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[^{11}C]Methyl(2-thienyl)cuprates, New ^{11}C-Precursors Used in the Syntheses of ^{11}C-Labelled Methyl Ketones and Octane

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^{11}C-Labelled methyl(2-thienyl)cuprates were obtained from [^{11}C]methyl iodide, via conversion into [^{11}C]methyllithium and subsequent reaction with lithium (2-thienyl)cuprates or by a one-step reaction using a reactive zero-valent copper complex. In reactions with carboxylic acid chlorides, [*methyl*-^{11}C]acetophenone and [*methyl*-^{11}C]acetone were obtained in 47–90% decay-corrected radiochemical yield within 15 min, counted from [^{11}C]methyl iodide. In reactions with heptyl iodide, [1-^{11}C]octane was obtained in 7–42% decay-corrected radiochemical yield within 25 min. The ^{11}C-labelled products were isolated by semi-preparative HPLC affording products with radiochemical purities greater than 98%. Position-specific labelling was assessed by ^{13}C NMR analysis of (α-*methyl*-^{13}C)methyl pentadecyl ketone obtained from (^{13}C)methyl(2-thienyl)cyanocuprate.

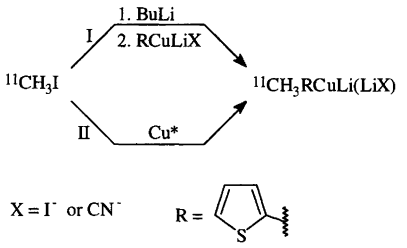
Tracers labelled with short-lived positron-emitting radionuclides (e.g., ^{11}C, $t_{1/2}$=20.3 min), in combination with positron emission tomography (PET), are used in non-invasive human or animal *in vivo* studies.[1] Special synthetic procedures are required for the production of these tracers because of the radioactivity, the short half-lives and the submicromole amounts of the labelled substances.[2] An important part of the elaboration of these procedures is the development of new ^{11}C-labelled precursors, which are important not only for labelling new types of compounds, but also for increasing the possibility of labelling a given compound in different positions.[3]

In the synthesis of ^{11}C-labelled compounds, [^{11}C]methyl iodide[4] is the precursor used most frequently. It is conveniently prepared and is useful for ^{11}C-labelling of a large number of biologically active substances.

To increase the labelling possibilities, it is valuable to have access to a ^{11}C-labelled nucleophilic methylation reagent that is comparable to [^{11}C]methyl iodide in its versatility. So far, reported examples are [^{11}C]methyllithium,[5] ^{11}C-labelled methylmagnesium halides[6] and [^{11}C]methylpalladium–tetrakis(triphenylphosphine) complex.[7] The only reported successful ^{11}C–C coupling with sp^3-carbons using [^{11}C]methyllithium, is the synthesis of [3-^{11}C]propanal from an activated alkyl bromide (2-bromomethyl-1,3-dioxolane).[8] The [^{11}C]methylpalladium complex, on the other hand, has been successfully used in various reactions with boron and tin reagents.[7]

A standard procedure to achieve C–C bond formation, between two unactivated sp^3-carbon centres, involves the use of organocuprates.[9] This type of reaction has been applied in the syntheses of methyl and methylene ^{11}C-labelled fatty acids using ^{11}C-labelled alkyl iodides and bis-Grignard reagents.[10] The use of organolithium and Grignard reagents, in contrast with organocopper reagents, excludes the presence of unprotected carbonyl groups. For this reason reactive ^{11}C-alkyl cuprates may be used in coupling reactions with carbonyl-containing alkyl halides as well as carboxylic acid chlorides, α,β-unsaturated ketones, epoxides and alkynes.

Two different routes to ^{11}C-labelled methyl(2-thienyl)cuprates were investigated (Scheme 1).



Scheme 1.

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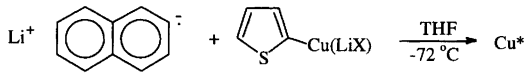
The ^{11}C-labelled cuprates were prepared either via [^{11}C]methyllithium (method I), or directly from [^{11}C]methyl iodide (method II), using a zero-valent copper complex[11] (Cu*, Scheme 2).



