Journal of Labelled Compounds and Radiopharmaceuticals
J. Labelled Cpd. Radiopharm. **XLI**, 647-656 (1998)

N.C.A. ^{11}C-LABELLING OF BENZENOID COMPOUNDS IN RING POSITIONS: SYNTHESIS OF 3-NITRO-[3-^{11}C]TOLUENE AND 4-NITRO-[4-^{11}C]TOLUENE AND THEIR CORRESPONDING TOLUIDINES

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SUMMARY

The paper describes the syntheses of n.c.a. 3-nitro-[3-^{11}C]toluene (**3a**) and 4-nitro-[4-^{11}C]toluene (**3b**) by reaction of nitro-[^{11}C]methane (**1**) with 5-dimethylamino-2(or 3)-methyl-penta-2,4-dienylidene-dimethylammonium tetrafluoroborate (**2a** or **2b**) in the presence of BuLi, utilizing the synchronous six-electron cyclization of hexatriene systems into aromatics. Starting from **1**, **3a** and **3b** were prepared in a radiochemical purity of about 87 % and 78 % and with a mean specific radioactivity of 1 Ci/μmol (37 GBq/μmol) within 10 min. Related to **1**, the reproducible radiochemical yields of **3a** and **3b** (decay-corrected) were 85±5 % and 75±5 %. Reduction of **3a** and **3b** by heating the above reaction mixture with aqueous Na_2S produced m-[1-^{11}C]toluidine (**7a**) of a radiochemical purity of about 82 % and p-[1-^{11}C]toluidine (**7b**) of a radiochemical purity of about 68 %. The reproducible radiochemical yields of **7a** and **7b** (decay-corrected) in relation to **1** were 78±5 and 65±5 %, the synthesis time from **1** was 21 min and 16 min.

Keywords: ^{11}C-ring labelling, nitro-[^{11}C]methane, 3-nitro-[3-^{11}C]toluene, 4-nitro-[4-^{11}C]-toluene, m-[1-^{11}C]toluidine, p-[1-^{11}C]toluidine

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INTRODUCTION

There are a multitude of aromatic compounds which exhibit key biochemical functions in the human body. Such compounds when labelled with ^{11}C could be radiotracers of interest for PET investigations. Because of the metabolic stability of aromatic rings, we are investigating the possibility of introducing the positron-emitting radionuclide ^{11}C into ring-positions of aromatics. These methods may also be useful for labelling with other carbon isotopes such as ^{13}C or ^{14}C.

The ^{11}C-ring labelling of benzenoid compounds by reaction of nitro-[^{11}C]methane with an appropriate pentamethinium salt in the presence of a base was recently described [1, 2]. This method

CCC 0362–4803/98/070647–10$17.50

Received 22 December 1997
Revised 30 January 1998
Accepted 8 February 1998

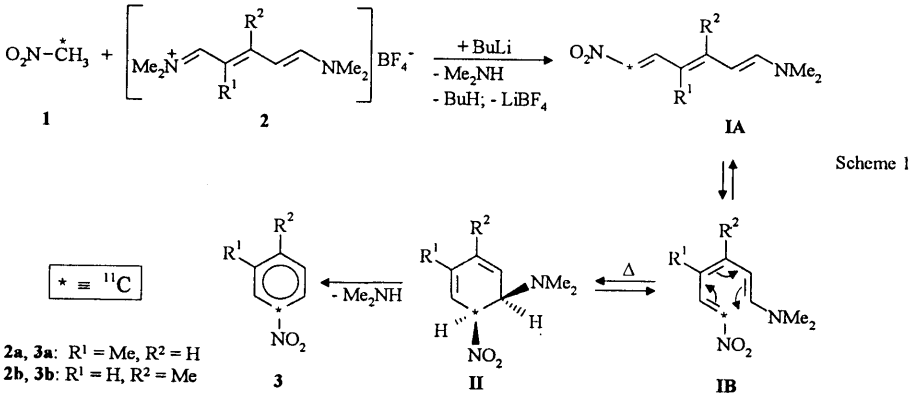
utilizes the principle of the synchronous six-electron cyclization of hexatriene systems into aromatics [3]. In this way unsubstituted and 3-methoxy-substituted nitro-[1-^{11}C]benzenes were synthesized at the n.c.a. level. By reducing these nitro compounds, the appropriate [1-^{11}C]anilines were obtained. In continuation of this work, methyl-substituted pentamethinium salts were prepared and tested as non-radioactive precursors. Thus, we were able to extend our synthesis strategy to the preparation of ^{11}C-ring-labelled nitrotoluenes and the derived [1-^{11}C]toluidines.

