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SYNTHESIS OF [^{11}C]CYANOALKYLTRIPHENYLPHOSPHORANES VIA [^{11}C]CYANIDE SUBSTITUTION ON HALOALKYLPHOSPHONIUM SALTS

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Summary

The synthesis of the ^{11}C-labelled bifunctional precursors 3-[^{11}C]cyanoethyltriphenylphosphonium bromide (**1'**), 4-[^{11}C]cyanopropyltriphenylphosphonium bromide (**2'**), 5-[^{11}C]cyanobutyltriphenylphosphonium bromide (**3'**), 4-[^{11}C]cyanopropyltriphenylphosphonium iodide (**4'**) and 5-[^{11}C]cyanobutyltriphenylphosphonium iodide (**5'**) is presented. The label was introduced using [^{11}C]cyanide in a substitution reaction on the ω-haloalkyltriphenylphosphonium salt (bromide or iodide salt). The phosphonium salts **1'**- **5'** were formed in 33-99% radiochemical yield in 5-10 min reaction time. After addition of epichlorohydrin as generator of base, the precursors **1-3** were formed. The potential of the intermediates **1-3** in Wittig reactions was shown in model reactions with aromatic and aliphatic aldehydes. The aromatic olefins obtained from **1'**- **5'** were formed in 85-96 % radiochemical yield, with *Z/E* ratios between 67/33-75/25. The aliphatic olefins were obtained in 60-78% radiochemical yield from **4'** and **5'**. In the reaction with **1'** and an aliphatic aldehyde, the yield decreased to 5-10%. The *Z/E* ratios were 100/0 for the aliphatic olefins. In an experiment starting with 2,7 GBq (73 mCi) hydrogen [^{11}C]cyanide, 451 MBq (12.2 mCi) olefin from **3'** and 4-nitrobenzaldehyde was obtained in 44 min from hydrogen [^{11}C]cyanide production, with a 55 % decay corrected radiochemical yield, the radiochemical purity was 96%.

Keywords: [^{11}C]cyanide, Wittig reaction, triphenylphosphine, 3-[^{11}C]cyanoethyltriphenylphosphorane, 4-[^{11}C]cyanopropyltriphenylphosphorane, 5-[^{11}C]cyanobutyltriphenylphosphorane

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Introduction

The PET (Positron Emission Tomography) method[1] is becoming increasingly important in the visualization of biological functions *in vivo*, and is therefore in growing need for useful labelled compounds. An important contribution is the development of new labelled precursors, which makes new synthetic approaches possible. In the last years, the

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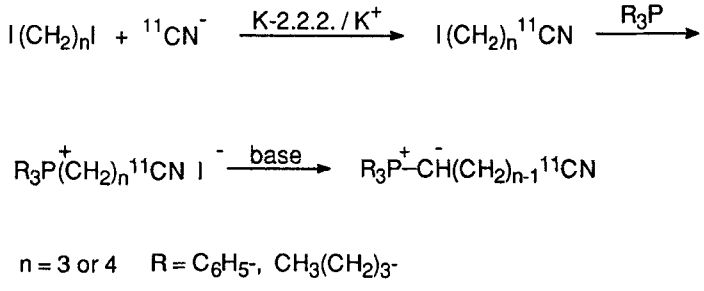
number of precursors specifically labelled with positron emitters has increased significantly. Labelled alkyl halides have been shown to be useful as precursors in labelling synthesis, [^{11}C]methyl iodide is an important example.[2] Other precursors include primary and secondary alkyl halides[3], phenethyl iodide[4] and benzyl iodides[5,6]. Methods for the synthesis of multifunctional precursors such as β- and carboxy ^{11}C-labelled pyruvic acid[7], acrylo[^{11}C]nitrile[8], [^{11}C]cinnamonitrile[8] and iodoalkyl[^{11}C] nitriles[9] have also been presented.

