

The synthesis of aliphatic and aromatic hydrocarbons
containing methyl groups labelled with ^{11}C

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SUMMARY

The synthesis of [$1-^{11}\text{C}$]pentane, [$1-^{11}\text{C}$]nonane, [$1-^{11}\text{C}$]undecane, 2- ^{11}C]methyl-naphthalene and [^{11}C]methyl-benzene (toluene) are reported. The hydrocarbons were prepared by the coupling reaction between [^{11}C]methyl iodide and the appropriate lithium organocuprate. Toluene was also labelled by the coupling reaction between phenyllithium and [^{11}C]methyl iodide. The reactions were carried out in ether giving the ^{11}C -labelled hydrocarbons in radiochemical yields > 90 % with short reaction times (3-13 min). The overall synthetic time from [^{11}C]carbon dioxide was 9-19 min.

Key words: [$1-^{11}\text{C}$]pentane, [$1-^{11}\text{C}$]nonane, [$1-^{11}\text{C}$]undecane, 2- ^{11}C]methyl-naphthalene, [^{11}C]toluene, ^{11}C -aliphatic hydrocarbons and ^{11}C -aromatic hydrocarbons.

INTRODUCTION

There is an increasing interest in ^{11}C -labelled aliphatic and aromatic hydrocarbons in both biochemical and physiological studies.

Aliphatic and aromatic hydrocarbons are frequently found as components in air pollutants. The toxicological studies of the effects of these compounds mostly involve examinations of the chronic effects on man.¹ Systematic investigation of the acute assault to man of these compounds is possible if they are labelled with ^{11}C . This is a positron emitting short-lived radio-nuclide. The in vivo distribution is studied using a dynamic imaging technique such as emission tomography.²

Aliphatic saturated and unsaturated hydrocarbons have been identified as pheromones among some ants and bees.³ The interest in these ^{11}C -labelled chemical messengers for in vivo studies has increased. In receptor-acceptor studies, there is often a need of labelled compounds with a high specific radioactivity. The theoretical value of the specific activity of ^{11}C is 9×10^9 Ci/mole. The highest specific activity achieved in labelling with ^{11}C so far is 2×10^6 Ci/mole using $\text{H}[^{11}\text{C}]\text{N}$ as the labelled precursor.⁴ Work is now in progress to improve the specific radioactivity of $[^{11}\text{C}]$ methyl iodide and other labelled synthetic reagents.⁵

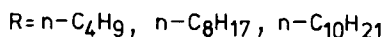
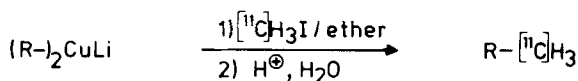
Rapid syntheses of aliphatic and aromatic hydrocarbons labelled with ^{11}C in a methyl group are described in this paper. The hydrocarbons chosen as model substances are pentane, nonane, undecane, 2-methylnaphthalene and toluene.

SYNTHETIC PATHWAYS

Starting materials for ^{11}C -labelling such as $[^{11}\text{C}]\text{O}$, $[^{11}\text{C}]\text{O}_2$, $\text{H}[^{11}\text{C}]\text{N}$,⁶ $[^{11}\text{C}]\text{OCl}_2$,⁷ $\text{H}[^{11}\text{C}]\text{HO}$,⁸ $[^{11}\text{C}]\text{H}_3\text{Li}$ ⁹ and $[^{11}\text{C}]\text{H}_3\text{I}$ ¹⁰ can either be obtained directly at the target or by synthesis from the target products. In order to perform a ^{11}C -labelling of a compound, it is necessary to select chemical routes where these precursors are used in a late phase of the synthesis.

In the preparation of these aliphatic and methyl containing aromatic hydrocarbons described in this work, $[^{11}\text{C}]\text{methyl iodide}$ was used as the ^{11}C -precursor.