RESULTS AND DISCUSSION

Method of labelling

The labelling procedure is based on the reaction route according to Scheme 1:

1. Nitro-[^{11}C]methane (**1**) reacts in the presence of a base (such as BuLi) with 5-dimethylamino-2(or 3)-methyl-penta-2,4-dienylidene-dimethylammonium tetrafluoroborate **2a** (or **2b**) to form a methyl-substituted 1-dimethylamino-6-nitro-[6-^{11}C]hexatriene **IA**, **IB** and dimethylamine.
2. The synchronous six-electron cyclization of [^{11}C]hexatriene **IB** into 3-nitro-[3-^{11}C]toluene (**3a**) or 4-nitro-[4-^{11}C]toluene (**3b**) *via* an [^{11}C]cyclohexadiene **II** occurs by elimination of the second dimethylamino group.



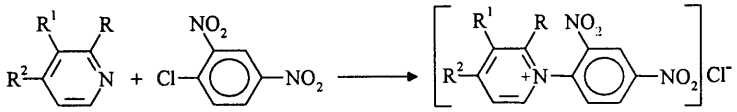
Scheme 1

The compounds **IA**, **IB** and **II** are intermediates which were not isolated or characterized.

Precursor synthesis

The method for the synthesis of the unsubstituted pentamethinium salt, the 5-dimethylamino-penta-2,4-dienylidene-dimethylammonium perchlorate, is described in [1, 4, 5]. Attempts to apply this method to the synthesis of methyl-substituted pentamethinium salts **2** were carried out according to Schemes 2 - 4, starting from 2-, 3- and 4-methylpyridine (α-, β-, γ-picoline) and 3,4-dimethylpyridine (3,4-lutidine):

1. Arylation of a methyl-substituted pyridine **4** with 1-chloro-2,4-dinitrobenzene to the appropriate N-(2',4'-dinitrophenyl)pyridinium chloride **5** according to Scheme 2:



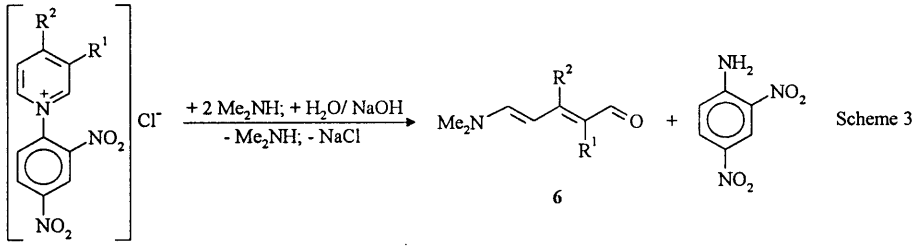
Scheme 2

4 **5**

4a, 5a: R = R^2 = H, R^1 = Me
4b, 5b: R = R^1 = H, R^2 = Me
4c, 5c: R = H, R^1 = R^2 = Me

The yields of the synthesized pyridinium salts **5** are listed in Table 1. Starting from α-picoline (R=Me; R^1=R^2=H), this reaction is not possible, probably due to the shielding effect of the α-methyl group on the pyridine nitrogen [6].

