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Synthesis of [^{11}C]Cyanoalkylphosphoranes and their Use in the Preparation of ^{11}C-Olefins

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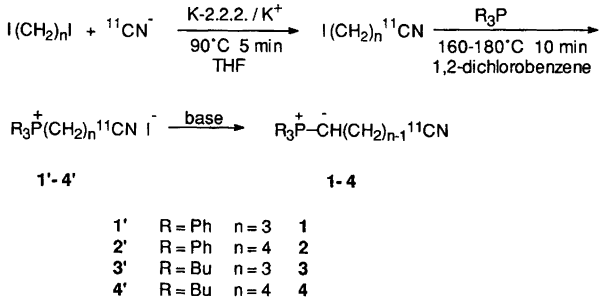
The synthesis of the ^{11}C-labelled bifunctional precursors 3-[^{11}C]cyanopropylidene(triphenyl)phosphorane (**1**), 4-[^{11}C]cyanobutylidene(triphenyl)phosphorane (**2**), 3-[^{11}C]cyanopropylidene(tributyl)phosphorane (**3**) and 4-[^{11}C]cyanobutylidene(tributyl)phosphorane (**4**) is presented. [^{11}C]Cyanide was introduced in a substitution reaction with the corresponding diiodoalkane. The iodoalkano[^{11}C]nitriles were then reacted with triphenylphosphine or tributylphosphine producing the labelled phosphonium salts **1′–4′**. The decay-corrected radiochemical yields were 90–99% in 10–15 min, counted from the end of production of hydrogen [^{11}C]cyanide. The phosphonium salts were treated with base to form the compounds **1–4**. The labelled phosphoranes **1–4** were used in one-pot model reactions with some aliphatic and aromatic aldehydes, to form olefins in 47–99% decay-corrected radiochemical yield. The *Z:E* ratios of the olefins were determined using HPLC. Using phosphoranes **1** and **2** the *Z:E* ratios were 71:29–100:0. When using phosphoranes **3** and **4** the *Z:E* ratios were 28:72–19:81. In a ^{11}C-experiment starting with 100 mCi [^{11}C]cyanide, one of the labelled olefins was obtained in 67% decay-corrected radiochemical yield within 55 min. The radiochemical purity of the olefin was >98%. The position of the label was confirmed by a ^{11}C/^{13}C synthesis using the same reaction pathway, and analysed by ^{13}C NMR spectroscopy.

^{11}C-Labelled compounds can be used in positron emission tomography (PET)[1] for studying biological processes *in vivo*. PET allows the non-invasive determination of the distribution and pharmacokinetics of biologically active molecules labelled with positron emitting isotopes, e.g., ^{11}C (half-life = 20.3 min). With the continuous development of PET, it is important that the arsenal of available tracers is increased. Consequently, it is necessary to extend the number of labelled building-blocks, precursors. These new precursors should enable new synthetic routes to be developed, which may be useful for labelling in different positions of the molecule. The possibility of designing the radiotracer by controlling the position of the label adds a new dimension to PET. For example, it makes it possible to study the different metabolic pathways of the labelled tracer.[2]

Many biochemically and pharmacologically interesting compounds contain carbon–carbon double bonds. One of the most versatile methods for the introduction of a double bond is the Wittig reaction.[3] The Wittig reaction proceeds with defined positional and chemo-selectivity.



Scheme 1.

Recently the ^{11}C-labelled Wittig reagent [^{11}C]methylene(triphenyl)phosphorane was applied to the synthesis of compounds containing a labelled methylene group.[4] In this paper, the syntheses of four new precursors, 3-[^{11}C]cyanopropylidene(triphenyl)phosphorane (**1**), 4-[^{11}C]cyanobutylidene(triphenyl)phosphorane (**2**), 3-[^{11}C]cyanopropylidene(tributyl)phosphorane (**3**) and 4-[^{11}C]cyanobutylidene(tributyl)phosphorane (**4**) are presented. The ^{11}C-precursors (**1–4**) were used in Wittig reactions, and allowed the preparation of olefins with a la-

