[^{11}C]Methylenetriphenylphosphorane, a new ^{11}C-precursor, used in a one-pot Wittig synthesis of [β-^{11}C]styrene

Tor Kihlberg, Per Gullberg and Bengt Långström*

Department of Organic Chemistry, Institute of Chemistry,
University of Uppsala, Box 531, S-751 21 Uppsala, Sweden

Summary

Preparation of [^{11}C]methyltriphenylphosphonium iodide and the *in situ* generation of [^{11}C]methylenetriphenylphosphorane directly from [^{11}C]methyl iodide, is described. Using this one-pot preparation, [β-^{11}C]styrene was synthesized conveniently, fast and with a minimum of manual handling. The synthesis was performed by using [^{11}C]methyl iodide, triphenylphosphine, epichlorohydrin and benzaldehyde in tetrahydrofurane/o-dibromobenzene, with a synthesis time of 40 min (counted from the end of [^{11}C]methyl iodide transfer), a radiochemical yield of 80-90% of [β-^{11}C]styrene and a specific radioactivity, of 100MBq/μmol. In a typical experiment starting with 960 MBq ^{11}C-methyl iodide, 200 MBq of [β-^{11}C]styrene was obtained within 42 min.

Key words: [^{11}C]methyltriphenylphosphonium iodide, [^{11}C]methylenetriphenylphosphorane, [β-^{11}C]styrene, one-pot Wittig.

Introduction

The development of precursors useful as labelled reagents or as starting materials for valuable synthons are important, since this might open up new synthetic pathways to labelled molecules in acceptable yields. Furtermore the short half-life of ^{11}C, 20.3 min., requires fast and efficient reactions with a minimum of technical handling and rapid work up proceduers. The limited availability of different ^{11}C-precursors (1) is one restriction for getting new interesting molecules applicable in Positron Emission Tomography (2,3,4). ^{11}C-precursors commonly used are carbon dioxide (5), hydrogen cyanide (5), formaldehyde (6,7), phosgene (8,9.10), various alkyl iodides (11) and benzyl iodides (12,13), methyllithium (14), diazomethane (15) and nitromethane (16).

In this paper the use of another ^{11}C-precursor, [^{11}C]methylenetriphenylphosphorane ([^{11}C]MTP), generated *in situ* from [^{11}C]methyl iodide in a one-pot synthesis of [β-^{11}C]styrene,

* To whom correspondence should be addressed.

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is presented. The ^{11}C-MTP, is precursor for a ^{11}C-methylene synthon suitable for ^{11}C-Wittig type reactions, making it possible to prepare molecules containing labelled methylene group from the corresponding carbonyl groups.

[β-^{11}C]Styrene was chosen as a model molecule for developing the technique and reaction conditions necessary using the [^{11}C]methylenetriphenylphosphorane. The [^{11}C]methyliodide and benzaldehyde was easily converted to [β-^{11}C]styrene by this one-pot technique using triphenylphosphine and epichlorohydrin in orthodibromorobenzene as solvent. The synthesis avoids manual additions of reagents, presented in the original stepwise procedure (17), giving enhanced reliability and increased radiochemical yield.

Experimental

General

The ^{11}C was produced at the tandem Van de Graaff accelerator,The Svedberg Laboratory, University of Uppsala by means of the 14N(p,α)^{11}C reaction using a nitrogen gas target. The ^{11}C produced was trapped as [^{11}C]carbon dioxide in a quartz glass tube containing molecular sieves (4 Å) kept in a an oven wich was a lead-shielded transport vessel. In the chemistry laboratory, the [^{11}C]carbon dioxide was converted to [^{11}C]methyl iodide using a one-pot system, described in detail elsewere (18).

LC analysis was performed either on a Hewlett-Packard 1090 equipped with a UV-diode array detector (using 214 nm)or a Waters system (501 pump, automated gradient controller, 440 absorbance detector) and both equipped with a β-flow detector (19) connected in series.

A 250 x 4.6 mm 10 micron RP-18 column was used at 40 °C, with 0.05 M ammonium formate (A) (pH 3.5), and methanol(B) as eluent.