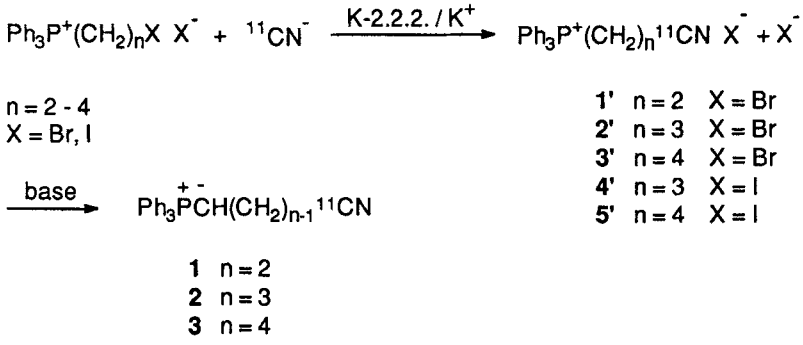
Recently, we presented the synthesis of some new multifunctional precursors to be used in Wittig reactions; 4-[^{11}C]cyanopropyltriphenylphosphorane, 5-[^{11}C]cyanobutyltriphenylphosphorane, 4-[^{11}C]cyanopropyltributylphosphorane and 5-[^{11}C]cyanobutyltributylphosphorane.[10] These precursors were prepared from ^{11}C-labelled iodoalkylnitriles[9] and triphenylphosphine or tributylphosphine (Scheme 1).



Scheme 1.

Treating the phosphonium salts with base and an aldehyde yielded olefins in 47-99 % radiochemical yield with the label in the terminal position. Labelled [^{11}C]methylenetriphenylphosphorane has been used in the reaction with various carbonyl compounds, yielding a product with a labelled methylene group.[11]

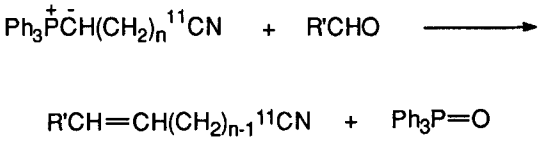
In this paper the synthesis of 3-[^{11}C]cyanoethyltriphenylphosphonium bromide (**1'**), 4-[^{11}C]cyanopropyltriphenylphosphonium bromide (**2'**), 5-[^{11}C]cyanobutyltriphenylphosphonium bromide (**3'**), 4-[^{11}C]cyanopropyltriphenylphosphonium iodide (**4'**) and 5-[^{11}C]cyanobutyltriphenylphosphonium iodide (**5'**) is presented (Scheme 2).



Scheme 2.

The [^{11}C]cyano group was incorporated in a substitution reaction with [^{11}C]cyanide directly on the corresponding ω-haloalkyltriphenylphosphonium salts[12,13], both the bromide- and iodide salts were used (Scheme 2). The products **1-3** were obtained using epichlorohydrin (1-chloro-2,3-epoxy-propane) as source of the base.

The potential of the intermediates **1-3** was shown in Wittig reactions with aromatic and aliphatic aldehydes (3-nitrobenzaldehyde, 4-nitrobezaldehyde, valeraldehyde and nonyl aldehyde). The olefins were produced in a one-pot reaction by adding a mixture of the proper aldehyde and epichlorohydrin in 1,2-dichlorobenzene to the phosphonium salts **1'-5'** (Scheme 2 and 3).



Scheme 3.