X = I⁻ or CN⁻

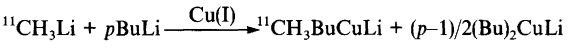
Scheme 2.

In this report on ^{11}C-labelled methyl cuprates, labelling reactions with alkyl halides and carboxylic acid chlorides were chosen as models.

Results and discussion

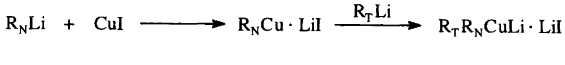
The possibility of obtaining a reactive ^{11}C-labelled Gilman cuprate by the common method of adding a copper(I) salt to an alkyllithium reagent was investigated. [^{11}C]Methyllithium, obtained by an exchange reaction with butyllithium as described previously,[5] was reacted with copper(I) bromide, but the resulting reagent did not give any ^{11}C-labelled coupling product (^{11}C-octane) when reacted with heptyl iodide. A reason for this lack of reactivity might be the excess of butyllithium (Scheme 3). In the coupling reaction with the dialkyl cuprate, the butyl group, rather than the methyl group, is transferred and the residual monoalkyl cuprate does not react.[12]

For this reason, mixed cuprates (RR_NCuLi) with one non-transferrable ligand, R_N,[13] were investigated (Scheme 4). Cuprate reagents obtained from reactions of copper(I) iodide with lithium thiophenoxide,[14] lithium-dicyclohexylamide[15] and 2-thienyllithium,[14] respectively, were used together with [^{11}C]methyllithium in reactions with heptyl iodide. ^{11}C-Labelled octane was, however, formed only when lithium (2-thienyl)iodocuprate was used. One reason is probably the exceptional thermal stability of the mixed cuprates derived from lithium



p=200-1000 (molar excess)

Scheme 3.



Examples of R_N (non-transferable ligands)

C_6H_5S-

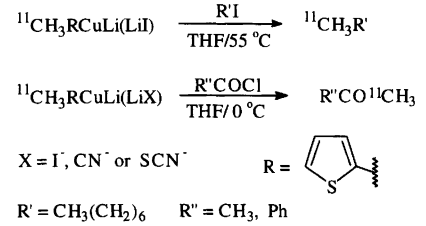
$(C_6H_{11})_2N$-

(2-thienyl)

Scheme 4.

(2-thienyl)iodocuprate. While most alkyl cuprates rapidly decompose to form Cu^0 at temperatures above 0 °C, lithium butyl(2-thienyl)cuprates can be kept at 60 °C for more than 20 min without any obvious sign of decomposition.

In conjunction with lithium (2-thienyl)iodocuprate, the corresponding cyano and thiocyano compounds were investigated. Using these reagents, obtained by method I (Scheme1), ^{11}C-octane and ^{11}C-labelled methyl ketones were synthesised according to Scheme 5.



Scheme 5.

In order to avoid the concomitant butyl reagent and to find a more rapid and simple route to the ^{11}C-labelled methylcuprates, a procedure developed by Rieke *et al.* was investigated. This approach is based on the use of highly reactive zero-valent copper complexes obtained from organocuprates or cuprate complexes obtained by lithium naphthalenide reduction.[11] The resulting zero-valent copper complex is then used to form an organocuprate reagent directly from the corresponding alkyl halide.

Using the lithium (2-thienyl)cuprates, a zero-valent copper complex (Cu*, Scheme 2) was formed, by means of which the ^{11}C-labelled methyl(2-thienyl)cuprate could be obtained directly from [^{11}C]methyl iodide. The ^{11}C-labelled cuprates obtained by this route (method II, Scheme 1) were used in the same reactions (Scheme 5) as those from method I.

