

SYNTHESIS OF TRIPHENYLARSONIUM [^{11}C]METHYLIDE, A NEW ^{11}C -PRECURSOR. APPLICATION IN THE PREPARATION OF [2- ^{11}C]INDOLE

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SUMMARY

The synthesis of the new and highly reactive ^{11}C -precursor triphenylarsonium [^{11}C]methylide **1** and its conversion into [2- ^{11}C]indole **6** is described. [^{11}C]Methyltriphenylarsonium iodide **4** was prepared by quaternization of triphenylarsine **2** with [^{11}C]methyl iodide **3** in a THF/DMSO mixture or ethanol. Starting from **3**, [^{11}C]methyltriphenylarsonium iodide **4** was obtained in a decay-corrected radiochemical yield of 55 % - 64 % depending on the reaction solvent. The arsonium ylide **1** was prepared *in situ* by treatment of **4** with butyllithium. Conversion of **1** with o-aminobenzaldehyde **5** in THF/DMSO mixtures yielded [2- ^{11}C]indole **6** in radiochemical yields of 23 - 27 % (decay-corrected, in relation to **3**). Preparation of **6** was completed after 15 - 20 min (starting from **3**). The specific radioactivity of **6** was about 37 GBq/ μmol (1 Ci/ μmol , related to EOB).

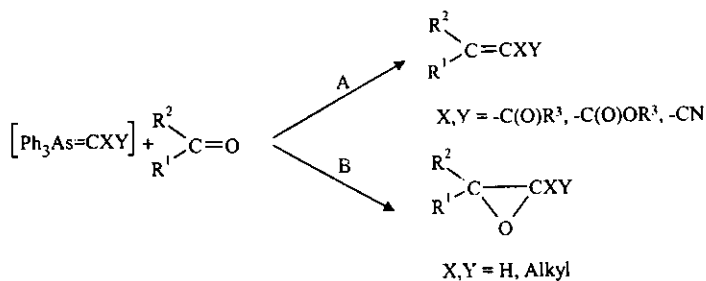
Keywords: PET, ^{11}C -labelling, [^{11}C]methyl iodide, [^{11}C]methyltriphenylarsonium iodide, triphenylarsonium [^{11}C]methylide, [2- ^{11}C]indole

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INTRODUCTION

The synthesis of radiotracers labelled with the short-lived positron-emitting radionuclide carbon-11 requires rapid and efficient synthesis procedures. The development of numerous ^{11}C -labelled precursors make it possible to introduce the label into various structural elements. One example is the synthesis of ^{11}C -alkenes utilizing triphenylphosphonium [^{11}C]methylide [1,2]. A suitable synthetic route has to comprise the quaternization of triphenylphosphine with [^{11}C]methyl iodide to form [^{11}C]methyltriphenylphosphonium iodide, dehydrohalogenation of this compound by treatment with a strong base and reaction of the resulting [^{11}C]methylide with the carbonyl compound. The applicability of this method was demonstrated by the preparation of various [β - ^{11}C]styrenes [1,2] and of [6- ^{11}C]-D-glucose [3].

Another class of ylides is based on analogous arsenic compounds. Depending on the reactivity of the arsonium ylide, the reaction of these ylides with the carbonyl group of aldehydes or ketones yields various products [4]. For example, arsonium ylides stabilized by acyl, alkoxyacetyl or cyano groups convert carbonyl compounds into alkenes according to the Wittig reaction mechanism (Scheme 1, Path A). Otherwise, reactive arsonium ylides such as triphenylarsonium methylide react to epoxides (Scheme 1, Path B).

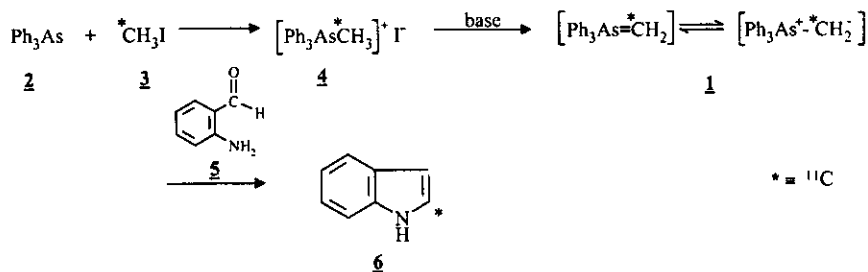


Scheme 1. Reaction of arsonium ylides with carbonyl compounds

These reactive arsonium ylides also permit access to five-membered heterocycles, if the carbonyl compound contains another suitable functional group [5]. In this way indoles are prepared from aminobenzoyl compounds [6].