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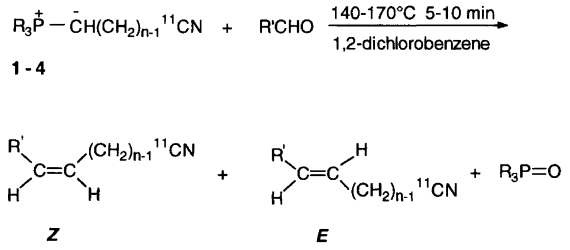
belled cyano group, two or three methylene groups away from the carbon–carbon double bond.

The [^{11}C]cyanoalkyl(triphenyl)phosphoranes (**1**, **2**) and [^{11}C]cyanoalkyl(tributyl)phosphoranes (**3**, **4**) were prepared according to Scheme 1. The labelled 4-iodobutyro[^{11}C]nitrile and 5-iodovalero[^{11}C]nitrile were synthesized by a substitution reaction with [^{11}C]cyanide and the corresponding diiodoalkanes.[5] The Wittig ylide was formed in a two-step process, involving nucleophilic attack of the phosphorus(III) reagent on the iodoalkano[^{11}C]nitrile, followed by deprotonation of the resulting phosphonium salt. To study the reactivity and utility of the phosphoranes (**1–4**), some aliphatic and aromatic aldehydes (benzaldehyde, 3-nitrobenzaldehyde, cinnamaldehyde, valeraldehyde and nonanal) were used as model substrates. The olefins were formed in a one-pot reaction by adding a mixture of the aldehyde and epichlorohydrin to the labelled phosphonium salts (Scheme 2).



R'= 3-$NO_2C_6H_4$, C_6H_5, $C_6H_5CH{=}CH$, $CH_3(CH_2)_3$, $CH_3(CH_2)_7$

n = 3 or 4

Scheme 2.

Experimental

General. The ^{11}C was produced by the Scanditronix MC-17 cyclotron at the Uppsala University PET Centre. A nitrogen target was bombarded with a 17 MeV proton beam producing ^{11}C by the ^{14}N(p,α)^{11}C nuclear reaction. Hydrogen [^{11}C]cyanide was produced in the Scanditronix RNP-17 gas processing system, as previously described.[6,7] The hydrogen [^{11}C]cyanide was trapped in tetrahydrofuran (THF) (500–700 µl) 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 1.5 µl of a 5 M aqueous solution of potassium hydroxide. Analytical HPLC was performed on a Hewlett-Packard 1090 liquid chromatograph with a UV-diode array detector, or on a Waters System (501 pump, automated gradient controller, 440 UV detector) with a β^+-flow detector in series. The analytical columns used were a 300 × 4.6 mm 10 micron RP-C18 Bondapak (A) and a 250 × 4.1 mm 10 micron Hamilton PRP-1 column (B). The mobile phases used were ammonium formate (0.05 M, pH 3.5) (C), potassium dihydrogen phosphate (0.01 M, pH = 4.6) (D), methanol (E) and acetonitrile–water (500:70 v:v) (F). Preparative LC was carried out using a Waters M-45 pump and a Spherisorb ODS-1 250 × 10 mm (i.d) 10 micron semipreparative column (G) in series with a Pharmacia Dual Path Monitor UV-2 and a β^+-flow detector. ^{1}H NMR (299.9 MHz) and ^{13}C NMR spectra (75.4 MHz) were recorded on a Varian XL-300 spectrometer with $CDCl_3$ or DMSO-d_6 as the solvent. 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. The glassware used was dried at 110°C.