Table 1 shows a comparison between methods I and II, as well as between the different cuprates, in the synthesis of [*methyl*-^{11}C]acetophenone (**1**). The reason why lithium [^{11}C]methyl(2-thienyl)cyanocuprate

Table 1. Radiochemical yields of [*methyl*-^{11}C]acetophenone utilizing method I or method II and various lithium (2-thienyl)cuprates.

Entry	Method, type of cuprate used	Radiochemical yield, acetophenone[a] (%)
1	I, Iodo	66 ± 10, $n=7$
2	I, Iodo[b]	25 ± 2, $n=3$
3	I, Cyano	82 + 8, $n=6$
4	I, Thiocyano	53 ± 3, $n=3$
5	I, None[c]	16 ± 5, $n=3$
6	II, Iodo	55 ± 3, $n=3$
7	II, Cyano	52 ± 5, $n=3$

[a]Decay-corrected, calculated from [^{11}C]methyl iodide. The radiochemical purity was in all cases higher than 98%. [b]One-tenth of the amount of benzoyl chloride used. [c]Benzoyl chloride reacted directly with [^{11}C]methyllithium.

(entry 3) gave a somewhat higher yield than the corresponding iodo compound (entry 1) is probably due to its stability. The yield of [*methyl*-^{11}C]acetophenone, using a large excess of benzoyl chloride, was similar to that of [^{11}C]methane obtained when the ^{11}C-labelled cuprate is quenched. The yield of the ^{11}C-labelled cuprates can be estimated by measuring the yield of [^{11}C]methane. As shown in Table 3, entry 3, the cyano compound gave about 15% higher yield of [^{11}C]methane, compared with the iodo compound.

The same argument can be used to explain why method I gave higher yields of [*methyl*-^{11}C]acetophenone than method II (Table 1, entries 3 and 7). As shown in Table 3, entry 3, the yield of [^{11}C]methane, obtained from the quenched ^{11}C-labelled cuprate, was about 15% higher using method I compared with method II.

The lower yield of [*methyl*-^{11}C]acetophenone obtained when lithium [^{11}C]methyl(2-thienyl)thiocyanocuprate was used (Table 1, entry 4) was mainly due to slower product formation. When the other cuprates were used, only trace amounts of [^{11}C]methane could be found in the crude product after 15 s reaction. The corresponding value using lithium (2-thienyl)thiocyanocuprate was 20–30%. Another disadvantage of this reagent was the precipitate that formed when the reaction was quenched.

In the standard [*methyl*-^{11}C]acetophenone synthesis, benzoyl chloride was used in relatively large amounts [86 μmol, 3.4 equiv. based on lithium (2-thienyl)cyanocuprate]. In applications requiring expensive, high molecular-weight substrates, minimizing the amount of carboxylic acid chloride is necessary. For this reason the yield of [*methyl*-^{11}C]acetophenone was optimised using method I and only 9 μmol benzoyl chloride.

The best results (Table 1, entry 2) were obtained when the total volume and the amounts of butyllithium and cuprate were decreased while the excess and concentration of benzoyl chloride was kept similar to the standard experiments.

When benzoyl chloride was reacted directly with [^{11}C]methyllithium (Table 1, entry 5), the [^{11}C]-methyllithium was consumed within 15 s, but the yield of [*methyl*-^{11}C]acetophenone was low.

In order to confirm the label position of the ^{11}C-labelled methyl ketones, (α-*methyl*-^{13}C)methyl pentadecyl ketone, was synthesised using method I and analysed by ^{13}C NMR spectroscopy. The ^{13}C NMR spectrum showed one main peak at δ 29.8, which was in accordance with values reported for methyl groups of alkyl methyl ketones.[16] The synthesis of (α-*methyl*-^{13}C)methyl pentadecyl ketone also shows that the procedures described in this paper (at least method I), should be useful for syntheses of ^{13}C-substituted compounds.