2. Cleavage of the pyridine ring of the pyridinium salt **5** with dimethylamine and subsequent addition of aqueous NaOH produced a methyl-substituted 5-dimethylamino-penta-2,4-dien-1-al **6** and 2,4-dinitroaniline according to Scheme 3:



Scheme 3

5 **6**

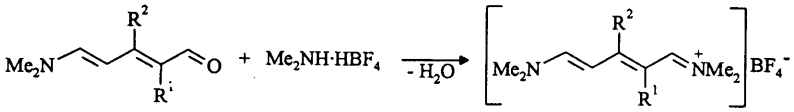
5a, 6a: R^1 = Me, R^2 = H
5b, 6b: R^1 = H, R^2 = Me

The yields of the prepared pentadienals **6** are listed in Table 1.

In the case of **5c** the desired reaction according to Scheme 3 does not take place. This fact is in accordance with the assessment of Hafner and Asmus [6] that the heterocyclic ring of dialkyl- and trialkyl-substituted pyridines can not be opened, using cyanogen bromide (instead of 1-chloro-2,4-dinitrobenzene) in the presence of aniline (instead of Me_2NH).

5-Dimethylamino-3-methyl-penta-2,4-dien-1-al (**6b**) could not be obtained as a pure substance. Its ^{13}C-NMR spectrum shows many signals which can not be interpreted, including broad signals indicating polymers. Nevertheless, the following reaction of the impure **6b** with dimethylamine tetrafluoroborate according to Scheme 4 yielded the pure pentamethinium salt **2b**.

3. Conversion of the substituted 5-dimethylamino-penta-2,4-dien-1-al **6** with dimethylamine tetrafluoroborate into the desired pentamethinium salt **2** by elimination of water according to Scheme 4:



6 **2** Scheme 4

2a, 6a: R^1 = Me, R^2 = H
2b, 6b: R^1 = H, R^2 = Me

The yields of the synthesized pentamethinium tetrafluoroborates **2** are listed in Table 1. These pentamethinium salts, which were purified by recrystallization from ethanol or n-propanol, are orange crystalline compounds.

Table 1: Yields of the compounds synthesized according to Schemes 2 - 4

Compound	Yield [%]		
	N-(2',4'-dinitrophenyl)-pyridinium chloride **5**	5-dimethylamino-penta-2,4-dien-1-al **6**	pentamethinium tetrafluoroborate **2**
a: R=R^2=H, R^1=Me	68	82	20
b: R=R^1=H, R^2=Me	87	54	59
c: R=H, R^1=R^2=Me	69	-	-

Besides the preparation of **2a** and **2b** described above, there are other possibilities of synthesizing these pentamethinium salts. A similiar synthesis of **2b** as perchlorate is described in [7]: The nonisolated pyridinium salt **5b** was converted with dimethylamine in a one-pot process. After separation of the 2,4-dinitroaniline from the aqueous solution, compound **2b** was precipitated as the perchlorate by addition of $NaClO_4$. This procedure avoids the preparation of the 5-dimethylamino-3-methyl-penta-2,4-dien-1-al (**6b**) by addition of sodium hydroxide. Köbrich [7] describes another possibility of synthesizing **2b** consisting in the reaction of 4-methylpyrylium perchlorate with dimethylamine.

Arnold and Holy [8] synthesized **2a** (as the perchlorate) as follows: condensation of 3-dimethylamino-acrylic acid t-butyl ester with 3-dimethylamino-2-methyl-acrolein in HOAc/Ac_2O in the presence of pyridinium perchlorate, hydrolysis of the butyl ester group of the pentamethinium perchlorate formed and subsequent decarboxylation of the carboxylic acid with HBr/HOAc.

Synthesis of 3-nitro-[3-^{11}C]toluene and 4-nitro-[4-^{11}C]toluene

The optimized reaction conditions elaborated for synthesizing 3-nitro-[3-^{11}C]anisole [2] proved to be suitable also for the ring closure reaction of the pentamethinium salts **2a** and **2b** with [^{11}C]CH_3NO_2 (**1**) to prepare 3-nitro-[3-^{11}C]toluene (**3a**) or 4-nitro-[4-^{11}C]toluene (**3b**). These conditions are:

Solvent:	250 µl HMPT
Precursor:	8 mg (30 µmol) 5-dimethylamino-2(or 3)-methyl-penta-2,4-dien-ylidene-1-dimethylammonium tetrafluoroborate (**2a** or **2b**)
Base:	25 µl 1.6 M BuLi in hexane (40 µmol)
Reaction temperature:	170 °C
Reaction time:	10 min

In this way **3a** was prepared in a radiochemical purity of about 87 % and with a mean specific radioactivity of 1 Ci/µmol. The reproducible radiochemical yield of **3a** in relation to **1** was in the range of 85±5 % (decay-corrected). An HPLC radiogram of unpurified **3a** is shown in Fig. 1.

