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^{11}C-LABELLING OF HETEROCYCLIC AROMATIC COMPOUNDS IN RING POSITIONS: SYNTHESIS OF [2-^{11}C]INDOLE

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SUMMARY

A first synthetic method for ^{11}C-labelling of the indole ring has been developed. The route involves the synthesis of β,2-dinitro-[β-^{11}C]styrene **3** by condensation of nitro-[^{11}C]methane **1** with o-nitrobenzaldehyde **2**. This reaction was carried out either in ethanol with sodium hydroxide as a catalyst or in glacial acetic acid with ammonium acetate. The subsequent reduction of β,2-dinitro-[β-^{11}C]styrene **3** using titanium(III) chloride yielded [2-^{11}C]indole **4**. The synthesis time was 22 min, starting from nitro-[^{11}C]methane **1**.

Keywords: PET, ^{11}C-labelling, nitro-[^{11}C]methane, β,2-dinitro-[β-^{11}C]styrene, [2-^{11}C]indole

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INTRODUCTION

In many cases radiotracers used for investigations with Positron Emission Tomography (PET) undergo metabolic processes. This may cause problems due to the loss of the label. For this reason we sought to develop tracers in which the label was positioned in the metabolically stable moiety of the molecules. An excellent possibility of synthesizing such stable radioligands is the introduction

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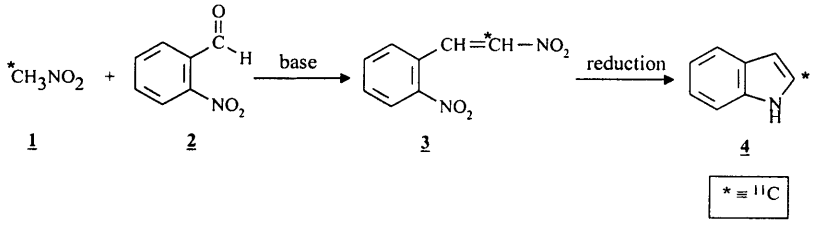
of the label into benzenoid or heteroaromatic rings. In special cases ring labelling may be the only possibility of isotopic labelling.

Ongoing research in our group is focused on developing labelling techniques for such molecules as ^{11}C-ring-labelled benzene and pyridine derivatives [1,2]. In continuation of this work various synthetic routes were investigated for ^{11}C-labelling of the indole skeleton, which is a constituent part of numerous important biologically active compounds.

^{11}C ($t_{1/2}$ = 20.4 min) is produced by the ^{14}N(p,α)^{11}C reaction and is available as [^{11}C]carbon dioxide or [^{11}C]methane. Subsequent reactions may lead to important ^{11}C precursors such as [^{11}C]methyl iodide, nitro-[^{11}C]methane or hydrogen [^{11}C]cyanide. Considering these ^{11}C precursors and the specific features of ^{11}C chemistry, only a very restricted number of the known indole syntheses can be applied to the formation of ^{11}C-labelled indole. We selected the reduction of β,2-dinitro-[β-^{11}C]styrene as one of the most suitable methods.

In this paper we present the results of our investigations for n.c.a. ^{11}C-labelling of indole. The two-step synthesis involves the condensation of nitro-[^{11}C]methane **1** with o-nitrobenzaldehyde **2**, using various catalysts, and the reduction of the resulting β,2-dinitro-[β-^{11}C]styrene **3**, yielding [2-^{11}C]indole **4** (Scheme 1).



Scheme 1

Results and Discussion

Synthesis of β,2-dinitro-[β-^{11}C]styrene

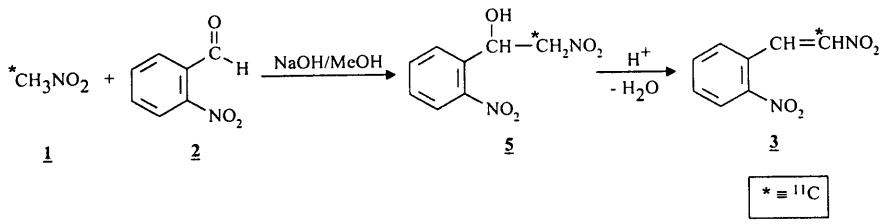
The condensation of nitroalkanes with benzaldehydes requires catalytic amounts of a base such as alkali hydroxides or ammonium acetate. These catalysts had been applied earlier in syntheses of β-nitro-[β-^{11}C]styrenes, starting from benzaldehydes without an aromatic bound nitro group [3-6].

Based on these investigations, two methods were tested for the synthesis of β,2-dinitro-[β-^{11}C]styrene **3**, using either sodium hydroxide (method A) or ammonium acetate in glacial acetic acid (method B) as catalysts.