^{11}C-Labelled triphenylphosphonium salts **1′** *and* **2′**. 4-Iodobutyro[^{11}C]nitrile and 5-iodovalero[^{11}C]nitrile were prepared in THF, as described elsewhere.[5] Triphenylphosphine (10 mg, 38 µmol) was dissolved in 100 µl 1,2-dichlorobenzene, added to the reaction vial which was subsequently heated at 160°C for 10 min. The labelled products **1′** and **2′** were then used directly in Wittig reactions with various aldehydes. Identity and radiochemical purity were determined by analytical HPLC using column A (solvents C–E 70:30 v/v linear gradient to 10:90 over 8–12 min, flow 2 ml min^{-1}, column temp 40°C, wavelength 254 nm). The retention times for **1′** and **2′** were 5.5 and 6.6 min, respectively.

^{11}C-Labelled tributylphosphonium salts **3′** *and* **4′**. The syntheses were carried out as above, except that 10 µl (40 µmol) tributylphosphine were used instead of triphenylphosphine. The reaction mixture was heated at 180°C for 5 min. Identity and radiochemical purity were determined by analytical HPLC using column A (solvents C–E 70:30 v/v linear gradient to 10:90 over 8–12 min, flow 2 ml min^{-1}, column temp 40°C, wavelength 254 nm). The retention times for **3′** and **4′** were 5.4 and 6.5 min, respectively.

General procedure for the Wittig reaction of phosphonium salts **1′**, **2′**, **3′** *and* **4′**. The phosphoranes **1–4** were formed by adding epichlorohydrin (1-chloro-2,3-epoxypropane), as precursor of the base, to the phosphonium salts **1′–4′**. The aldehyde (0.20 mmol) and 22 µl (0.28 mmol) epichlorohydrin were dissolved in 100 µl 1,2-dichlorobenzene and added to the phosphonium salts. The reaction vial was heated at 140–170°C for 10 min. Compound identity and radiochemical purity were determined by analytical HPLC. The retention times for the phosphonium salts (**1′–4′**) and the olefins and the analytical HPLC systems used are presented in Table 1.

6-(3-Nitrophenyl)-5-hexene[^{11}C]/[(^{13}C)nitrile. The [^{11}C]cyanide was trapped in THF (600 µl) containing 2.2 mg (33 µmol) potassium (^{13}C)cyanide, 16.2 mg (43 µmol) Kryptofix®222 and 5 µl distilled water. After trapping, 5 µl (38 µmol) 1,4-diiodobutane in 200 µl THF were added. The reaction mixture was heated at 90°C for 7 min. Triphenylphosphine (20 mg, 76 µmol) dissolved in

Table 1. Retention times and analytical HPLC systems used for the analysis of phosphonium salts **1′-4′** and the labelled olefins.

Entry	Reaction phosphonium salt + aldehyde	Retention time for the phosphonium salt	Retention times for the olefins *cis/trans*	Analytical HPLC system[a]
1	**1′** + 3-$NO_2C_6H_4CHO$	2.1	10.8/11.3	V
2	**1′** + C_6H_4CHO	5.0	8.4/9.0	I
3	**1′** + $C_6H_5CH{=}CHCHO$	5.5	10.7	III
4	**1′** + $CH_3(CH_2)_3CHO$	2.1	13.3	IV
5	**1′** + $CH_3(CH_2)_7CHO$	3.8	13.8	VI
6	**2′** + 3-$NO_2C_6H_4CHO$	6.5	7.1/8.1	II
7	**2′** + C_6H_4CHO	5.7	9.4/9.9	I
8	**2′** + $C_6H_5CH{=}CHCHO$	6.6	11.8	III
9	**2′** + $CH_3(CH_2)_3CHO$	6.6	12.2	III
10	**2′** + $CH_3(CH_2)_7CHO$	6.7	13.4	III
11	**3′** + 3-$NO_2C_6H_4CHO$	2.0	10.8/11.3	V
12	**3′** + $CH_3(CH_2)_7CHO$	4.4	13.2/14.0	VI
13	**4′** + 3-$NO_2C_6H_4CHO$	5.9	7.1/8.1	II
14	**4′** + $CH_3(CH_2)_3CHO$	6.5	12.3/13.2	III
15	**4′** + $CH_3(CH_2)_7CHO$	5.3	13.3/14.2	III