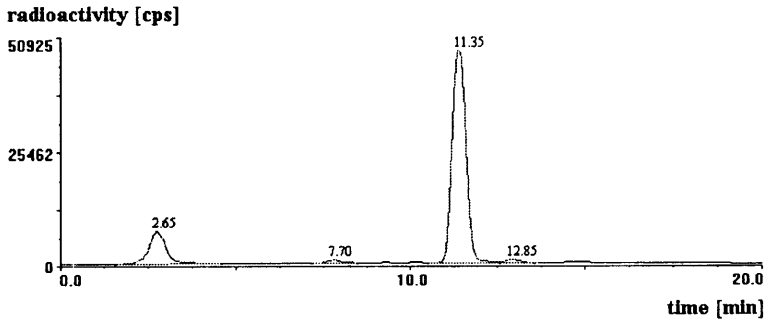


Fig. 1: HPLC radiogram obtained from the reaction mixture of the 3-nitro-[3-^{11}C]toluene (**3a**) synthesis
2.65 min: [^{11}C]CH_3ONO; 11.1 %
11.35 min: 3-nitro-[3-^{11}C]toluene (**3a**); 87.3 %
(radioactivity [%] is decay-corrected)

4-Nitro-[4-^{11}C]toluene (**3b**) was prepared in a radiochemical purity of about 78 % and with a mean specific radioactivity of 1 Ci/µmol. The reproducible radiochemical yield of **3b** in relation to **1** was in the range of 75±5 % (decay-corrected). A typical HPLC radiogram of unpurified **3b** is shown in Fig. 2.

However, 26 % [^{11}C]methylnitrite and 10 % of **1** were found, i.e. t-BuOK was less suitable for the synthesis of **3b**.

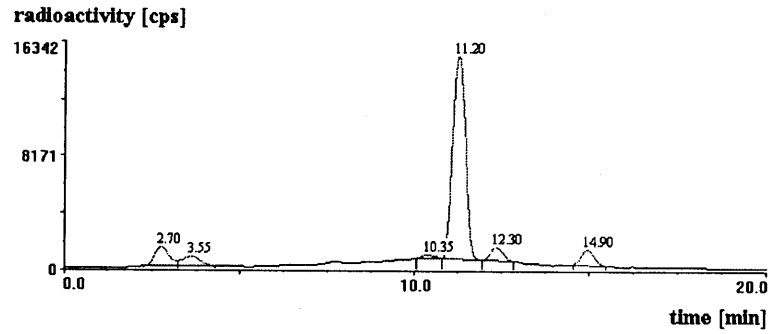
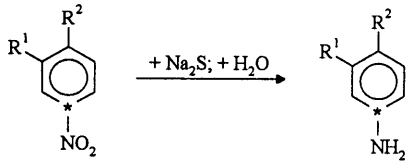


Fig. 2: HPLC radiogram obtained from the reaction mixture of the 4-nitro-[4-^{11}C]toluene (**3b**) synthesis
2.70 min: [^{11}C]CH_3ONO; 6.0 %
3.55 min: [^{11}C]CH_3NO_2 (**1**); 3.6 %
11.20 min: 4-nitro-[4-^{11}C]toluene (**3b**); 77.9 %
12.30 min: unidentified product; 5.0 %
14.90 min: unidentified product; 6.2 %
(radioactivity [%] is decay-corrected)

Under the same reaction conditions as mentioned above but using solid potassium tert-butylate (3.5 mg; 30 µmol) instead of BuLi, only 59 % of **3b** was obtained in this ring closure reaction.