The Corey-House coupling reaction¹¹ between a lithium organocuprate and $[^{11}\text{C}]\text{methyl iodide}$ was used in these syntheses.

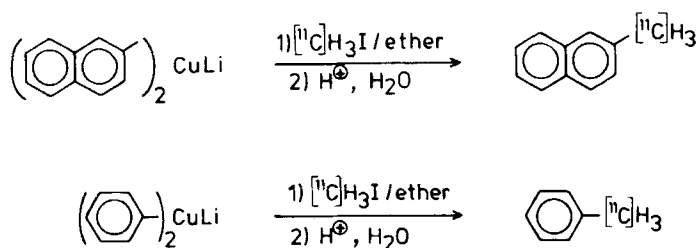


Scheme 1.

The syntheses of $[1\text{-}^{11}\text{C}]\text{pentane}$, $[1\text{-}^{11}\text{C}]\text{nonane}$ and $[1\text{-}^{11}\text{C}]\text{undecane}$ are shown in Scheme I. The appropriate lithium dialkylcuprate was prepared according to a procedure of House *et al.*,¹¹ where copper(I)iodide in ether was cooled to -78°C and the alkyl lithium slowly added. The lithium dialkylcuprate was obtained by heating and shaking the mixture until it acquired a red-brown colour. This preparation was made shortly before or during the synthesis of $[^{11}\text{C}]\text{methyl iodide}$, which was, with some technical improvements,¹² made from $[^{11}\text{C}]\text{carbon dioxide}$,

according to the procedure originally described by Comar *et al.*⁵ The [^{11}C]methyl iodide was then trapped in the reaction flask at -78°C which was thereafter placed in a bath maintained at 30°C .

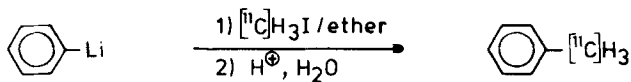
The ^{11}C -hydrocarbons were then obtained in the ether phase after acid hydrolysis.



Scheme II.

^{11}C -labelled 2-methylnaphthalene and toluene were prepared in a similar way (Scheme II). The lithium diarylcuprates were obtained as above.

^{11}C -toluene was also synthesized by the direct coupling of phenyllithium with [^{11}C]methyl iodide in ether followed by hydrolysis according to Scheme III.



Scheme III.

RESULTS

The radiochemical yields from these reactions, based on the [^{11}C]methyl iodide produced, the times for the coupling reactions and the overall times for the syntheses are shown in Table 1.

Table 1. Yields and times for the synthesis of some ^{11}C -hydrocarbons.

Compound	Radiochemical yield ($[^{11}\text{C}]\text{H}_3\text{I}$)	Time min	Time (total) min
pentane	97	7	14
nonane	95	7	14
undecane	95	5	12
2-methyl-naphthalene	95	6	12
toluene a)	99	13	19
b)	90	3	9

a) Corey-House coupling

b) direct coupling

The coupling reaction time was counted from the time when the mixture of the lithium organocuprate and the trapped [^{11}C]methyl iodide was removed from the cooling bath up to the time when the sample, taken from the mixture, was hydrolysed. The overall time used for the synthesis was counted from the time, the [^{11}C]carbon dioxide was released from the molecular sieves up to the hydrolysis of the sample. In general, the synthesis of [^{11}C]methyl iodide took 5-7 min. The reaction between the

lithium organocuprate and [^{11}C]methyl iodide was followed by taking samples, which were hydrolysed and analyzed on GC or LC. The identity of the labelled products was established by comparison of the retention times of the labelled starting materials and the labelled products with the retention times of reference samples of the starting material and the expected products.

In some cases, this comparison was made on two different chromatographic systems. No further proof of the identity of the labelled compounds was considered necessary, since the coupling reaction used is a well established synthetic method.