A large number of indole derivatives are important biologically active substances bearing a source of potential PET tracers. In a previous study we reported a first method of labelling the indole ring with the positron emitter carbon-11, starting from nitro-[¹¹C]methane [7]. Triphenylarsonium [¹¹C]methylide can also be a useful intermediate for preparing ¹¹C-labelled indole derivatives in a rapid and efficient procedure.

In this paper we describe the preparation of the new ¹¹C-precursor triphenylarsonium [¹¹C]methylide **1** and its conversion into [2-¹¹C]indole **6**. The procedure includes the synthesis of [¹¹C]methyltriphenylarsonium iodide **4** from triphenylarsine **2** and [¹¹C]methyl iodide **3** and the *in situ* formation of arsonium ylide **1**, which was then reacted with o-aminobenzaldehyde **5** to produce [2-¹¹C]indole **6** (Scheme 2).



Scheme 2. Preparation of triphenylarsonium [¹¹C]methylide **1** and its conversion into [2-¹¹C]indole **6**

RESULTS AND DISCUSSION

[¹¹C]Methyltriphenylarsonium iodide

[¹¹C]Methyltriphenylarsonium iodide **4** is the parent compound of triphenylarsonium [¹¹C]methylide **1**. This compound was prepared by quaternization of triphenylarsine **2** with [¹¹C]methyl iodide **3** (see Scheme 2).

The quaternization reaction was carried out at the optimized reaction temperature of 120 °C in a reaction time of 10 min. Higher reaction temperatures (140 °C) and a prolongation of the reaction time did not result in higher radiochemical yields of **4**. The radiochemical yield of the arsonium salt **4** was strongly influenced by the polarity of the reaction solvent (see Table 1).

In THF, the reaction of **2** with [^{11}C]methyl iodide **3** proceeded without measurable formation of [^{11}C]methyltriphenylarsonium iodide **4**. Under similar conditions the related [^{11}C]methyltriphenylphosphonium iodide was formed in yields of about 90 % [1]. This behaviour is caused by the lower reactivity of arsines compared with the related phosphines [8].

Table 1. Radiochemical yields of [^{11}C]methyltriphenylarsonium iodide **4**

Triphenylarsine (mg)	Solvent	Solvent volume (μl)	Temperature ($^{\circ}\text{C}$)	Reaction time (min)	Radiochemical yield of 4 ¹⁾ (%)
25	THF	250	120	20	< 1
27-30	acetone	250	120	10	35 \pm 10
29	THF/HMPT	250/125	120	10	63
20-29	ethanol	250	120	10	76 \pm 10
					55 \pm 10 ²⁾
25	THF/DMSO	250/30	120	10	24
23-30	THF/DMSO	250/90	120	10	64 \pm 12
25-29	THF/DMSO	250/150	120	10	76 \pm 4

1) decay-corrected, in relation to [^{11}C]methyl iodide **3**, determined by HPLC

2) after evaporation of ethanol

More polar solvents or solvent mixtures than THF promoted the quaternization reaction. Using acetone, arsonium iodide **4** was obtained in a radiochemical yield of 35 % and in the case of a THF/HMPT mixture the radiochemical yield of **4** was increased by a factor of about 2. Unfortunately, the subsequent conversion of **4** into [^{11}C]indole **6** did not take place in this mixture.

The radiochemical yields of **4** increased to 76 % when the reaction of triphenylarsine **2** with methyl iodide **3** was carried out in ethanol. However, the protic solvent ethanol prevents ylide formation and has to be removed before preparing **1**. The evaporation of ethanol in a nitrogen stream at 120 $^{\circ}\text{C}$ was completed within 2 min. Unfortunately, this step was accompanied by partial decomposition of **4** into the starting compounds **2** and **3**, which decreased the overall radiochemical yield of **4**.

Satisfactory radiochemical yields of **4** were also obtained using a THF/DMSO mixture (2.8:1). Higher proportions of DMSO led to higher radiochemical yields, but the resulting amounts of DMSO caused substantial amounts of by-products to be formed during the subsequent [2- ^{11}C]indole preparation.