Synthesis of m-[1-^{11}C]toluidine and p-[1-^{11}C]toluidine

By reduction of the nitro-[^{11}C]toluenes **3a** and **3b** with aqueous Na_2S according to Scheme 5, the appropriate [1-^{11}C]toluidines **7a** (m-[1-^{11}C]toluidine or 3-methyl-[1-^{11}C]aniline or 3-amino-[3-^{11}C]toluene) and **7b** (p-[1-^{11}C]toluidine or 4-methyl-[1-^{11}C]aniline or 4-amino-[4-^{11}C]toluene) were synthesized in an analogous manner to the synthesis of [1-^{11}C]aniline [1] and 3-amino-[3-^{11}C]anisole [2].



3 **7**

Scheme 5

* ≡ ^{11}C

3a, **7a**: R^1 = Me, R^2 = H
3b, **7b**: R^1 = H, R^2 = Me

Starting from the reaction mixture obtained in the synthesis of a nitro-[^{11}C]toluene **3a** or **3b** mentioned above, the following reduction was carried out by adding an aqueous Na_2S solution and subsequent heating at 170 °C in a one-pot process.

Using the reaction mixture of **3a** (radiochemical purity 87 %), we determined the optimum reduction conditions. It was found that the radiochemical yield of **7a** increased as a function of the amount of sodium sulphide added. Using 79 µmol $Na_2S{\cdot}9H_2O$ in 100 µl H_2O and heating the reaction mixture at 170 °C for 10 min, **7a** was obtained in a radiochemical purity of about 82 %.

The reproducible radiochemical yields of **7a** (decay-corrected) were in the range of 78±5 %, within a synthesis time from [^{11}C]CH_3NO_2 of 21 min. An HPLC radiogram of unpurified **7a** is shown in Fig. 3.

By contrast only 20 % **7a** and 62 % unconverted **3a** were obtained, when merely 50 µmol $Na_2S{\cdot}9H_2O$ in 100 µl H_2O were used and the reaction mixture was heated at 170 °C for 5 min. Additional heating for 10 min gave 37 % of **7a** and 41 % of unconverted **3a**.

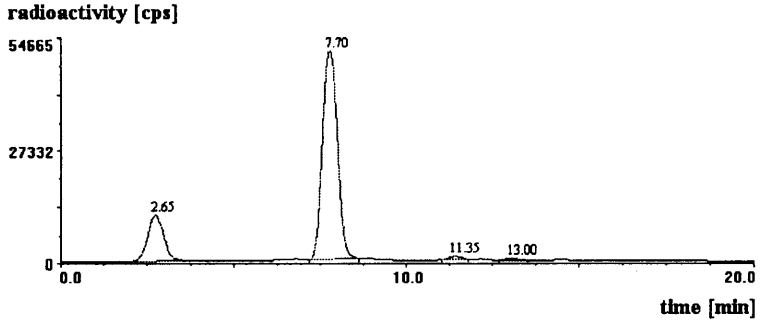


Fig. 3: HPLC radiogram obtained from the reaction mixture of the 3-methyl-[1-^{11}C]aniline (**7a**) synthesis
2.65 min: [^{11}C]CH_3ONO and probably ionic compounds[1]; 15.5 %
7.70 min: 3-methyl-[1-^{11}C]aniline (**7a**); 82.5 %
(radioactivity [%] is decay-corrected)

In the same manner, using the reaction mixture of **3b** (radiochemical purity 78 %) and 50 µmol $Na_2S{\cdot}9H_2O$ in 100 µl H_2O, **7b** of radiochemical purity of about 68 % was produced at 170 °C within 5 min. The reproducible radiochemical yields of **7b** (decay-corrected) are in the range of 65±5 %, within a synthesis time from [^{11}C]CH_3NO_2 of 16 min. An HPLC radiogram of unpurified **7b** is shown in Fig. 4.