[a] Analytical HPLC systems:
I, Column A: solvents C–F 60:40 v/v linear gradient to 10:90 over 8–12 min.
II, Column A: solvents C–F 70:30 v/v linear gradient to 10:90 over 8–14 min.
III, Column A: solvents C–F 70:30 v/v linear gradient to 10:90 over 8–12 min.
IV, Column B: solvents C–F 40:60 v/v linear gradient to 10:90 over 10–15 min.
V, Column B: solvents C–F 50:50 v/v linear gradient to 10:90 over 10–15 min.
VI, Column B: solvents C–F 40:60 v/v linear gradient to 10:90 over 7–12 min.
In all analytical HPLC systems the following conditions were used: flow 2 ml min^{-1} column temp. 40°C, wavelength 254 nm for the aromatic olefins and 230 nm for the aliphatic olefins.

50 µl 1,2-dibromobenzene was added and the mixture was kept at 180°C for 10 min. After cooling the reaction vial in a water bath to room temperature, a mixture of 30 mg (0.20 mmol) 3-nitrobenzaldehyde and 22 µl (0.28 mmol) epichlorohydrin in 50 µl 1,2-dibromobenzene was added and the reaction mixture was heated at 180°C for 10 min. The crude product was diluted with 200 µl acetonitrile and purified by HPLC using the semi-preparative system described under *General*. Conditions used: flow 3 ml min^{-1}, solvents C–E 20:80. The retention time for the labelled *Z*- and *E*-olefins was ca. 18 min. The collected fraction was diluted with 15 ml brine and extracted with ether (2 × 10 ml). The organic phase was dried with sodium sulfate, filtered and evaporated. The residue was redissolved in 0.6 ml $CDCl_3$. The ^{13}C NMR spectrum showed two peaks at δ 119.15 and 119.27, which are consistent with the nitrile carbons in (*Z*)- and (*E*)-6-(3-nitrophenyl)-5-hexenenitrile.

Results and discussion

The synthesis of nitriles from cyanide by a displacement reaction is a useful method for extending a carbon chain by one carbon. The cyano group can subsequently be transformed into various functional groups, e.g., carboxylic acid, amide or amine. Recently, we have presented a method for the synthesis of ^{11}C-labelled iodoalkanonitriles (4-iodobutyro[^{11}C]nitrile and 5-iodovalero-[^{11}C]nitrile) from [^{11}C]cyanide and the corresponding diiodoalkanes.[5] With the aim of making these iodoalkano[^{11}C]nitriles further useful as precursors, involving the carbon–carbon bond forming approach, we here present a procedure for their conversion into triphenylphosphonium or tributylphosphonium salts, useful in Wittig reactions as shown in Schemes 1 and 2.

The ^{11}C-labelled iodoalkanonitriles were prepared using THF as the solvent. In the preparation of **1′** and **2′**, triphenylphosphine was dissolved in 1,2-dichlorobenzene and added to the reaction mixture, which then was heated. The quaternization step was efficient at high temperatures, after 10 min at 160°C, radiochemical yields of 90–99% were obtained for the labelled **1′** and **2′**, calculated from the iodoalkano[^{11}C]nitriles. When using a lower reaction temperature, 130°C for 10 min, the yields of the phosphonium salts **1′** and **2′** decreased to 60–65%. The tributylphosphonium salts **3′** and **4′** were prepared by addition of tributylphosphine in 1,2-dichlorobenzene to the labelled iodoalkanonitriles. The reaction mixture was heated at 180°C for 5 min producing the compounds **3′** and **4′**, respectively. The radiochemical yields were 98–99% for **3′** and **4′**, calculated from the iodoalkano[^{11}C]nitriles. The yields decreased when a lower reaction temperature was used. When the concentrations of diiodoalkane and phosphine were reduced to one tenth or even one half of the amounts mentioned in the Experimental section (ca. 20 µmol diiodoalkane and 40 µmol phosphine) the yields of the phosphonium salts decreased significantly. To obtain as high yields as above, longer reaction times were needed, around 20 min. However, even if the radiochemical yield is very high after one

half-life, it may be more favourable to quench the reaction earlier, since the radioactive decay has to be taken into account to obtain the highest absolute radiochemical yield.[8]