In Table 2 the yield of [1-^{11}C]octane obtained in reactions with heptyl iodide is shown. In these experiments, benzoyl chloride was added after the reaction with heptyl iodide. As discussed above, the reactive ^{11}C-labelled methyl(2-thienyl)cuprate is nearly quantitatively converted into [*methyl*-^{11}C]acetophenone. Through this procedure the residual amount of reactive ^{11}C-labelled methyl(2-thienyl)cuprate, which was not directly measurable, was determined as the amount of [*methyl*-^{11}C]acetophenone formed. This procedure should be generally useful for yield optimization in reactions with ^{11}C-labelled cuprates.

The best yield of [1-^{11}C]octane (42%) was obtained when method II and lithium (2-thienyl)iodocuprate were used (entry 5). Using method I (entry 3), the product was formed much more slowly and the yields were lower. As shown in Table 2, the yield was independent of the cuprate type when method I was used (entries 1 and 3), while a considerable difference in yield was observed with different cuprate types in the case of method II (entries 7 and 8).

This difference in reactivity was probably due to the π-acidic nature of cyanide, leading to strong binding to the copper atom and stabilization of the electronic structure.[15]

An advantage of method II is its simple and rapid procedure, which may be valuable in the context of automation (Table 3). In method II the ^{11}C-labelled cuprate is obtained directly after trapping [^{11}C]methyl iodide, while in method I two successive additions of reagents are required before the ^{11}C-labelled cuprate could be obtained. In the preparation of [^{11}C]methyllithium, using small amounts of butyllithium (< 100 μmol), better results were obtained when butyllithium was added after the trapping of [^{11}C]methyl iodide. When butyllithium was added to the reaction vial prior to [^{11}C]methyl iodide trapping, low yields of the desired product was obtained due to formation of a labelled polar side product, presumably [^{11}C]methanol.

Method II gives a lower radiochemical yield of ^{11}C-labelled methyl cuprate than method I. This difference was, however, partly compensated by the fact that the production time was shorter when method I was used.

Purification of the crude product is another important aspect in which a difference between the two methods can be perceived. For example, when separation of the ^{11}C-labelled product from naphthalene is a problem, method I should be used instead of method II. On the other hand, if separation of the ^{11}C-labelled product from the product obtained from the butylcuprate is a problem, method II is preferred (Table 3).

For coupling reactions with alkyl iodides, higher yields are obtained and shorter reaction times result if the alkyl iodide is first reacted with Cu* and then with [^{11}C]methyl iodide, instead of using a ^{11}C-labelled methyl cuprate. The application of this method in the synthesis of [18-^{11}C]linoleic acid and some ^{11}C-labelled saturated fatty acids will be presented elsewhere.

Work is in progress to investigate the use of the lithium [^{11}C]methyl(2-thienyl)iodo- and -cyano-cuprates in reactions with other substrates such as α,β-unsaturated ketones, epoxides and alkynes.

Table 2. Radiochemical yields of [1-^{11}C]octane and [*methyl*-^{11}C]acetophenone in reactions with heptyl iodide followed by benzoyl chloride, utilizing method I or method II and various lithium (2-thienyl)cuprates.

Entry	Method, type of cuprate used	*t*/min	*T*/°C	Radiochemical yield, octane[a] (%)	Radiochemical yield, acetophenone[b] (%)
1	I, Iodo	10	80	25	<1
2	I, Iodo	5	80	25	<1
3	I, Cyano	10	80	25 ± 1	3 ± 1
4	I, Cyano	5	80	14	7
5	II, Iodo	5	80	42	0
6	II, Iodo	2	50	41	0
7	II, Iodo	1.5	50	40	0
8	II, Cyano	3	80	11	42
9	II, Cyano	2	50	7	42

[a]Decay-corrected, calculated from [^{11}C]methyl iodide. The radiochemical purity was greater than 98%. [b]Decay-corrected, calculated from [^{11}C]methyl iodide, using the HPLC-determined purity of [*methyl*-^{11}C]acetophenone in an early fraction.

Table 3. Comparison of methods A and B with respect to various production aspects.