In addition to arsonium iodide **4**, a second polar ^{11}C -labelled product was formed during the quaternization reaction under these conditions. The proportion of this unidentified compound varied between 2 and 20 %, decreasing the yield of **4**. The formation of this by-product can be suppressed by using freshly recrystallized **2**.

Triphenylarsonium [^{11}C]methylide and its conversion into [2- ^{11}C]indole

The preparation of triphenylarsonium [^{11}C]methylide **1** by treatment of [^{11}C]methyltriphenylarsonium iodide **4** with a strong base is depicted in Scheme 2. The ylide **1** is a highly reactive compound and cannot be directly detected by common methods. An indirect confirmation of ylide formation is possible by its conversion into [2- ^{11}C]indole **6**, which is formed in a subsequent reaction of **1** with o-amino-benzaldehyde **5** (Scheme 2).

The synthesis of **1** and its conversion into indole **6** was performed in THF and several THF/DMSO mixtures. Various bases (methylsulphonyl sodium, lithium diisopropylamide, potassium bis(trimethylsilyl)-amide, and butyllithium) were tested to release ylide **1** from [^{11}C]methyltriphenylarsonium iodide **4**. Independent of the reaction solvent, butyllithium proved to be the most suitable base on account of the highest radiochemical yields of [2- ^{11}C]indole **6**.

The product composition was largely determined by the DMSO concentration. The results are summarized in Table 2 and discussed in detail below.

*Preparation of [2- ^{11}C]indole **6** in THF*

The use of THF as reaction solvent for the ylide formation required the synthesis of the starting arsonium iodide **4** in ethanol. After evaporation of ethanol, the residue was dissolved in THF containing o-aminobenzaldehyde **5**. Butyllithium was added to this solution at $-25\text{ }^{\circ}\text{C}$ and the reaction mixture warmed to ambient temperature. At room

temperature compound **4** was only attacked to a lesser degree by butyllithium within 2 min. The desired indole **6** was not formed. When the reaction mixture was heated to 120 °C for 2 min, compound **4** was nearly completely converted into a product mixture containing indole **6** in a proportion of 10 % (decay-corrected, determined by HPLC). The formation of indole **6** confirmed existence of triphenylarsonium [¹¹C]methylide **1**. The ¹¹C-labelled main product with a percentage of 53 % could not be identified. The formation of o-[β-¹¹C]vinylaniline **7** by a Wittig reaction mechanism was excluded by HPLC analysis with coelution of the nonradioactive reference substance.

Preparation of [2-¹¹C]indole **6** in THF/DMSO (50:1)

The parent [¹¹C]methyltriphenylarsonium iodide **4** was prepared in ethanol as described above. As in the reaction in THF, treatment of arsonium iodide **4** with butyllithium at ambient temperature yielded no indole **6**. Most of the arsonium salt **4** remained unchanged under these conditions. After heating the reaction mixture to 120 °C for 2 min, 47 % of compound **4** (decay-corrected, determined by HPLC) was converted into indole **6**. A typical HPLC radiogram of the product mixture is shown in Fig. 1.

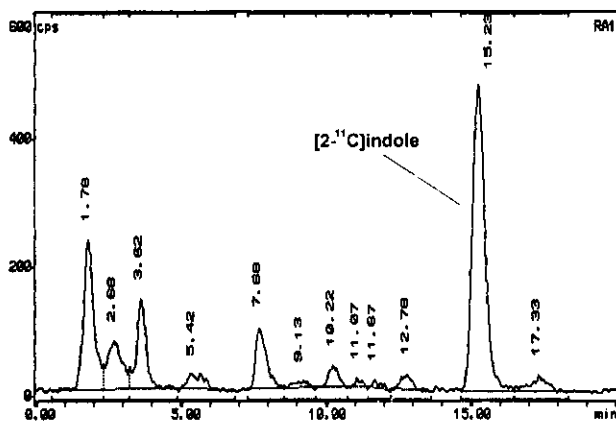


Fig. 1. HPLC radiogram obtained after reaction (120 °C, 2 min) of ylide **1** with **5** in THF/DMSO (50:1)

The use of the cosolvent DMSO reduced the amount of the unknown product, which was obtained by using THF as reaction solvent (see Table 2). A THF/DMSO ratio of at least 50:1 was necessary to completely prevent the formation of this by-product.