*1. Synthesis of β,2-dinitro-[β-^{11}C]styrene **3** catalysed by sodium hydroxide - Method A*

The condensation of nitroalkanes with o-nitrobenzaldehydes in the presence of alkali hydroxides frequently does not lead to the related β,2-dinitrostyrenes. Under these conditions the formation of the intermediate 1-hydroxy-2-nitro-1-(2-nitrophenyl)alkanes is favoured [7].

The reaction of nitro-[^{11}C]methane **1** with o-nitrobenzaldehyde **2** in methanol catalysed by sodium hydroxide at ambient temperatures yielded 1-hydroxy-2-nitro-1-(2-nitrophenyl)-[2-^{11}C]ethane **5** as the main product (Scheme 2) in decay-corrected yields of 68 - 77 % (in relation to **1**, determined by HPLC). The formation of **3** was not observed. Besides **5**, the reaction mixture contained unreacted nitro-[^{11}C]methane **1** (1 - 4 %) and [^{11}C]methyl nitrite (2 - 10 %).



Scheme 2

The radiochemical yield of **5** was strongly dependent on the order in which the reagents were added. The above-mentioned yields were only obtained by adding the base to the methanolic solution of the precursor **2** after trapping **1**. Any other order caused lower yields of **5**. Varying the amount of sodium hydroxide from 9 to 40 μmol did not affect the product composition.

Dehydration of nonradioactive 1-hydroxy-2-nitro-1-(2-nitrophenyl)ethanes was generally performed by treatment of the isolated substance with sodium acetate in acetic anhydride [7]. Application of this route to the dehydration of **5** would involve a time-consuming step. This method is therefore probably not practicable for preparation of **3**.

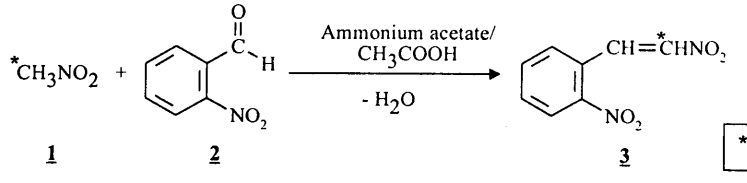
Nonradioactive 1-hydroxy-2-nitro-1-(2-nitrophenyl)ethanes were also converted into β,2-dinitrostyrenes by treatment with hydrochloric acid, but under these conditions dehydration was often not complete [7]. Nevertheless, we used this method to prepare β,2-dinitro-[β-^{11}C]styrene **3**. The dehydration was carried out by adding of hydrochloric acid in methanol to the reaction solution resulting from the condensation step. At ambient temperatures 57 % of **5** were converted into **3** corresponding to a decay-corrected radiochemical yield of 34 % (in relation to **1**). In addition to compound **3**, the product mixture contained nonconverted **5**, **1** and polar by-products.

The yield of **5** was reduced by a lower hydrogen chloride concentration and by using diluted hydrochloric acid. Phosphoric acid (85 %) and toluene-p-sulphonic acid were also tested for dehydration of **5**. With these acids, longer reaction times were necessary and the yields of **3** were lower compared with dehydration by hydrogen chloride.

The synthesis of β,2-dinitro-[β-^{11}C]styrene **3** according to method A was completed after 10 min (starting from nitro-[^{11}C]methane).

2. Synthesis of β,2-dinitro-[β-^{11}C]styrene 3 catalysed by ammonium acetate - Method B

Condensation of **1** with **2** in glacial acetic acid catalysed by ammonium acetate resulted in the direct formation of β,2-dinitro-[β-^{11}C]styrene **3** (Scheme 3).



1 **2** **3**

Scheme 3

After heating the reaction mixture at 145 °C for 7 min, 44 % of **1** (decay-corrected) were converted into **3**. An extension of the reaction time up to 10 min did not result in a higher degree of conversion. Higher reaction temperatures led to decreasing yields of **3**. The isomerization of **1** to [^{11}C]methyl nitrite is of minor importance. The total synthesis time of **3**, including separation by solid phase extraction (see below), was 12 min (starting from nitro-[^{11}C]methane). In summary, due to higher radiochemical yields and better reproducibility, method B is the preferred route to synthesizing **3**.

Synthesis of [2-^{11}C]indole

The reduction of nonradioactive β,2-dinitrostyrenes, followed by cyclization of the intermediate β,2-diaminostyrenes while loss of ammonia, yields indoles (Scheme 1). Appropriate reducing agents are molecular hydrogen with palladium catalysts [7], iron in acetic acid [7], ammonium formate with palladium catalysts [8], or titanium(III) chloride [9,10]. With the exception of the latter, these agents are not practicable for the reduction of ^{11}C-labelled compounds. In contrast, titanium(III) chloride provides the most suitable conditions, these being reaction in a homogeneous medium and a short reaction time.

For all reduction experiments to prepare **4**, the starting material **3** was synthesized using the conditions of method B.