Entry	Production aspect	Method I	Method II
1	Number of additions[a]	2	0
2	Production time[b]/min	5	0
3	Maximum yield of cuprate[c] (%)	80 (95)	65 (80)
4	Compounds in the crude product[d]	Substrate,[e] thiophene	Substrate,[e] thiophene, naphthalene

[a]Number of added reagents, from trapping of [^{11}C]methyl iodide to obtained labelled cuprate. [b]Time from trapping of [^{11}C]methyl iodide to to obtained labelled cuprate. [c]Fraction of formed [^{11}C]methane at quench of labelled cuprate; the first value refers to the use of the iodocuprate, the value in parentheses refers to the use of the cyanocuprate. [d]In amounts higher than 20 μmol, excluding solvent. [e]For example, alkyl halide or product formed from carboxylic acid chloride.

Conclusions

Two simple and rapid methods for the production of reactive ^{11}C-labelled methyl cuprates have been developed. Lithium [^{11}C]methyl(2-thienyl)iodocuprate and lithium [^{11}C]methyl(2-thienyl)cyanocuprate were prepared by both methods and tested in reactions with three different substrates. In general, both methods using either cuprate are valuable, but depending on the type of substrate and labelling reaction, one combination may be superior to the other. Method I should also be useful for syntheses of ^{13}C-substituted compounds.

Experimental

General. [^{11}C]Carbon dioxide was prepared by use of the Scanditronix MC-17 cyclotron at the Uppsala University PET Centre. The ^{14}N(p,α)^{11}C reaction was performed in a gas target containing nitrogen (AGA, Nitrogen 6.0) and 0.1% oxygen (AGA, Oxygen 4.8) bombarded with 17 MeV protons.

HPLC was performed with a Beckman 126 gradient pump and a Beckman 166 variable wavelength UV-detector in series with a β^+ flow detector. The following mobile phases were used: 0.05 M ammonium formate pH 3.5 (A), 0.01 M KH_2PO_4 (B), CH_2Cl_2–MeOH, (50:50 v/v) (C) and acetonitrile–water (50:7 v/v) (D). For analytical HPLC, a Beckman Ultrasphere ODS C_{18}, 5 μm, 250 × 4.6 mm ID column was used at a flow of 2 ml min^{-1}. For semi-preparative HPLC, a Beckman Ultrasphere ODS C_{18}, 5 μm, 250 × 10 mm, column was used at a flow of 5 ml min^{-1}. Synthia, an automated synthesis system,[17] was used for HPLC injection and fraction collection. Data collection and HPLC control were performed with the use of a Beckman System Gold chromatography software package. Analytical GC was performed on a Shimadzu GC-14A with a flame ionisation detector, in combination with a Raytest Raga 93 radiodetector and a GS-Alumina 50 m × 0.548 mm column (J&W Scientific) with a 12 ml min^{-1} flow of hydrogen gas. In the analysis of the ^{11}C-labelled compounds, authentic, unlabelled reference substances were used for comparison in all GC runs and in the HPLC runs in which compounds suitable for UV detection were to be analysed. ^{13}C NMR spectra were recorded on a Varian XL 300 spectrometer at 75.4 MHz with chloroform-d_1 as an internal standard.

THF was distilled under nitrogen from sodium–benzophenone. Lithium (2-thienyl)cyanocuprate and the copper(I) salts were purchased from Aldrich. In the preparation and use of the [^{11}C]methyl cuprates, a glass reaction vial consisting of a 0.3 ml tube attached to a superior spherical 1.5 ml expansion chamber was used.

Preparation of reagents. Lithium naphthalenide and the lithium (2-thienyl)cuprates were prepared and stored under argon. Some of the lithium (2-thienyl)cyanocuprate used was prepared as described.[18]

Lithium (2-thienyl) iodocuprate.[19] To a stirred solution of thiophene (0.30 ml, 3.75 mmol) in THF (2 ml) at 0 °C, butyllithium (3.5 mmol in 2.20 ml hexane) was added and the mixture was warmed to 30 °C. After 30 min the mixture was cooled to 0 °C and added to a stirred slurry of copper(I) iodide (0.66 g, 3.45 mmol) in THF (2 ml) at 0 °C. The mixture was stirred vigorously at 0 °C for 30 min and then warmed to room temperature over 20 min. The stirring was stopped and the supernatant was removed. THF (10 ml) was added, and the resulting solution was stored in the reaction flask. The concentration of the resulting cuprate solution was estimated to be 0.25 M.