House et al¹¹ reported that the metal-halogen exchange in these reactions was of minor importance. The present investigation generally confirms this observation. In two experiments on the preparation of [^{11}C]pentane, however, metal-halogen exchange took place, as confirmed by the presence of [^{11}C]methane after hydrolysis. The radiochemical yield of [^{11}C]H₄ in these experiments was of the order of 20 %.

It would seem that the yield of ^{11}C -labelled hydrocarbon obtained after hydrolysis of the coupling reaction products very much depended on the preparation of the lithium organocuprate. There were indications that the highest yield of ^{11}C -labelled hydrocarbons was obtained in preparations where the concentration of copper(I)iodide was in excess compared to the alkyl- or aryllithium.

That the coupling reaction was slow at low temperatures was shown by the following experiment: the mixture of lithium dibutylcuprate and [^{11}C]methyl iodide in ether was kept at $-40\text{ }^{\circ}\text{C}$

for 10 min. in one experiment. After hydrolysis, [^{11}C]methyl iodide was the only labelled product to be found on analysis with GC. This can be compared with halogen-metal exchange reactions at -78°C for similar reaction times where butyl- or tert. butyllithium and [^{11}C]methyl iodide in ether after hydrolysis only gave [^{11}C]methane, as confirmed by GC.⁹ In two experiments, tetrahydrofuran was used as solvent instead of ether in the synthesis of [$1-^{11}\text{C}$]pentane, with no significant changes of the yields of the hydrocarbons. The specific activity of the labelled hydrocarbons in these preparations is related to the specific radioactivity of the [^{11}C]methyl iodide. In our preparations, [^{11}C]methyl iodide has been obtained with specific radioactivity of the order of 10-30 mCi/ μmole .

The syntheses of these ^{11}C -labelled hydrocarbons have not been optimized with respect to reaction times. Moreover the technical handling of the synthesis has not been adapted for operation on routine bases.

The labelling procedures presented here should be applicable generally for labelling aliphatic and aromatic hydrocarbons containing methyl groups.

EXPERIMENTAL

General. LC was performed on a Waters system (pump 6000 equipped with a UV 440) in series with a well counter (NaI(Tl) crystal). The GC was performed on a Varian 202-B equipped with a thermal conductivity detector in series with a similar radio-detector as above. The unlabelled starting materials and expected hydrolysis products like methyl iodide, methane, pentane, nonane, undecane, toluene and 2-methylnaphthalene were used to

optimise the separation conditions.

The ^{11}C was produced at the tandem van de Graaff accelerator at the University of Uppsala using a gas target and the ^{14}N -(p, α) ^{11}C reaction.¹³ The ^{11}C was obtained as [^{11}C]carbon dioxide trapped in 5 Å activated (320 °C at 0.1 torr) molecular sieves at room temperature. All the lithium organocuprates were prepared shortly before or during the synthesis of [^{11}C]methyl iodide from [^{11}C]carbon dioxide. Ether and tetrahydrofuran were of high quality (p.a, 99.5 % or better) and dried over molecular sieves or over sodium wire.

Butyllithium was commercially available. Octyl- and decyllithium were prepared according to the method described for decyllithium¹⁴ by using lithium containing 1 % of sodium. It was possible to use a pure lithium in the preparation of phenyllithium. Phenyllithium and 2-naphthyllithium were also prepared according to the procedure of Ladenberger.¹⁵ The copper(I)iodide used in the preparations of the lithium organocuprates was flamed dry in an nitrogen atmosphere shortly before.