Experimental

General

The ^{11}C was produced using the Scanditronix MC-17 cyclotron at the Uppsala PET Centre, University of Uppsala. 17 MeV Protons were used in the ^{14}N(p,α)^{11}C reaction on a target containing nitrogen (AGA 6.0) with 0.1 % oxygen (AGA 4.8). Hydrogen

[^{11}C]cyanide was produced in the Scanditronix RNP-17 gas processing system, by a procedure described elsewhere.[14,15] The hydrogen [^{11}C]cyanide was trapped in 0.4-0.5 ml THF or MeCN containing 2.5-3.5 mg (7.5-9.3 μmol) Kryptofix®222 (4,7, 13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane) and 1.0 μl 1.0 M aqueous potassium hydroxide. Analytical HPLC was performed on a Hewlett-Packard 1090 liquid chromatograph with a UV-diode array detector in series with a β^+-flow detector, or on a Waters System (501 pump, automated gradient controler, 440 UV detector) with a β^+-flow detector in series. The analytical columns used were either a 300 x 4.6 mm 10 micron RP-C18 Bondapak (A) or a 250 x 4.1 mm 10 micron Hamilton PRP-1 column (B). The mobile phases used were 0.05 M ammonium formate (pH 3.5) (C), acetonitrile (MeCN):water 50:7 v:v (D) and methanol (E). Preparative LC was carried out using Beckman System Gold: Beckman 126 pump and a Spherisorb ODS-1 10 micron semi-preparative column (250 x 10 mm) connected to a Beckman 166 UV-detector in series with a β^+-flow detector. A modified Gilson 231 auto sampler was used for injection and fraction collection. ^{1}H NMR- (299.9 MHz) and ^{13}C NMR-spectra (75.4 MHz) were recorded on a Varian XL-300 spectrometer with chloroform ($CDCl_3$) or dimethyl-sulfoxide (DMSO-d_6) as solvent. Tetrahydrofuran (THF) was dried by distillation over sodium/benzophenone under a nitrogen gas atmosphere. 1,2-Dichlorobenzene was dried by distillation and stored over 4-Å molecular sieves. All other chemicals were used without further purification. Anhydrous MeCN was purchased from Aldrich.

*[^{11}C]Cyanoalkyltriphenylphosphonium bromides (**1'**, **2'** and **3'**) and [^{11}C]Cyanoalkyltriphenylphosphonium iodides (**4'** and **5'**).*

The appropriate ω-haloalkyltriphenylphosphonium salt[12,13] (9-19 μmol) was dissolved in 100 μl THF, 1,2-dichlorobenzene or MeCN. The solution was added with an air-tight syringe to the [^{11}C]cyanide trapped in THF or MeCN. The reaction mixture was heated and shaken at 90°C for 5-10 min. The identity and radiochemical purity of compounds **1'**- **5'** were determined by HPLC. Retention times and analytical systems used are presented in Table 1.

Table 1. Retention times and analytical HPLC-conditions used in the analysis of phosphonium salts **1'-5'** and labelled olefins.

Entry	Reaction	Retention time for the phosphonium salt (min)	Retention times for the olefins *cis/trans* (min)	Analytical HPLC-system
1	**1'**+ $CH_3(CH_2)_7CHO$	4.3	11.3	a
2	**1'**+ 4-$NO_2C_6H_4CHO$	4.3	13.2/14.0	a
3	**1'**+ 3-$NO_2C_6H_4CHO$	4.3	15.1/16.3	a
4	**1'**+ $CH_3(CH_7)CHO$	6.3-6.4	16.3	b
5	**2'**+ 4-$NO_2C_6H_4CHO$	9.1	12.6/13.0	b
6	**4'**+ 4-$NO_2C_6H_4CHO$	9.0-9.1	12.6/12.9	b
7	**4'**+ $CH_3(CH_2)_3CHO$	2.1	13.3	c
8	**3'**+ 3-$NO_2C_6H_4CHO$	9.9-10.0	13.2/13.7	b
9	**3'**+ 4-$NO_2C_6H_4CHO$	7.2	8.8/9.9	e
10	**5'**+ 3-$NO_2C_6H_4CHO$	10.0	13.1/14.1	b
11	**5'**+ $CH_3(CH_2)_7CHO$	6.7	13.4	d

HPLC-conditions:
a) column A: solvents C/D 60/40 v/v linear gradient to 10/90 over 5-15 min.
b) column B: solvents C/D 70/30 v/v linear gradient to 10/90 over 7-12 min, 10/90 12-17 min.
c) column B: solvents C/D 40/60 v/v linear gradient to 10/90 over 10-15 min.
d) column A: solvents C/D 70/30 v/v linear gradient to 10/90 over 8-12 min, 10/90 12-15 min.
e) column A: solvents C/D 60/40 v/v linear gradient to 10/90 over 4-12 min.
In a)-e): flow 2 ml min^{-1}, column temp 40 °C, wavelength 254 nm for the aromatic olefins and 230 nm for the aliphatic olefins.