Lithium (2-thienyl) thiocyanocuprate. Lithium (2-thienyl)-thiocyanocuprate was prepared in a similar manner to the lithium (2-thienyl)iodocuprate. Copper(I) thiocyanate (0.313 g, 3.5 mmol) was reacted with 2-thienyllithium (from 0.290 ml, 3.62 mmol thiophene and 3.5 mmol BuLi). After the mixture had become homogenous, THF (6 ml) was added.

Lithium naphthalenide. Lithium (86 mg, 12.5 mmol) and naphthalene (1.86 mg, 14.5 mmol) was reacted in THF (50 ml) at room temperature.

[^{11}C]Methyl iodide. [^{11}C]Carbon dioxide was delivered to a solution of lithium aluminium hydride (25 μmol, 0.25 ml THF) in a stream of nitrogen. After evaporation of THF, hydriodic acid (57%, 0.4 ml) was added and the reaction mixture was refluxed. During this process [^{11}C]methyl iodide was distilled off and transferred by a stream of nitrogen to the reaction vessel.[4] The synthesis was performed automatically with Synthia.[17]

[^{11}C]Methyl(2-thienyl) cuprates via [^{11}C]methyllithium (method I). [^{11}C]Methyl iodide was trapped in a reaction vial containing diethyl ether (100 μl) cooled to −72 °C. A solution of butyllithium in hexane (15 μl, 1.6 M, 24 μmol) was added. After 1 min a solution of lithium (2-thienyl)iodo- or -cyanocuprate in THF (100 μl, 0.25 M, 25 μmol) was added. The vial was agitated manually in such a manner that the solution became thoroughly mixed without getting dispersed on the surface of the glass and septum. The solution was then reacted for 0.5 min at 0 °C.

[^{11}C]Methyl(2-thienyl) cuprates via Cu and [^{11}C]-methyl iodide (method II).* A reaction vial was charged with lithium (2-thienyl)iodo- or -cyanocuprate (100 μl, 0.25 M, 25 μmol) and cooled to −72 °C. Lithium naphthalenide (100 μl, 0.25 M, 25 μmol) was added, the vial was agitated and the solution left for 20 min prior to [^{11}C]methyl iodide trapping. The ^{11}C-labelled methyl(2-thienyl)cuprates were used immediately after [^{11}C]methyl iodide trapping.

[^{11}C]Methyl(2-thienyl) cuprates, analysis and characterization. Ethanol (300 μl) was added to the ^{11}C-labelled methylcuprate at −72 °C and a sample was taken for HPLC and GC analysis. The amount of radioactivity was measured and the vial was placed in an ice bath. To remove [^{11}C]methane, a stream of argon (30 ml min^{-1}) was blown through the solution for 5 min and the amount of radioactivity was measured again. The residue was analysed by HPLC: mobile phase A–D 50:50, 5 min, gradient to A–D 100:0 over 5 min. Analytical GC: column temperature 50 °C. t_R = 1.0 min ([^{11}C]methane).

[Methyl-^{11}C]acetophenone, standard method. To the ^{11}C-labelled methyl cuprate obtained from lithium (2-thienyl)iodo-, -cyano- or -thiocyanocuprate (25 μmol), kept at 0 °C, benzoyl chloride (10 μl, 86 μmol) was added, the vial was agitated and the mixture was reacted for 15 s. A mixture of 1 M HCl–EtOH (1:3, 0.5 ml) was added, and the resulting solution was injected into a semi-preparative HPLC column: mobile phase A–D 60:40, after 1 min gradient to A–D 0:100 over 8 min, after 10 min from start change to C, t_R = 7.5 min. Analytical HPLC: mobile phase A–D 60:40, after 7 min gradient to A–D 5:95, t_R = 4.6 min.