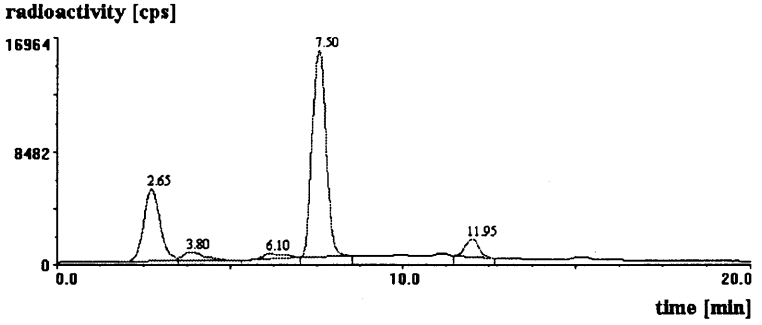


Fig. 4: HPLC radiogram obtained from the reaction mixture of the 4-methyl-[1-^{11}C]aniline (**7b**) synthesis
2.65 min: [^{11}C]CH_3ONO and probably ionic compounds[1]; 22.9 %
3.80 min: [^{11}C]CH_3NO_2; 1.7 %
7.50 min: 4-methyl-[1-^{11}C]aniline (**7b**); 68.4%
11.95 min: unidentified product; 6.2 %
(radioactivity [%] is decay-corrected)

[1] After the ring closure reaction the peak at 2.65 min indicates [^{11}C]methylnitrite. An increase in the area of this peak was observed after all the reductions of **3a** and **3b** with Na_2S. We assume that this peak includes both [^{11}C]methylnitrite and ^{11}C-labelled ionic compounds caused by SO_3^{2-} impurities in the Na_2S ("Piria" reaction [9]). Such possible by-products could be N-[^{11}C]phenylsulphamic acids and sulphamidic [^{11}C]benzenesulphonic acids.

EXPERIMENTAL

The ^{13}C NMR spectra were recorded on a Bruker MSL 300 NMR spectrometer at 75.475 MHz, the ^{1}H-NMR spectra on a Bruker WH 90 DS at 90.02 MHz.
1-Chloro-2,4-dinitrobenzene, t-BuOK, BuLi (1.6 M in hexane) and HMPT were purchased from Merck and were of synthesis quality. 2-Picoline 98 %, 3-picoline 99 %, 4-picoline 98 %, 3,4-lutidine 98 % and $Na_2S{\cdot}9H_2O$ 98 % were obtained from Aldrich, 60 % aqueous dimethylamine and $AgNO_2$ from Riedel-de Haën. Dimethylamine tetrafluoroborate was prepared according to [2].
For HPLC investigations the following reference substances were used: methyl iodide for synthesis (Merck), nitromethane 99 %, 3-nitrotoluene 99 %, 4-nitrotoluene 99 %, m-toluidine 99 %, and p-toluidine 99.7 % (Aldrich).
To determine the extent of the reaction conversion, the radiochemical purity of the reaction products and the specific radioactivity of the nitro-[^{11}C]toluenes **3a** and **3b**, an HPLC system (Merck-Hitachi) was used, including a gradient pump (L-6200A), a Rheodyne injector with a 20 µl loop, a LiChrospher 100 RP-18 endcapped column (5µm, 150 x 3.3 mm, Merck) and a UV detector coupled in series to a radioactivity detector FLO-ONE\Beta A500 (Canberra Packard). The mobile phase consisted of phosphate buffer pH 7 (c[NaH_2PO_4] = 0.26 mM; c[Na_2HPO_4] = 0.51 mM) and acetonitrile at a flow rate of 0.5 ml/min, with the following linear gradient of the eluents: 0 min - 70 % buffer/ 30 % MeCN; 10 min - 0 % buffer/ 100% MeCN; 20 min - 0 % buffer/ 100 % MeCN.

Synthesis of the precursors

(Di)methyl-substituted N-(2',4'-dinitrophenyl)pyridinium chlorides ***5***
A mixture of 1-chloro-2,4-dinitrobenzene (20.2 g; 0.1 mol) and the appropriate picoline or lutidine **4** (0.1 mol) was refluxed in ethanol (50 ml) for 3 h. The pyridinium salts crystallized when the solutions were cooled to room temperature. The salts were filtered through a frit glass filter, washed with diethyl ether and dried.