Wittig reactions using phosphonium salts 1'-5'.

The proper aldehyde (0.10-0.13 mmol) and epichlorohydrin (20 µl, 0.25 mmol) were dissolved in 100 µl 1,2-dichlorobenzene. The solution was added to the [^{11}C]cyanoalkyltriphenylphosphonium bromides or iodides **1'**, **2'**, **3'**, **4'** or **5'** in THF, THF/1,2-dichlorobenzene or MeCN, prepared as described above. The reaction vial was heated and shaken at 140-150°C for 10 min. The identity and radiochemical purity of the olefins were determined by HPLC. Retention times and analytical systems used are presented in Table 1. For purification with semi-preparative LC, the reaction mixture was diluted with 0.2-0.3 ml ethanol prior injection. The LC-system used is described under *General*, flow 6 ml/min solvents C/E 65/35 v/v linear gradient to 20/80 over 4-9 min.

Results and discussion

3-[^{11}C]Cyanoethyltriphenylphosphorane (**1**), 4-[^{11}C]cyanopropyltriphenylphosphorane (**2**) and 5-[^{11}C]cyanobutyltriphenylphosphorane (**3**) were prepared as shown in Scheme 2. A nucleophilic substitution reaction was carried out using [^{11}C]cyanide and the corresponding ω-haloalkyltriphenylphosphonium salts, and the compounds **1'**, **2'**, **3'**, **4'** and **5'** were formed in 33-99 % radiochemical yield in 5-10 min (Table 2). No considerable increase in yield could be obtained using longer reaction times. However, to obtain the highest absolute radiochemical yield, it can be favourable to stop the reaction earlier, since the radioactive decay has to be taken into account.[16] The reactions were carried out either in THF, MeCN, or in a mixture of THF/1,2-dichlorobenzene (Table 2).

Table 2. Yields of labelled phosphonium salts from [^{11}C]cyanide and ω-haloalkyltriphenylphosphonium salts.

$$Ph_3P^+(CH_2)_nX\ X^- + {}^{11}CN^- \xrightarrow[\text{solvent}]{\text{K 2.2.2./K}^+} Ph_3P^+(CH_2)_n{}^{11}CN\ X + X^-$$

Entry	n	X	Solvent*	Product	Reaction temp.(°C)	Reaction time (min)	Radiochemical yield (%)
1	2	Br	MeCN	**1'**	90	5	63-93
2	2	Br	THF	**1'**	90	5	55-88
3	2	Br	THF/ODCB	**1'**	90	5	55-60
						10	91-94
4	3	Br	MeCN	**2'**	90	10	42-60
5	3	I	MeCN	**4'**	90	5	50-90
6	3	Br	THF/ODCB	**2'**	90	10	76-80
7	3	I	THF/ODCB	**4'**	90	10	33-40
8	4	Br	MeCN	**3'**	90	10	34-56
9	4	I	MeCN	**5'**	90	10	96-99
10	4	Br	THF/ODCB	**3'**	90	10	62-75
11	4	I	THF/ODCB	**5'**	90	5	78-93
						10	87-97
12	4	I	THF/ODCB	**5'**	130	5	78-84
						10	78-89