This method of preparing [2- ^{11}C]indole **6**, including the synthesis of [^{11}C]methyltriphenylarsonium iodide **4**, was completed within 20 min (starting from [^{11}C]methyl iodide **3**). The overall decay-corrected radiochemical yield of [2- ^{11}C]indole **6** was $23 \pm 3\%$ (in relation to **3**, determined by HPLC), using a THF/DMSO ratio of 50:1. The specific radioactivity of indole **6** was about 37 GBq/ μmol (1 Ci/ μmol , related to EOB).

Table 2. Reaction of triphenylarsonium [^{11}C]methylide with o-aminobenzaldehyde: radiochemical yields

Preparation of 4 in	Solvent	Radiochem. yield ¹⁾ of 6 (%)	Radiochem. yield ¹⁾ of an unidentified product (%)
ethanol	THF	10	53
ethanol	THF/DMSO (175:1)	31	13
ethanol	THF/DMSO (50:1)	47 ± 4	-
THF/DMSO (2.8:1)	THF/DMSO (4:1)	40 ± 6	-

1) in relation to **4**, determined by HPLC, decay-corrected

Preparation of [2- ^{11}C]indole **6** in THF/DMSO (4:1)

[^{11}C]Methyltriphenylarsonium iodide **4** can also be prepared in a THF/DMSO mixture (2.8:1) in satisfactory radiochemical yields. In this case the subsequent ylide formation and conversion of **1** into **6** can be performed without change of the solvent. The THF/DMSO ratio was increased to about 4:1 by addition of o-aminobenzaldehyde **5** dissolved in THF. After cooling to $-25\text{ }^\circ\text{C}$, butyllithium was added.

Initially the reaction mixture contained unreacted [^{11}C]methyl iodide **3**, which was rapidly converted by reaction with butyllithium at temperatures below $25\text{ }^\circ\text{C}$. Up to 50% of the arsonium iodide **4** was simultaneously converted into polar products. No indole **6** was formed. After heating to $120\text{ }^\circ\text{C}$ for 2 min, the arsonium iodide **4** was completely

converted into a product mixture consisting of the desired indole **6** and polar by-products (see Fig. 2).

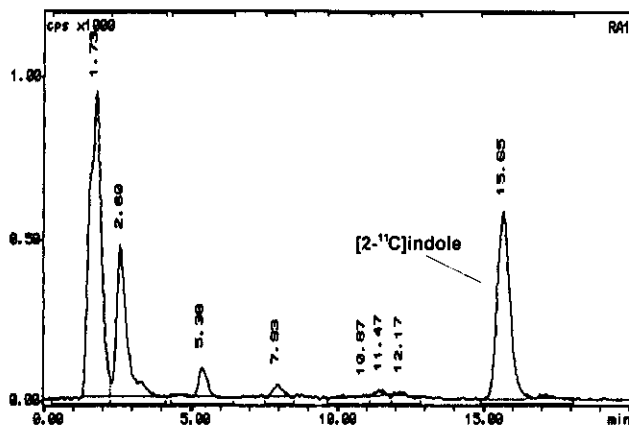


Fig. 2. HPLC radiograms obtained after reaction (120 °C, 2 min) of ylide **1** with **5** in THF/DMSO (4:1)

This procedure, including the preparation of **4**, was completed within 15 min. In this process $27 \pm 3\%$ of **3** (decay-corrected, determined by HPLC) was converted into indole **6**. The specific activity of **6** was about $37 \text{ CBq}/\mu\text{mol}$ ($1 \text{ Ci}/\mu\text{mol}$, calculated to EOB).

CONCLUSION

In summary, the new ^{11}C -precursor triphenylarsonium [^{11}C]methylide **1** was easily prepared by treatment of [^{11}C]methyltriphenylarsonium iodide **4** with butyllithium. The parent **4** was obtained by quaternization of triphenylarsine **2** with [^{11}C]methyl iodide **3** in ethanol or THF/DMSO. Ylide **1** was detected by its subsequent reaction with *o*-aminobenzaldehyde **5**. In this reaction [$2\text{-}^{11}\text{C}$]indole **6** was obtained in good radiochemical yields. The complete preparation can be carried out as a one-pot synthesis. Compared with the method based on the synthesis of **4** in ethanol, the procedure utilizing THF/DMSO mixtures as solvents for preparation of **4** requires shorter synthesis times and its radiochemical yields of [$2\text{-}^{11}\text{C}$]indole **6** are only slightly higher.