[Methyl-^{11}C]acetophenone, minimal amount of benzoyl chloride. The [^{11}C]methyl iodide was trapped in a reaction vial containing THF (30 μl) cooled to −72 °C. A solution of butyllithium in hexane (2 μl, 1.6 M, 3.2 μmol) was added. After 1 min a solution of lithium (2-thienyl)iodocuprate in THF (13 μl, 0.25 M, 3.25 μmol) was added. The vial was agitated and the mixture was reacted for 0.5 min at 0 °C. Benzoyl chloride (1 μl, 9 μmol) was added, the vial was agitated and the mixture was reacted for 1 min at 50 °C. The work-up and analysis was then performed as described previously.

[Methyl-^{11}C]acetophenone, reaction between [^{11}C]-methyllithium and benzoyl chloride. The synthesis was performed as described for the standard method except that THF (100 μl) was added instead of the lithium (2-thienyl)cuprate solution.

[Methyl-^{11}C]acetone. To the ^{11}C-labelled methylcuprate obtained from lithium (2-thienyl)cyanocuprate (25 μmol), kept at 0 °C, acetyl chloride (10 μl, 153 μmol) was added, the vial was agitated and the mixture was reacted for 15 s. A mixture of 1 M HCl–EtOH (4:1, 0.5 ml) was added, and the resulting solution was injected into a semi-preparative HPLC column: mobile phase A–D 95:5, after 4 min, gradient to A–D 25:75 over 9 min, t_R = 5.3 min. Analytical HPLC: mobile phase B–D 90:10, wavelength 260 nm, t_R = 4.3 min.

(α-Methyl-^{13}C)methyl, pentadecyl ketone. The [^{11}C]-methyl iodide was trapped in a reaction vial containing diethyl ether (250 μl) cooled to −72 °C. A solution of $^{13}CH_3I$ in heptane (10 μl, 3.2 M, 32 μmol), and then butyllithium in hexane (50 μl, 1.6 M, 80 μmol) were added. After 5 min a solution of lithium (2-thienyl)-

cyanocuprate in THF (300 µl, 0.25 M, 75 µmol) was added. The vial was agitated and the mixture was reacted for 2 min at 0 °C. A solution of palmitic acid chloride in THF (160 µl, 1 M, 160 µmol) was added and the resulting mixture was reacted for 5 min. HCl (0.5 ml 0.5 M) was added, and the resulting solution was injected into a semi-preparative HPLC column: mobile phase A–D 30:70, 2 min gradient to A–D 0:100 over 3 min, after 2 min change to 100% C, $t_R = 13.8$ min. The collected fraction was concentrated to a residue (8 mg) and redissolved in $CDCl_3$ (0.7 ml). The product was analysed by ^{13}C NMR spectroscopy.

[1-^{11}C]Octane. To the [^{11}C]methylcuprate obtained from lithium (2-thienyl)iodo- or cyanocuprate (25 µmol), heptyl iodide (10 µl, 62 µmol) was added at 0 °C. The vial was agitated and heated. At the end of the reaction time, the vial was cooled to 0 °C and 10 µl benzoyl chloride was added. After 15 s a mixture of 1 M HCl–EtOH (1:3, 500 µl) was added and the resulting solution injected into a semi-preparative HPLC column: mobile phase A–D 95:5, 2 min, gradient to A–D 100:0 over 2 min, after 5 min from start change to C. The fractions containing [*methyl*-^{11}C]acetophenone (2.5–5.4 min), and [1-^{11}C]octane ($t_R = 9.9$ min) were collected. Analytical GC: column temperature 70(10)250 °C, $t_R = 7.8$ min.

