Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXXIX, No. 7

N.C.A. ^{11}C-LABELLING OF BENZENOID COMPOUNDS IN RING POSITIONS: [^{11}C]ANISOLE DERIVATIVES

P. Mäding*, J. Steinbach and B. Johannsen

Institut für Bioanorganische und Radiopharmazeutische Chemie,

Forschungszentrum Rossendorf e.V., D-01314 Dresden, Postfach 510119, Germany

SUMMARY

The synthesis route to n.c.a. 3-nitro-[3-^{11}C]anisole (**3**) by use of the principle of synchronous six-electron cyclization of hexatriene systems into aromatics is described and discussed. Nitro-[^{11}C]-methane (**1**) reacts with the prepared precursor 5-dimethylamino-2-methoxy-penta-2,4-dienyli-dene-1-dimethylammonium tetrafluoroborate (**2b**) in the presence of BuLi to form 1-dimethyl-amino-4-methoxy-6-nitro-[6-^{11}C]hexatriene (**IA**, **IB**), followed by cyclization/ aromatization into **3**. Starting from **1**, 3-nitro-[3-^{11}C]anisole of a radiochemical purity of about 65 % and a mean specific radioactivity of 1 Ci/μmol was obtained within 10 min. Related to [^{11}C]CH_3NO_2, the reproducible radiochemical yield of **3** (decay-corrected) was 60±5 %. Reduction of **3** by heating the above reaction mixture with aqueous Na_2S gave 3-amino-[3-^{11}C]anisole (**4**) of a radiochemical purity of about 50 %. The reproducible radiochemical yield of **4** (decay-corrected) in relation to **1** was 45±5 %, the synthesis time from **1** was 16 min.

Keywords: PET, ^{11}C-ring labelling, nitro-[^{11}C]methane, 3-nitro-[3-^{11}C]anisole, 3-amino-[3-^{11}C]-anisole

*Author for correspondence

CCC 0362–4803/97/070585–15$17.50

Received 27 February 1997
Revised 10 March 1997

INTRODUCTION

The availability of ^{11}C-labelled radiotracers for PET investigations requires rapid and efficient routes of synthesis. A widespread variety of naturally occurring compounds are aromatics. This is also true of a considerable number of biologically active agents. Such compounds could be radiotracers of interest. For this reason we have been aiming at simple and efficient synthesis routes to introduce ^{11}C into aromatic rings. Labelling in ring positions is expected to provide metabolically stable tracers. In special cases it may be the only possibility of labelling at all.

Recently we described the synthesis of nitro-[1-^{11}C]benzene, the first n.c.a. ^{11}C-ring labelled benzenoid compound [1], by reaction of nitro-[^{11}C]methane with 5-dimethylamino-penta-2,4-dienylidene-dimethylammonium perchlorate (a pentamethinium salt, used as a suitable precursor) in hexamethylphosphoric triamide (HMPT) in the presence of potassium tert-butylate. This synthesis is based on using the principle of synchronous six-electron cyclization of hexatriene systems into aromatics according to [2]. Reduction of nitro-[1-^{11}C]benzene with aqueous Na_2S gave [1-^{11}C]aniline [1].

Now we are reporting on an extension of the synthesis strategy to include other substituted ^{11}C-ring labelled benzenoid compounds, particularly methoxy-substituted nitro-[1-^{11}C]benzenes and their appropriate [1-^{11}C]anilines. This involves the synthesis of suitable nonradioactive precursors in the form of pentamethinium salts containing a methoxy group at the carbon skeleton.

RESULTS AND DISCUSSION

Method of labelling

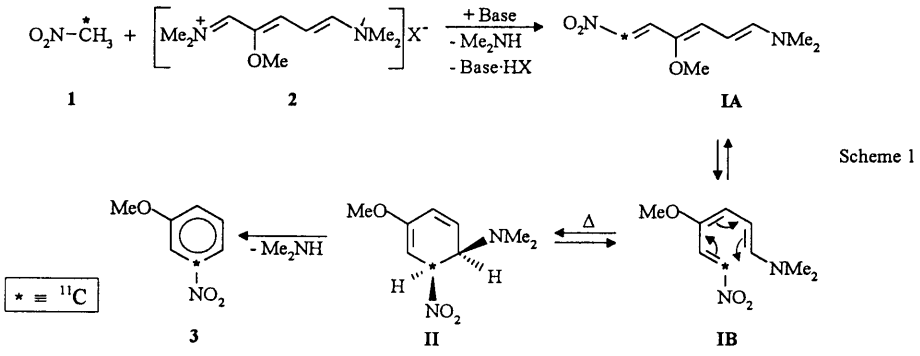
The labelling method is based on the reaction route according to Scheme 1:

1. In the presence of a base the C-H-acid nitro-[^{11}C]methane (**1**) reacts as a nucleophile with the

5-dimethylamino-2-methoxy-penta-2,4-dienylidene-1-dimethylammonium salt **2** to form 1-dimethylamino-4-methoxy-6-nitro-[6-^{11}C]hexatriene (**IA**, **IB**) and dimethylamine.