[^{11}C]pentane. A suspension of 0.090 g (0.47 mmole) copper(I)iodide in 3.0 mL of ether was cooled to -78 °C and then 0.70 mL of a 1.3 M (0.91 mmole) of butyllithium in hexane was added dropwise. The reaction flask was shaken vigorously for 3 min. during which the temperature rose to about -30 °C. The mixture had by then acquired a red-brown colour, and almost all the copper iodide had been dissolved. The mixture was cooled to -78 °C and kept at this temperature. The [^{11}C]H₃I, prepared according to references (5) and (12), was trapped in the -78 °C solution. After the trapping process the reaction flask was placed in a

water bath kept at 30 °C. Samples were then withdrawn and hydrolysed in an equal volume of 2 M hydrochloric acid. GC analyses were performed on the ether phase and, in some cases, even on the gas phase obtained after hydrolysis. The GC was performed on a 1.5 m Porapak T column (100-120 mesh) (column temperature 180 °C with 50 mL/min flow of He). This system distinguished between methane, methyl iodide and pentane. The second system consisted of a 4.5 m 15 % Carbowax 20-M on Varaport-30 (100-120 mesh) (column temperature 50 °C with 20 mL/min flow of He) which distinguished between pentane and methyl iodide, and a 1.5 m Porapak Q (100-120 mesh) (column temperature 210 °C with 40 mL/min flow of He) which distinguished between methane and pentane.

[1-¹¹C]nonane. The lithium dioctylcuprate was prepared with 0.020 g (0.10 mmole) of copper(I)iodide in 1.5 mL of ether and 0.80 mL of a 0.21 M solution of octyllithium¹⁴ (0.17 mmole) in hexane. This was used with [¹¹C]H₃I in the coupling reaction by analogy with the procedure described for [1-¹¹C]pentane. After sampling and hydrolysis, the ether phase was analysed with GC on 1.5 m SE-30 (20 % on Chromosorb W (60-80 mesh)) (column temperature 175 °C with 50 mL/min flow of He).

[1-¹¹C]undecane. The lithium didecylcuprate was prepared with 0.020 g (0.10 mmole) of copper(I)iodide in 1.5 mL of ether and 1.1 mL of a 0.14 M solution of decyllithium (0.15 mmole) in hexane. This was used in a coupling reaction with [¹¹C]H₃I in analogy with the procedure described for [1-¹¹C]pentane. After sampling and hydrolysis as above the ether and the gas phases were analyzed as described for [1-¹¹C]nonane.

2- $[^{11}\text{C}]\text{H}_3$ -naphthalene. The lithium dinaphthylcuprate was prepared with 0.090 g (0.47 mmole) of copper(I)iodide in 3.0 mL of ether, and 2.0 mL of a 0.26 M solution of 2-naphthyllithium in ether (0.52 mmole). This was used in the coupling reaction with $[^{11}\text{C}]\text{H}_3\text{I}$ by analogy with the procedure described for $[1-^{11}\text{C}]\text{pentane}$. After sampling and hydrolysis as above the ether and gas phases were analyzed with LC on a reverse phase column Partisil 10/25 ODS (Reeve Angel) (water/methanol 75/25 (v/v)).

1- $[^{11}\text{C}]\text{H}_3$ -benzene.

a) The lithium diphenylcuprate was prepared with 0.090 g (0.47 mmole) of copper(I)iodide in 3.0 mL of ether and 2.6 mL of a 0.23 M solution of phenyllithium (0.60 mmole) in ether. This was used in the coupling reaction with $[^{11}\text{C}]\text{H}_3\text{I}$ by analogy with the procedure described for $[1-^{11}\text{C}]\text{pentane}$. After sampling and hydrolysis as above the ether and gas phases were analyzed with GC on a 1.5 m Porapak T (100-120 mesh) (column temperature 205 °C and 60 mL/min flow of He) and with LC on a reverse phase column Partisil 10/25 ODS (Reeve Angel) (water/methanol 50/45 (v/v)).

b) 1.0 mL of a 0.23 M solution of phenyllithium in ether was added to the reaction flask and cooled to -78 °C prior to the preparation of $[^{11}\text{C}]\text{H}_3\text{I}$. The $[^{11}\text{C}]\text{H}_3\text{I}$ was trapped in the flask at -78 °C and the flask then placed in a bath kept at 30 °C. Samples were withdrawn and hydrolysed as above. Analysis was performed as described previously.

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