EXPERIMENTAL

General

Triphenylarsine (>97 %) was purchased from Aldrich and purified by recrystallization from ethanol. Absolute ethanol, THF, HMPT, butyllithium (1.6 M solution in n-hexane) and indole were obtained from Merck, anhydrous DMSO from Aldrich and o-nitrobenzaldehyde from Fluka. THF was dried by distillation over sodium. All other solvents or reagents were used without further purification.

[^{11}C]CO₂ was produced by the $^{14}\text{N}(p,\alpha)^{11}\text{C}$ reaction on an IBA CYCLONE 18/9 cyclotron. For most experiments, the nitrogen target (nitrogen 5.0 with 0.2 % oxygen) was irradiated with a current of 5 μA for 4 min giving, on average, 3.0 GBq of [^{11}C]carbon dioxide at the end of the bombardment. [^{11}C]Carbon dioxide was trapped in a Carbosphere (Alltech) loop at ambient temperature and released at 110 °C. [^{11}C]Methyl iodide was prepared by the standard one-pot procedure [9] *via* reduction of [^{11}C]carbon dioxide with lithium aluminium hydride, hydrolysis and treatment with hydroiodic acid.

NMR measurements were carried out by using a Varian INOVA 400 NMR spectrometer. The spectral data were obtained from CDCl₃ solutions. The chemical shifts were recorded in ppm from TMS using CHCl₃ as internal standard.

HPLC measurements were performed by a JASCO HPLC system consisting of a pump, Rheodyne injector with a 20 μl loop, an RP 18 column (Purospher RP-18 from Merck, 5 μm , 125 mm x 3 mm) and a UV detector set at 254 nm coupled in series with a radioactivity detector FLO-ONE/beta 150 TR from Canberra Packard.

Syntheses of starting and reference substances

o-Aminobenzaldehyde (**5**)

The precursor *o*-aminobenzaldehyde was prepared by reduction of *o*-nitrobenzaldehyde with iron(II) hydroxide according to the reported procedure [10], with modifications.

Iron(II) sulphate heptahydrate (21.0 g, 75.5 mmol) was dissolved in water (75 ml) containing 1 M hydrochloric acid (1.2 ml). *o*-Nitrobenzaldehyde (1.2 g, 7.9 mmol) was added to this solution followed by the immediate addition of ammonia (12 ml, 25 %). The

resulting black suspension was shaken a few times and heated to 80 °C for 10 min while stirring. Then the reaction mixture was heated to boiling and 40 ml distillate were collected. The distillate was extracted with dichloromethane, the organic phases were dried with magnesium sulphate and evaporated to give a yellow oil (0.91g, 95 %) which crystallized on standing at ambient temperature. The compound can be stored under argon at -18 °C for a few months.

$^1\text{H-NMR}$ δ (ppm) 6.13 (s, br, 2H, NH_2), 6.64 (d, 1H, aryl), 6.74 (m, 1H, aryl) 7.31 (m, 1H, aryl), 7.47 (dd, 1H, aryl), 9.87 (s, 1H, CHO);

o-Vinylaniline (**7**)

As a first step *o*-nitrostyrene was prepared by decarboxylation of *o*-nitrocinnamic acid according to [11]. The crude product was flashed over silica gel using petrol ether/diethyl ether (15:1) as an eluent to yield a yellow oil.

$^1\text{H NMR}$: δ (ppm) 5.47 (dd, 1H, $\text{CH}=\text{CH}_2$, $^2\text{J}_{\text{HH}}=1$ Hz, $^3\text{J}_{\text{HH}}=11$ Hz), 5.74 (dd, 1H, $\text{CH}=\text{CH}_2$, $^2\text{J}_{\text{HH}}=1$ Hz, $^3\text{J}_{\text{HH}}=17.6$ Hz), 7.16 (dd, 1H, $\text{CH}=\text{CH}_2$, $^3\text{J}_{\text{HH}}=11$ Hz, $^3\text{J}_{\text{HH}}=17.6$ Hz), 7.40 (dt, 1H, aryl), 7.55-7.63 (m, 2H, aryl), 7.92 (dd, 1H, aryl)