GC analysis was performed on a Hewlett-Packard 5880 equipped with a β-flow detector (20) connected in series with the FID. A 1.8 m x 1.8 mm glass column with SE 52 on Chromosorb was used in combination with nitrogen as carrier gas.

Preparative LC, a 250 x 10 mm 10 micron RP-18 column was performed at room temperature with 0.05 M ammonium formate (A) (PH 3.5), and methanol (B) as eluent.

All analyses were performed by the addition of authentic samples.

[^{11}C]Methyltriphenylphosphonium iodide ([^{11}C]MTPI) from [^{11}C]methyl iodide.

In a 1.5-ml conical shaped vial (equipped with a septum) 22 mg (0.10 mmol) triphenylphosphine was dissolved in 0.3 ml dry tetrahydrofuran. The [^{11}C]methyl iodide, prepared as described elsewhere (18), was transferred in a nitrogen gas stream into the cooled (-72 °C) vial via a needle through the septa. At the end of [^{11}C]methyl iodide transfer the vial was placed in a heating block, kept at 90 °C for 6 min. LC analysis was performed using the C-18 column and (A)/(B) 45/55 at flow 2 ml/min.

[β-^{11}C]Styrene by the stepwise procedure via [^{11}C]Methylenetriphenylphosphorane from [^{11}C]MTPI.

The vial containing the [^{11}C]MTPI-solution was then cooled to about -78 °C and thereafter placed in a lead block at room temperature. Approximately 50 µl of a 1 M solution of

butyllithium in hexane was added via a syringe until a yellow colour was produced. An excess of benzaldehyde (0.1 mmol) was added and the solution became colourless. The ^{11}C-styrene was then analysed by LC using the C-18 column with A/B 45/55 at flow 2 ml/min. and by GC at 70° C with a nitrogen flow of 40 ml/min.

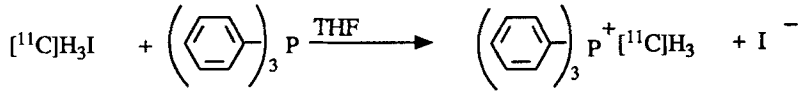
[β-^{11}C]Styrene in a one-pot synthesis

In a 1.5-ml cone-shaped vial, 22 mg (0.084 mmol) triphenylphosphine was dissolved in 0.30 mL tetrahydrofuran. The vial was sealed with a septum and the [^{11}C]methyl iodide produced according to our laboratory procedure was transferred in a nitrogen gas stream to the cooled vial (-78°C). The vial was placed in a heating block, kept at 90 °C for 6 min. The tetrahydrofuran was then removed by a stream of nitrogen gas and 0.10 ml 1.2-dibromobenzene, 18 µl (0.18 mmol) freshly distilled benzaldehyde and 22 µl (0.28 mmol) epichlorohydrin was added to the vial which was placed in the heating block and kept at 160°C for 7 min. The vial was cooled to room temperature and the reaction mixture was injected directly on the preparative LC column.

Semi-preparative LC was performed at room temperature using 80% metanol in formate buffer flow 7ml/min. The appropriate radioactive fractions were collected. The radiochemical purity and the specific radioactivity were then determined by LC using the C-18 column and solvents A/B 45/55 flow 2 ml/min.

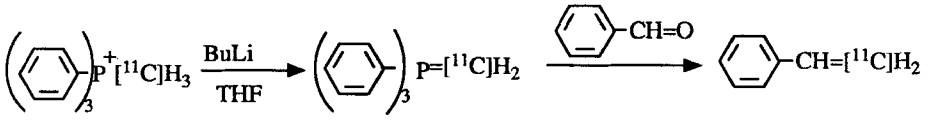
Results and discussions

In the search for a practical procedure of performing Wittig syntheses using the short lived ^{11}C, we started by investigating the use of the original stepwise procedure (17). This was performed by using the phosphonium salt synthesis starting from the appropriate alkyl halide and triphenylphosphine. [^{11}C]Methyl iodide was used as the alkylating reagent produced conveniently in a one-pot system (18). The [^{11}C]methyl iodide was trapped from the gas stream into the triphenylphosphine solution, and reacted according to scheme 1 upon heating to form [^{11}C]methyltriphenylphosphonium iodide in a radiochemical yield in the order 90%.