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References

1. (a) Phelps, M., Mazziotta, J. and Schelbert, H. *Positron Emission Tomography and Autoradiography: Principles and Applications for the Brain and Heart*, Raven Press, New York 1986; (b) Wagner H. N., Jr., Szabo, Z. J. and Buchanan, W. *Principles of Nuclear Medicine*, Saunders, Philadelphia 1995.
2. Emran, A. *New Trends in Radiopharmaceutical Synthesis, Quality Assurance, and Regulatory Control*, Plenum Press, New York 1991.
3. (a) Kihlberg, T., Valind, S. and Långström, B. *Int. J. Appl. Radiat. Isot., Part B: Nucl. Med. Biol. 21* (1994) 1067; (b) Kihlberg, T., Valind, S. and Långström, B. *Int. J. Appl. Radiat. Isot., Part B: Nucl. Med. Biol. 21* (1994) 1053; (c) Långström, B., Andersson, Y., Antoni, G., Axelsson, S., Bjurling, P., Fasth, K. J., Gee, A. D., Kihlberg, T., Ulin, J. and Watanabe, Y. *Acta Radiol. Suppl. 31* (1989) 376.
4. Långström, B., Antoni, G., Gullberg, P., Halldin, C., Malmborg, P., Någren, K., Rimland, A. and Svärd, H. *J. Nucl. Med. 28* (1987) 1037.
5. (a) Reiffers, S., Vaalburg, W., Wiegman, T., Wynberg, H. and Woldring, M. G. *J. Appl. Radiat. Isot. 31* (1980) 535; (b) Långström, B. *On the Synthesis of ^{11}C-Compounds*, Acta Univ. Ups., 1980.
6. Elsinga, P. H., Keller, E., De Groot, T. J., Visser, G. M. and Vaalburg, W. *Appl. Radiat. Isot. 46* (1995) 227.
7. Andersson, Y., Cheng, A. and Långström, B. *Acta Chem. Scand. 49* (1995) 683.
8. Kihlberg, T. *Development of Methods for ^{11}C–C Bond Formation. Synthesis and* in vivo *Evaluation of ^{1}H and ^{2}H Fatty Acids ^{11}C-labelled in Selected Positions*, Acta Univ. Ups., 1994, pp. 30–31.
9. Billington, D. C. *Coupling Reactions Between sp^3 Carbon Centers, in Comprehensive Organic Synthesis, Selectivity, Strategy and Efficiency in Modern Organic Chemistry*, Pergamon Press, Oxford 1991.
10. Kihlberg, T. and Långström, B. *Acta Chem. Scand. 48* (1994) 570.
11. (a) Wehmeyer, R. M. and Rieke, R. D. *J. Org. Chem. 52* (1987) 5056; (b) Rieke, R. D. Wehmeyer, R. M., Wu, T. C. and Ebert, G. W. *Tetrahedron 45* (1989) 443; (c) Rieke, R. D., Wu, T. C., Stinn, D. E. and Wehmeyer, R. M. *Synth. Commun. (Engl.) 19* (1989) 1833.
12. Posner, G. H. *Org. React. 19* (1972) 1.
13. Lipshutz, B. H. and Sengupta, S. *Org. React. 41* (1992) 186.
14. Posner, G. H., Whitten, C. E. and Sterling, J. J. *J. Am. Chem. Soc. 95* (1973) 7788.
15. Bertz, S. H., Dabbagh, G. and Villacorta, G. M. *J. Am. Chem. Soc. 104* (1982) 5824.
16. Johnson, L. F. and Jankowski, W. C. *Carbon-13 NMR Spectra. A Collection of Assigned, Coded, and Indexed Spectra*, Wiley, New York 1972.
17. Bjurling, P., Reineck, R., Westerberg, G., Schultz, J., Gee, A., Sutcliffe, J. and Långström, B. *Synthia, a Compact Radiochemistry System for Automated Production of Radiopharmaceuticals.* VIth Workshop on Targetry and Target Chemistry (1995).
18. Lipshutz, B. H., Koerner, M. and Parker, D. A. *Tetrahedron Lett. 28* (1987) 945.
19. Nilsson, M. and Ullenius, C. *Acta Chem. Scand. 24* (1970) 2379.

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