The use of ^{11}C-labelled phosphonium iodides (**1'–4'**) in Wittig reactions was studied using both aliphatic and aromatic aldehydes, see Scheme 2 and Table 2. The carbonyl compounds used were 3-nitrobenzaldehyde, benzaldehyde, cinnamaldehyde, valeraldehyde and nonanal. Epichlorohydrin was used as precursor of the base to form the phosphorane.[9] The epoxide opens in the reaction with the free iodide ions (formed when **1'–4'** are produced) generating the basic alkoxide ion. The amount of base *versus* the amount of phosphonium salt is thereby controlled *in situ*. The use of a strong base, such as butyllithium in THF, resulted mostly in the formation of side products, since it is very difficult to control the exact amount of base that is required under the existing conditions. Generating base *in situ* from an epoxide makes it possible to mix the aldehyde and epoxide and then add them to the labelled phosphonium salt. This procedure has the advantage of no losses of radioactivity by transfers between reaction vials. It also causes less radiation exposure to the chemist, simplifies handling and gives reproducible yields. In the Wittig reactions with the triphenylphosphoranes **1** and **2** and the aldehydes, the radiochemical yields were 59–98%. In the Wittig reactions when the tributylphosphoranes **3** and **4** were used, the radiochemical yield decreased to 47–65%. Three different labelled olefins, synthesized as in entries 8, 9 and 11 in Table 1, were purified by semipreparative HPLC. The olefins were obtained in 60–67% decay-corrected radiochemical yields in 35–55 min, counted from the end of [^{11}C]cyanide production. The radiochemical purities of the olefins were 98–99%.

Table 2. cis/trans ratios and yields for the ^{11}C-labelled olefins produced in the reactions with the aldehydes and ylides **1–4**.

Entry[a]	Aldehyde	Ylide	*cis*:*trans*[b]	Yield (%)[c,d]	
1	3-$NO_2C_6H_4CHO$	**1**	74:26	>99	
2	C_6H_5CHO	**1**	75:25	>90	
3	$C_6H_5CH{=}CHCHO$	**1**	100:0	>99	
4	$CH_3(CH_2)_3CHO$	**1**	100:0	59–60	
5	$CH_3(CH_2)_7CHO$	**1**	100:0	65–70	
6	3-$NO_2C_6H_4CHO$	**2**	72:28±1*	98–99	
7	C_6H_5CHO	**2**	75:25	92–93	
8	$C_6H_5CH{=}CHCHO$	**2**	100:0	>99	(67)
9	$CH_3(CH_2)_3CHO$	**2**	100:0	>99	(63)
10	$CH_3(CH_2)_7CHO$	**2**	100:0	63–68	(60)
11	3-$NO_2C_6H_4CHO$	**3**	19:81	61–65	
12	$CH_3(CH_2)_7CHO$	**3**	28:72	51–55	
13	3-$NO_2C_6H_4CHO$	**4**	20:80	63–65	
14	$CH_3(CH_2)_3CHO$	**4**	28:72	52–60	
15	$CH_3(CH_2)_7CHO$	**4**	27:73	47–52	

At least three repeated experiments.

[a] All reactions were carried out with the base generated from epichlorohydrin. The solvent used was 1,2-dichlorobenzene. [b] The *cis/trans* ratio was determined by HPLC analysis as described in the Experimental. [c] Determined by HPLC analysis of the reaction mixture, decay-corrected and based on the total amount of phosphonium salt. The values in parentheses are decay-corrected radiochemical yields after purification with semipreparative HPLC, based on the amount of [^{11}C]cyanide trapped. *The *cis:trans* ratio was the same after heating the reaction mixture at 90°C for an additional 30 min.