Scheme 1

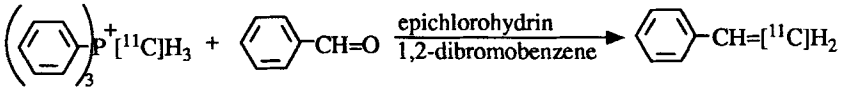
In the next step, the phosphorane ([^{11}C]methylenetriphenylphosphorane) was generated by adding one equivalent of a strong base such as butyllithium to the cooled reaction mixture. This was then followed by an addition to the appropriate aldehyde like benzaldehyde to give the desired labelled methylene compound, as shown in Scheme 2 for [β-^{11}C]styrene.



Scheme 2

The yield of the ^{11}C-labelled product varied considerably using the stepwise technique,sometimes giving several labelled side products. The first reaction step, the quarternization, was fast when performed at elevated temperatures and gave no labelled side products. The second step, the generation of the [^{11}C]methylenetriphenylphosphorane, however resulted in several side products. One reason for this variation could be that the amount of phosphonium salt formed probably varied due to variations in the amount of [^{11}C]methyl iodide trapped in the reaction mixture or by water/HI not being efficiently trapped in the methyl iodide product. The reproducibility of the amount of butyllithium added via the syringe was another problem, due to that the butyllithium solution is sensitive to moisture and the volumes used were small. The large variations in the radiochemical yield was therefore most likely caused by molar inequalities between the base and phosphonium salt.

The problem of generating the phosphorane by addition of a strong base, such as butyllithium, was avoided by using an epoxide as the precursor of the base. The epoxide reacted with the iodide ions liberated during the quarternization and a ring opening occurred giving a basic alkoxide ion. The amount of base versus amount of phosphonium salt was therefore controlled *in situ*. Furthermore, if hydriodic acid obtained in the reaction mixture due to the synthesis of [^{11}C]methyl iodide was transferred, the epoxide would also act as a buffer. Generating the base *in situ* from an epoxide as a base-precursor also made it possible to mix all the reagents (21,22,23) prior to the transfer of the [^{11}C]methyl iodide. The 'one-pot' synthesis is presented in Scheme 3, exemplified by a model reaction that is the synthesis of [β-^{11}C]styrene.



Scheme 3

In that case the following results were obtained. Radiochemical yield was 86% with a radiochemical purity of the crude product around 94%. The radiochemical purity of the purified product was 99%, with a specific radioactivity of 100MBq/μmol. No residues of 1,2-dibromobenzene was observed in the purified product. The total synthesis time, was around 40 min. In a typical experiment starting with 960 MBq ^{11}C-methyl iodide, 200 MBq of [β-^{11}C]styrene was thus obtained within 42 min.

The 'one-pot' synthesis is of particular interest for submicro scale syntheses, which is important when aiming for high specific radioactivity. The one pot approach also minimize radioactive losses caused by transfer between reaction flasks. In this case, the synthesis of [β-^{11}C]styrene, the Wittig reaction was performed in 1,2-dibromobenzene, in order to make

possible to perform a straight forward workup of the reaction mixture by semi-preparative LC. However, other solvents like 1,2-dichlorobenzene and high boiling ethers are useful as solvents in the Wittig reaction step. The choice of the epoxide was for convenience epichlorohydrin (1-chloro-2,3-epoxypropane), but other epoxides might be usable. Reactivity of the epoxide and the basicity of the resulting alkoxide ion are the main factors to consider, as has been discussed elsewhere (21,22,23). Side reactions caused by epoxides can be envisaged (23) (e.g. between triphenylphosphine and epichlorohydrin (24)) but such reactions were not detected in the investigation. Benzaldehyde was chosen as a substrate but other aldehydes or ketones, not to sterically hindered, can be applied by this Wittig labelling procedure. The exception is very base-sensitive substrates. The use of labelled triphenylphosphoranes in other Wittig syntheses is now in progress, since other ^{11}C-labelled alkyl iodides and benzyl iodides are available (11,12,13).

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