The *o*-nitrostyrene was reduced with zinc and ammonium chloride according to a modified literature procedure [12]. *o*-Nitrostyrene (450 mg, 3.0 mmol) was dissolved in acetone (10 ml) and an ammonium chloride solution (330 mg, 6.2 mmol in 2 ml water) was added. The reaction mixture was heated to boiling and zinc dust (670 mg, 10 mmol) was added. The mixture was refluxed for 30 min. The hot suspension was filtered. The filter-cake was washed with acetone. The combined filtrates were diluted with water (15 ml) and basified to pH 12 with 1 M NaOH. This solution was extracted with diethyl ether, the organic extracts were washed with water, dried with magnesium sulphate and evaporated to yield a brown oil. Flash chromatography over silica gel 60 (petrol ether/diethyl ether 25:10) yielded a yellow oil (100 mg, 28 %).

$^1\text{H NMR}$: δ (ppm) 3.76 (b, 2H, NH_2) 5.33 (dd, 1H, $\text{CH}=\text{CH}_2$, $^2\text{J}_{\text{HH}}=1.4$ Hz, $^3\text{J}_{\text{HH}}=11.4$ Hz), 5.64 (dd, 1H, $\text{CH}=\text{CH}_2$, $^2\text{J}_{\text{HH}}=1.6$ Hz, $^3\text{J}_{\text{HH}}=17.4$ Hz), 6.69 (dd, 1H, aryl), 6.75-6.79 (m, 2H, aryl and $\text{CH}=\text{CH}_2$), 7.10 (dt, 1H, aryl), 7.30 (dd, 1H, aryl)

Radiosyntheses

[^{11}C]Methyltriphenylarsonium iodide (4) - synthesis in THF/DMSO

A solution of triphenylarsine (25 mg, 82 μmol) in THF (250 μl) was placed in a conical 2 ml reaction vessel and sealed with a silicone septum. [^{11}C]Methyl iodide was trapped in this vessel while cooling with methanol/dry ice. Then the reaction solution was warmed to ambient temperature and DMSO (80 μl) was added. This solution was heated to 120 $^{\circ}\text{C}$ for 10 min. After the reaction, the mixture was cooled to ambient temperature. A sample was diluted with HPLC eluent and analysed by isocratic HPLC with water/acetonitrile (50:50 with 0.1 M ammonium formate) as the eluent at a flow rate of 0.5 ml/min.

[^{11}C]Methyltriphenylarsonium iodide (4) - synthesis in ethanol

[^{11}C]Methyl iodide was trapped in a 2 ml reaction vessel containing a solution of triphenylarsine (25 mg, 82 μmol) in ethanol (250 μl) under the same conditions as described above. Then the reaction mixture was heated to 120 $^{\circ}\text{C}$ for 10 min. After cooling to ambient temperature the products were determined by HPLC of a sample under the same conditions as described above.

The solvent was removed in a nitrogen stream while heating to 120 $^{\circ}\text{C}$ within 1 - 2 min. The residue was used in this form for preparation of [$2\text{-}^{11}\text{C}$]indole.

[$2\text{-}^{11}\text{C}$]Indole (6) - general procedure.

A solution of o-aminobenzaldehyde **5** (10 - 20 mg, 80 - 160 μmol) dissolved in THF was added to the reaction vessel containing [^{11}C]methyltriphenylarsonium iodide. The mixture was cooled to -25 $^{\circ}\text{C}$ (methanol/dry ice) and butyllithium (15 μl , 1.6 M in hexane) was added. The vessel was warmed to room temperature within 2 min and then heated to 120 $^{\circ}\text{C}$ for 2 min.

A sample of the reaction mixture was analysed by isocratic HPLC with water/acetonitrile (70:30 with 0.1 M ammonium formate) as the eluent at a flow rate of 0.5 ml/min.

*[$2\text{-}^{11}\text{C}$]Indole - starting from **4** prepared in THF/DMSO*

The precursor **5** dissolved in THF (50 μl) was added to the solution of **4** and the reaction mixture was treated as described.

*[2-¹¹C]Indole - starting from **4** prepared in ethanol*

The residue obtained by synthesis of compound **4** was dissolved in a THF/DMSO mixture (50:1, 200 μ l) containing the precursor **5**. The formation of ylide **1** and its conversion with **5** proceeded as above described.

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