In the Wittig reactions 1,2-dichlorobenzene was used as the solvent, owing to its polar, aprotic properties. In dimethyl sulfoxide (DMSO) with epichlorohydrin as precursor of the base, no olefin products were formed. In THF (with epichlorohydrin as precursor of the base) olefins were formed but in low yields, probably due to the lower polarity and boiling point.[10]

The *Z:E* ratios of the olefin products were determined using reversed-phase HPLC (see Table 2). When the Wittig reaction is carried out with triphenylphosphoranes in a solution free from inorganic salts, especially lithium salts, the *Z*-alkene is the major product.[3,11] The *Z*-olefin was formed exclusively when the aliphatic aldehydes were used. Using aromatic aldehydes, the ratios were ca. 75:25. It is misleading to extrapolate the behaviour from aromatic aldehydes to aliphatic aldehydes because there are distinct differences in the reactions of aliphatic and aromatic aldehydes with regard to reversibility of the initial addition products. Vedejs and co-workers[12] have given evidence that salt-free Wittig reactions with unbranched aliphatic aldehydes occur with less than 2% equilibration and are therefore under kinetic control. Their studies suggest that the *Z:E* ratios correspond to a kinetic selectivity in the addition step. While *cis*-oxaphosphetanes can equilibrate, the more stable *trans* intermediates do not. Replacement of the 'traditional' phenyl groups on phosphorus by electron-donating alkyl groups, in this case butyl groups, resulted in the formation of the labelled *E*-alkene as the major product. In these reactions the *Z:E* ratios were 28:72–19:81, Table 2. The alkyl groups reduce the positive charge on the phosphorus and the equilibrium between the two oxaphosphetane intermediates and/or a steric interaction hinders the pathway which produces the *Z*-product.[12] Milder reaction conditions can usually be used in reactions with tributyl reagents compared with those of triphenyl reagents. The *Z:E* ratio may vary as the base and the halide is changed, and may also be solvent-dependent.[11]

To confirm that the position of the label was correct a [^{11}C]/(^{13}C)-synthesis was carried out. The same procedure as described for the reaction between ylide **2** and 3-nitrobenzaldehyde was repeated with potassium (^{13}C)cyanide added to the trapping solution, see the Experimental. After purification using HPLC and work-up, the residue was dissolved in $CDCl_3$. The ^{13}C NMR spectrum showed two peaks at 119.15 and 119.27 ppm, which are consistent with the signals from the nitrile carbons in (*Z*)- and (*E*)-6-(3-nitrophenyl)-5-hexenenitrile.

The identity and radiochemical purity of the ^{11}C-labelled phosphonium salts **1–4** and the olefins were determined using HPLC. The reference substances of the phosphonium salts and the olefins were synthesized ac-

cording to standard procedures in the literature. The substances were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy and in some cases COSY. 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′–4′** makes it interesting to study further the application of these ^{11}C-labelled precursors in the production of ^{11}C-labelled olefins. The arsenal of other available ^{11}C-labelled alkyl halides[13] may also be used in the reaction with phosphines. Subsequent reaction with a base and a carbonyl compound would produce labelled alkenes with various structures. It is possible to perform further transformations on the labelled olefins, for example addition to the double bond, conversion of the cyano group into the corresponding labelled acid, amine or amide group. The main advantage presented here is that it is possible to obtain olefins with *cis-* or *trans-* stereochemistry in high radiochemical yields within a reasonable synthesis time, with respect to ^{11}C-labelling.

Conclusions

In the synthesis of ^{11}C-labelled olefins with precursors **1′–4′**, the stereochemistry of the double bond can be controlled by using an appropriate phosphonium reagent. When triphenylphosphoranes were used in the reaction with aldehydes under salt-free reaction conditions, the *Z:E* ratios were 71:29–100:0. Conversely, when the tributylphosphoranes were used in the olefin synthesis the major product was the *trans*-isomer. In these reactions, the *Z:E* ratios were 28:72–19:81.

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