N-(2',4'-Dinitrophenyl)-3-methylpyridinium chloride (5a)
Yield: 20.1 g ≙ 68 %; greyish brown crystals; m.p. 216-217 °C
^{13}C-NMR: 75.475 MHz, CD_3OD, TMS ≙ 0, δ in ppm
18.6 (3-CH_3); 123.2 (CH, C(3')); 128.8 (CH, C(5)); 131.1 (CH, C(5')); 132.7 (CH, C(6')); 140.1 (C, C(1')); 141.7 (C, C(3)); 144.4 (CH, C(6)); 144.6 (C; C(2')); 146.6 (CH, C(2)); 150.6 (CH, C(4)); 151.2 (C, C(4'))

N-(2',4'-Dinitrophenyl)-4-methylpyridinium chloride (5b)
Yield: 25.7 g ≙ 87 %; black hygroscopic crystals
^{13}C-NMR: 75.475 MHz, CD_3OD, TMS ≙ 0, δ in ppm
22.8 (4-CH_3); 123.1 (CH, C(3')); 130.0 (CH, C(3) and C(5)); 131.1 (CH, C(5')); 132.8 (CH, C(6')); 140.0 (C, C(1')); 144.9 (C; C(2')); 145.9 (CH, C(2) and C(6)); 151.2 (C, C(4')); 165.6 (C, C(4))

N-(2',4'-Dinitrophenyl)-3,4-dimethylpyridinium chloride (5c)
Yield: 21.4 g ≙ 69 %; green powder; after a few days' storage ochre solid; m.p. 202-203 °C
^{13}C-NMR of: 75.475 MHz, CD_3OD, TMS ≙ 0, δ in ppm
17.0 (3-CH_3); 20.9 (4-CH_3); 123.1 (CH, C(3')); 129.6 (CH, C(5)); 131.1 (CH, C(5')); 132.8 (CH, C(6')); 140.0 (C, C(1')); 140.3 (C, C(3)); 143.6 (CH, C(6)); 144.7 (C; C(2')); 144.9 (CH, C(2)); 151.0 (C, C(4')); 164.2 (C, C(4))

5-Dimethylamino-2(or 3)-methyl-penta-2,4-dien-1-al (6a or 6b)
5a or **5b** (15 g; 0.05 mol) in ethanol (150 ml) was treated with 60 % aqueous dimethylamine (9.5 ml; 0.1 mol). The mixture was heated to 70 °C for 30 min, evaporated under reduced pressure, and treated with cold water (100 ml). The precipitated 2,4-dinitroaniline was separated by filtration and the filtrate made alkaline with sodium hydroxide (3 g; 0.075 mol) in water (15 ml). This mixture was extracted with methylene chloride (4 x 40 ml), the combined extracts were dried with Na_2SO_4. Evaporation of the filtered extract left a brownish solid (2-methyl compound **6a**) or a brownish liquid (impure 3-methyl compound **6b**). These products were used for the following synthetic step without further purification.

5-Dimethylamino-2-methyl-penta-2,4-dien-1-al (6a)
^{13}C-NMR: 75.475 MHz, $CDCl_3$, TMS ≙ 0, δ in ppm
9.0 (2-CH_3); 40.7 (5-N(CH_3)$_2$); 94.9 (CH, C(4)); 126.0 (C, C(2)); 151.2 (CH, C(5)); 153.2 (CH, C(3)); 192.4 (CHO, C(1))
^{1}H-NMR: 90 MHz, $CDCl_3$, TMS ≙ 0, δ in ppm
1.73 (s, 3H, 2-CH_3); 2.93 (s, 6H, 5-N(CH_3)$_2$); 5.21 (m, 1H, H-C(4)); 6.75 (m, 1H, H-C(5)); 6.81 (m, 1H, H-C(3)); 9.14 (s, 1H, CHO)

