analytical LC-systems and co-elution of the authentic reference compounds and the ^{11}C-labelled products.

The identity of **7** was verified by LC-MS analysis, where the positively charged protonated molecular ion was detected, *m*/*z* 162. For further verification, **2** was also analysed by LC-MS and here a peak at *m*/*z* 196, which represents $[M + H]^+$, was present during the analysis of both the reference compound and the labelled product. Simultaneous labelling of **1** with ^{11}C and ^{13}C was employed in order to record a ^{13}C NMR spectrum. The product gave a signal at 127.5 ppm which corresponds to a vinyl carbon in the (*E*)-stilbene reference. A labelled side product eluting approximately one minute after the main product on analytical LC was detected in each Heck reaction. Commercially available (*Z*)-stilbene was used to verify this product in the analysis of the reaction mixture after synthesis of **1**. The radiochemical yields of the by-products assumed to be the *cis*-compounds were in the order of 5–10%.

Conclusion

^{11}C-Labelled internal alkenes have been synthesised from the readily available precursor [^{11}C]methyl iodide *via* a general method. The synthesis sequence could be performed in one pot when tri-*o*-tolylphosphine was used in the Wittig reaction. The cross-coupling reaction was compatible with many different functional groups on the halides and no protective groups were necessary in the cases presented herein. An advantage of this method is the availability of labelling positions in carbon–carbon bonds that are not bonded to heteroatoms. This should be a rather stable position regarding biological processes, which makes the method an interesting option when alternative labelling positions are necessary. Furthermore, the method could be used for the incorporation of other carbon isotopes *e.g.* the synthesis of ^{13}C-labelled stilbene, which in this case was used to verify the position of the label by ^{13}C NMR.

Experimental

General

[^{11}C]Carbon dioxide was prepared by the ^{14}N(p, α)^{11}C nuclear reaction using a nitrogen (AGA Nitrogen 6.0) gas target (containing 0.05% oxygen, AGA Oxygen 4.8) and 17 MeV protons produced by the Scanditronix MC-17 cyclotron at the Uppsala University PET Centre. [^{11}C]Carbon dioxide was converted to [^{11}C]methyl iodide by reaction with lithium aluminium hydride and subsequent reaction with hydriodic acid,[17] using a semi-automated synthesis system, Synthia.[18]

Chromatography

LC was performed using a Beckman 126 pump and a Beckman 166 UV detector in series with a β^+-flow detector. Data collection was performed using the Beckman System Gold chromatography software package for semi-preparative LC and the Beckman System Nouveau Chromatography Software Package for analytical LC. The analytical LC column used was a Beckman Ultrasphere 5 μm Octyl, (250 × 4.6 mm) and the semi-preparative LC column was a Jones Chromatography Genesis C-18 (250 × 10 mm). Mobile phases were 0.05 M ammonium formate pH 3.5 (A), 0.025 M potassium dihydrogenphosphate pH 4.7 (B) and acetonitrile–water (50 : 7) (C). The LC was performed at room temperature and the UV-detection at 254 nm. LC-MS equipment consisted of a Beckman 126 pump, a CMA 240 autosampler (CMA Micro-

dialysis, Stockholm, Sweden) and a VG Quattro mass spectrometer (Micromass, Manchester, UK) equipped with pneumatically assisted electrospray. The column in the LC-MS system was a Beckman Ultrasphere 5 μm Octyl, (250 × 4.6 mm). A post column split was used, with 1% of the total flow of 1 ml min^{-1} delivered to the electrospray probe and 99% delivered to a Beckman 166 UV detector in series with a Bioscan Flow-count β^+-detector. Mobile phases were 100 mM TFA in water (D) and methanol (E). Isocratic elution 0–6 min with D : E (75 : 25) and a linear gradient to D : E (95 : 5) after 6 min was employed to elute the analytes.