Each experiment have been repeated 3-8 times.
*ODCB=1,2-dichlorobenzene

In the synthesis of **1'** and **4'**, the highest yields were generally obtained in MeCN. In the synthesis of **5'**, high yields were obtained in both MeCN and in the mixture of THF/1,2-dichlorobenzene. The ω-haloalkyltriphenylphosphonium salts were synthesized from the corresponding bromo- or iododalkanes and triphenylphosphine, according to literature procedures.[12,13]

The use of [^{11}C]cyanoalkyltriphenylphosphoranes **1-3** has been studied on some aromatic and aliphatic aldehydes (3-nitrobensaldehyde, 4-nitrobensaldehyde, valeraldehyde and nonyl aldehyde). To form the phosphorane from the phosphonium salt, an alkoxide ion was used as the base.[18] The alkoxide was formed from the epoxide epichlorohydrin (1-chloro-2,3-epoxypropane) which was opened in the reaction with the halide ions released in the labelling substitution reaction. The generation of the base *in situ* makes it possible to add the aldehyde and epoxide together to the phosphonium salt.[11] The labelled olefins were formed in 5 to >95 % radiochemical yield, based on the phosphonium salts. The aromatic olefins from **1'- 5'** were formed in 85-96 % radiochemical yield. The *Z/E* ratios were between 67/33 - 75/25, as determined by HPLC. The aliphatic olefins were obtained in 60-78 % radiochemical yield from **4'** and **5'**, in the reaction with **1'** the yields decreased to 5-10 %. The *Z/E* ratios were 100/0 for the aliphatic olefins. The labelled olefins, prepared as shown in entry 9 and 10 in Table 1, were purified by semi-preparative HPLC. The olefins were obtained in 55-62 % decay corrected radiochemical yield in 38-44 min from hydrogen [^{11}C]cyanide production. The radiochemical purity were 96-97 %. When using other bases in the Wittig reaction, it is possible that the stereochemical outcome is changed. Generally, when Z-alkenes are the desired product, non-stabilized ylides are used, and salt-free reaction conditions (especially free from lithium salts) are employed.[17] The *Z/E* ratio may vary as the halide is changed from chloride to bromide to iodide, and it may also be solvent-dependent. In this case, we did not observe any change in the stereochemical outcome when using the bromide or iodide salt.

It was not possible to use the route presented in Scheme 1 in the synthesis of **1'**, since there is not an established method for synthesizing haloethyl[^{11}C]nitriles. Thus we adopted the presented procedure for the preparation of labelled phosphonium salts with

shorter carbon-chains and approached the problem by carrying out the quaternization before the [^{11}C]cyanide was introduced. Furthermore, the synthesis time for obtaining **2'** and **3'** with this method was shorter (5-10 min) compared to the earlier method (15 min), counted from [^{11}C]cyanide.

It has been shown that these ω-haloalkyltriphenylphosphonium salts may undergo an intramolecular nucleophilic displacement, which can lead to cyclic products (Figure 1).[12] We have not noticed any decrease in radiochemical yields due to this phenomenon.

X = Br, I

Figure 1.

The identity of the ^{11}C-labelled phosphonium salts **1'** - **5'** and the olefins was determined by addition of reference substances, characterized by ^{1}H NMR- and ^{13}C NMR-spectroscopy. In the HPLC analysis, the signal from the radio detector was simultaneous with the UV-signal, corrected for the time delay between the detectors. To verify that all the radioactive material injected into the HPLC analytical column had been eluted, the radioactivity at the outlet of the column was compared with the amount in the injected volume.

The high yields in the syntheses of phosphonium salts **1'-5'** makes it interesting to further investigate the utility of these ^{11}C-labelled precursors in the production of ^{11}C-labelled olefins. A variety of functional groups can be generated from the terminal cyano group, e.g., transformation into an acid, amide or amine group. We anticipate that it is possible to synthesize labelled precursors with longer carbon chains by the use of the above presented methods. Subsequent reaction with a base and a carbonyl compound would produce labelled alkenes with various structures, e.g., analogues of fatty acids and prostaglandins.

Acknowledgement

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