5-Dimethylamino-2-methyl-penta-2,4-dienylidene-1-dimethylammonium tetrafluoroborate (2a)
6a (2 g; 0.014 mol), dimethylamine tetrafluoroborate (1.91 g; 0.014 mol), and ethanol (8 ml) were refluxed for 2 h. The mixture was evaporated under reduced pressure, and the oily residue treated with ether. The separated salt was filtered through a frit glass filter and recrystallized from n-propanol. The orange crystals had m.p. 135-138 °C.
Yield: 0.72 g ≙ 19.7 %.
^{13}C-NMR: 75.475 MHz, $CDCl_3$, TMS ≙ 0, δ in ppm
12.4 (2-CH_3); 38.0 and 46.1 (1-=N(CH_3)$_2$); 44.5 broad (5-N(CH_3)$_2$); 99.7 (CH, C(4)); 110.3 (C, C(2)); 162.2 (CH, C(5)); 163.8 (CH, C(1)); 167.5 (CH, C(3))
^{1}H-NMR: 90 MHz, $CDCl_3$, TMS ≙ 0, δ in ppm
2.00 (s, 3H, 2-CH_3); 3.08 (s, 3H, 1-=NCH_3); 3.30 (s, 3H, 1-=NCH_3); 3.33 (s, 6H, 5-N(CH_3)$_2$); 5.49 (m, 1H, H-C(4)); 7.39 (s, 1H, H-C(1)); 7.60 (m, 2H, H-C(3) and H-C(5))
Analysis calcd. for $C_{10}H_{19}N_2BF_4$: C, 47.28; H, 7.49; N, 11.03. Found: C, 47.01; H, 7.41; N, 10.82.

5-Dimethylamino-3-methyl-penta-2,4-dienylidene-1-dimethylammonium tetrafluoroborate (2b)
6b (3.8 g; 0.027 mol), dimethylamine tetrafluoroborate (3.6 g; 0.027 mol), and ethanol (12 ml) were refluxed for 6.5 h. The salt separated after cooling was recrystallized from ethanol. The brownish orange crystals had m.p. 183-188 °C.
Yield: 4.1 g ≙ 59.1 %
^{13}C-NMR: 75.475 MHz, CD_3OD, TMS ≙ 0, δ in ppm
13.5 (3-CH_3); 38.1 and 46.4 (1-=N(CH_3)$_2$ and 5-N(CH_3)$_2$); 106.6 (CH, C (2) and C(4)); 157.6 (CH, C (1) and C(5)); 170.6 (C, C(3))
Analysis calcd. for $C_{10}H_{19}N_2BF_4$: C, 47.28; H, 7.49; N, 11.03. Found: C, 47.01; H, 7.65; N, 10.92.

Radiosyntheses

Nitro-[^{11}C]methane (**1**) was prepared as previously described [1], starting from [^{11}C]CO_2 *via* [^{11}C]CH_3I.

3-Nitro-[3-^{11}C]toluene (3a) and 4-nitro-[4-^{11}C]toluene (3b)
The [^{11}C]CH_3NO_2 (**1**) thus produced was trapped in a cooled 2 ml vessel (10 °C) containing 250 µl HMPT, 8 mg (30 µmol) pentamethinium tetrafluoroborate **2a** or **2b** and 25 µl 1.6 M BuLi in hexane (40 µmol). Cyclization/ aromatization into the nitro-[^{11}C]toluenes **3a** or **3b** was achieved by heating the well sealed vessel at 170 °C for 10 min.

m-[1-^{11}C]Toluidine (7a) and p-[1-^{11}C]toluidine (7b)
Reduction to obtain the [1-^{11}C]toluidines **7a** or **7b** was performed by adding an excess of $Na_2S{\cdot}9H_2O$ in 100 µl water to the above reaction mixture of **3a** or **3b** and heating at 170 °C: **7a**: 19 mg $Na_2S{\cdot}9H_2O$ (79 µmol) and 10 min heating; **7b**: 12 mg $Na_2S{\cdot}9H_2O$ (50 µmol) and 5 min heating.

ACKNOWLEDGEMENTS

The authors would like to thank Dr. D. Scheller of the Dresden University of Technology for recording the NMR spectra. The authors also thank Dr. J. Römer of our institute for his helpful discussion of this work.

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