Chemicals

Iodobenzene, 4-bromoaniline, 4-iodoaniline, 2-iodobenzyl alcohol, 4-iodotoluene, styrene, (*Z*)-stilbene, (*E*)-stilbene, benzaldehyde, butyraldehyde, (*E*)-1-phenylpent-1-ene, pent-1-ene, *N*,*N*-dimethylformamide (DMF), tri-*o*-tolylphosphine (P(*o*-Tol)$_3$), and tris(dibenzylideneacetone)dipalladium(0) (Pd_2(dba)$_3$) were purchased from Aldrich® and used without further purification. 1,2-Dichlorobenzene (*o*-DCB) and epichlorohydrin were used freshly distilled. 3-Iodoethyl benzoate was synthesised from 3-iodobenzoic acid in an esterification reaction. Reference compounds for the labelled products, (*E*)-stilbene, (*E*)-4-aminostilbene, (*E*)-stilbene-2-methanol, (*E*)-3-ethoxycarbonylstilbene and (*E*)-4-methylstilbene, were synthesised from styrene with iodobenzene, 4-bromoaniline, 2-iodobenzyl alcohol, 3-iodoethyl benzoate and 4-iodotoluene, respectively, using an established method.[16] The reference compounds were characterised by ^{1}H and ^{13}C NMR (300 and 75.4 MHz respectively), on a Varian XL-300 spectrometer with $CDCl_3$ as solvent.

Compounds **1**, **2**, **3**, **4** and **5** were synthesised according to the general method described below using benzaldehyde for the Wittig reaction and compounds **6** and **7** were synthesised using the same procedure with butyraldehyde. The halides used in the Heck reactions are mentioned under chemicals.

General procedure for the synthesis of compounds 1–7

[^{11}C]Methyl iodide was distilled through a Sicapent® drying tower and was trapped in a solution of P(*o*-Tol)$_3$ (5 mg, 16 μmol) in 200 μL *o*-DCB. After trapping of [^{11}C]methyl iodide the solution was heated for 3 min at 150 °C. Epichlorohydrin (80 μL, 1.0 mmol) and benzaldehyde (20 μL, 0.2 mmol) or butyraldehyde (18 μL, 0.2 mmol) were added to the solution and the mixture was heated for an additional 2 min. To this solution Pd_2(dba)$_3$ (2 mg, 2.2 μmol), P(*o*-Tol)$_3$ (2.2 mg, 7.2 μmol) and halide (90 μmol) in 200 μL DMF were added. The resulting mixture was heated for 5 min at 150 °C whereafter a sample was withdrawn from the reaction mixture for analysis. The identity and radiochemical yield were determined by analytical LC with isocratic elution 1.5 mL min^{-1} (B : C) (70 : 30, v : v). When semi-preparative LC was performed the reaction mixture was diluted to a total volume of 3 mL with acetonitrile–water and injected onto a semi-preparative LC-column. The column was eluted isocratically at a flow of 5 mL min^{-1} with solvents A : C (75 : 25, v : v) followed by a linear gradient 6–12 min (5 : 95). The radiochemical purity and identity of the collected fraction was determined by analytically LC as described above.

[β-^{11}C]- and [β-^{13}C]Stilbene

[^{11}C]Methyl iodide was distilled through a Sicapent® drying tower and was trapped in a solution of P(*o*-Tol)$_3$ (5 mg, 16 μmol) in 200 μL *o*-DCB. After trapping of [^{11}C]methyl iodide, 15 μmol (^{13}C)CH_3I (99% ^{13}C) in 10 μL DMF was added to the solution and the resulting mixture was heated for 5 min at 150 °C. Epichlorohydrin (80 μL, 1.0 mmol) and benzaldehyde (20 μL, 0.2 mmol) were added to the solution and the mixture was heated for an additional 5 min. To the mixture a solution of Pd_2(dba)$_3$ (2 mg, 2.2 μmol), P(*o*-Tol)$_3$ (2.2 mg, 7.2 μmol) and iodobenzene (10 μL, 90 μmol) in 200 μL DMF was added. The resulting mixture was heated for 7 min at 150 °C whereafter a sample was withdrawn from the reaction mixture for analysis. The mixture was diluted to a total volume of 3 mL with acetonitrile–water and injected onto a semi-preparative LC-column. The column was eluted with an isocratic elution at a flow of 5 mL min^{-1} with solvents A : C (75 : 25) followed by a linear gradient 6–12 min (5 : 95). The product was collected after approximately 9 min and the collected fraction was diluted with water and concentrated on a C-18 solid phase extraction column. After washing with water the product was eluted with ethanol. The identity and radiochemical purity of the collected fraction was verified using analytical LC with the authentic reference added to the solution. The ethanol was evaporated and the residue was dissolved in $CDCl_3$. ^{13}C NMR δ 127.5.

Acknowledgements

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