The condensation according to method B as well as the reduction of **3** with titanium(III) chloride require acetic acid as a solvent. For this reason both reactions were expected to be carried out as a two-step one-pot synthesis. Unfortunately, in this case **3** was completely decomposed without the formation of **4**. This decomposition was observed irrespective of the solvent used for the titanium(III) chloride (such as acetic acid or diluted hydrochloric acid). We concluded that this undesirable reaction course was caused by the catalyst ammonium acetate, which therefore had to be removed. The purification step was performed by solid phase extraction, using an RP 18 cartridge. When purified **3** was reduced with a solution of titanium(III) chloride in hydrochloric acid, only 7 % of **3** were converted into **4**. This value corresponds to a radiochemical yield of 3 % (determined by HPLC, decay-corrected, in relation to **1**). Most of **3** was decomposed into polar products by hydrochloric acid.

The yield of **4** was increased by using titanium(III) chloride dissolved in glacial acetic acid. For complete reduction of **3**, a high excess of titanium(III) chloride was necessary. This was due to utilization of the reducing agent in the reduction of unreacted **2**, which was not removed by solid phase extraction. A ratio of titanium(III) chloride to **2** of at least 3.5:1 led to the complete conversion of **3**. Besides the desired conversion of **3** into **4**, the formation of polar by-products was observed. The resulting product mixture contained the ^{11}C-labelled indole **4** in a percentage of

24 %, which is equivalent to a decay-corrected radiochemical yield of 10 % (in relation to **1**). The complete synthesis of **4** starting from nitro-[^{11}C]methane was completed after 22 min.

In conclusion it can be said that the presented method utilizing the reduction of β,2-dinitro-[β-^{11}C]styrene **3** with titanium(III) chloride provides the first access to ^{11}C-labelled indole in a sufficient radiochemical yield.

EXPERIMENTAL

Sodium hydroxide p.a., ammonium acetate p.a., o-nitrobenzaldehyde, hydrochloric acid (37 %), toluene-p-sulphonic acid monohydrate and titanium(III) chloride were purchased from Fluka. Methanol (extra pure) and titanium(III) chloride solution (15 % in hydrochloric acid (10 %)) were obtained from Merck, glacial acetic acid p.a. and phosphoric acid (85 %) from Feinchemie Apolda (Germany). These reagents and solvents were used without further purification.

HPLC measurements were performed by means of an HPLC system from JASCO consisting of a pump, Rheodyne injector with a 20 µl loop, RP 18 column (LiChrospher 100 from Merck, 5 µm, 150 mm x 3.3 mm), a UV/VIS detector coupled in series with a FLO-ONE/beta 150TR radioactivity detector from Canberra Packard. A mixture of acetonitrile and water (50/50) containing 0.1M ammonium formate was used as the eluent. The HPLC was run with a flow of 0.5 ml/min in an isocratic mode. Indole from Merck was used as HPLC reference substance.

Nitro-[^{11}C]methane **1** was prepared *via* [^{11}C]methyl iodide according to the method of Schoeps [11] as described in [1].

β,2-Dinitro-[β-^{11}C]styrene (method A)

Methanol (250 µl) and **2** (33 µmol) were placed into a 2 ml reaction vessel and **1** was trapped while cooling with methanol/dry ice. After reaching a constant radioactivity level, sodium hydroxide (15 µmmol) dissolved in methanol (10 µl) was added. The reaction mixture was allowed to warm up to room temperature within 5 min.

For dehydration, hydrochloric acid (37 %, 15 µl) diluted with methanol (1 ml) was added to the reaction mixture obtained after condensation. The reaction was carried out at room temperature for 3 min.

β,2-Dinitro-[β-^{11}C]styrene (method B)

Glacial acetic acid (250 µl), **2** (70 µl) and ammonium acetate (350 µmol) were placed into a 2 ml reaction vessel. Nitro-[^{11}C]methane **1** was trapped in this solution at 10 °C, then the sealed vial was heated at 145 °C for 7 min.

Compound **3** was isolated after condensation by solid phase extraction with a C18 Sep Pak Classical Cartridge (Waters). The reaction mixture was diluted with water (10 ml). The resulting solution was passed through the cartridge (prewashed with 5 ml methanol and 5 ml water), followed by washing with water (5 ml) and elution with glacial acetic acid (1 ml). This eluate was used in the subsequent reduction experiments.

[2-^{11}C]Indole

The synthesis of **4** was performed by using of **3** prepared by method B.

Titanium(III) chloride (either 15 % $TiCl_3$ in HCl, 200 µl or solid $TiCl_3$, 300 µmol) was placed into a sealed reaction vessel, which had been purged with nitrogen. The eluate from solid phase extraction containing **3** was added to this vessel. After 7 min at room temperature a sample of the reaction mixture was diluted with the HPLC eluent, filtered and analysed by HPLC.

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