2. The synchronous six-electron cyclization of the [^{11}C]hexatriene **IB** into 3-nitro-[3-^{11}C]anisole (**3**) takes place in two steps [2]:
   - The thermal cyclization of **IB** into a [^{11}C]cyclohexadiene **II** is a reversible process.
   - The irreversible conversion of **II** into **3** occurs by elimination of the second dimethylamino group (a suitable leaving group). The dimethylamino group at C-1 of **II**, however, must be arranged in trans position to the proton at C-6.

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



1 **2** **IA** **3** **II** **IB**

Scheme 1

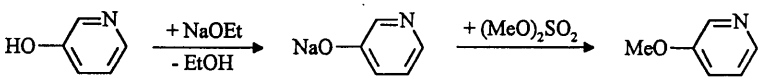
Precursor synthesis

The method for the synthesis of the unsubstituted pentamethinium salt, the 5-dimethylamino-penta-2,4-dienylidene-dimethylammonium perchlorate, is described in [1, 3, 4]. Attempts to apply this method to the synthesis of methoxy-substituted pentamethinium salts were carried out as follows, starting from 3-methoxypyridine (**4**: R^1=OMe, R^2=H) or 4-methoxypyridine (**5**: R^1=H, R^2=OMe).

1. Synthesis of the starting compounds **4** and **5**

3-Methoxypyridine (**4**)

4 was obtained by means of the Williamson ether synthesis, starting from 3-hydroxypyridine, sodium ethylate and dimethyl sulphate in yields of about 20 % according to Scheme 2:

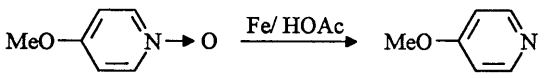


Scheme 2

4

4-Methoxypyridine (**5**)

5 was prepared by reduction of 4-methoxypyridine-N-oxide with iron powder in acetic acid analogously to Bax et al. [5] in yields of 64-76 % (Scheme 3).

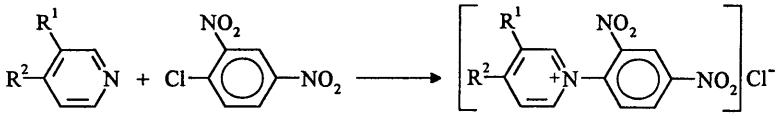


Scheme 3

5

2. Arylation of the methoxypyridines

4 and **5** were converted with 1-chloro-2,4-dinitrobenzene into N-(2',4'-dinitrophenyl)-3-methoxypyridinium chloride (**6**) and N-(2',4'-dinitrophenyl)-4-methoxypyridinium chloride (**7**) according to Scheme 4:



Scheme 4

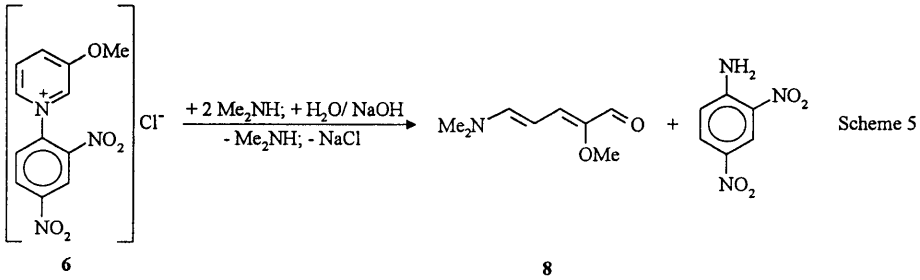
4, 5 **6, 7**

4, 6: R^1 = OMe, R^2 = H
5, 7: R^1 = H, R^2 = OMe

The yields of the synthesized pyridinium salts are 31 % for **6** and 77 % for **7**.

3. Cleavage of the pyridine ring of the pyridinium salts

Reaction of **6** with dimethylamine and subsequent addition of aqueous NaOH gave the desired 5-dimethylamino-2-methoxy-penta-2,4-dien-1-al (**8**) and 2,4-dinitroaniline (Scheme 5):

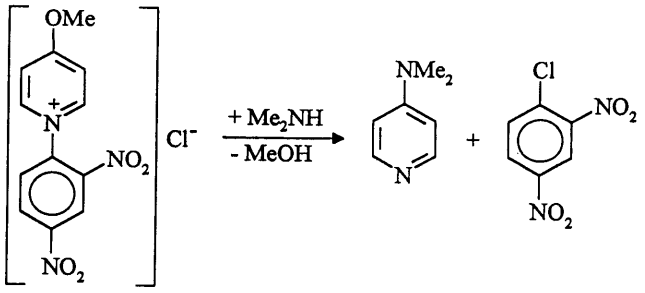


Scheme 5

6 **8**

The yield of the pentadienal **8** was about 53 %.

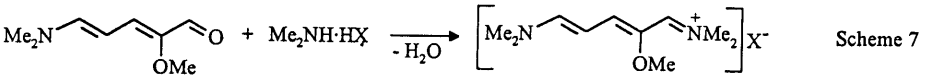
The cleavage of **7** with dimethylamine does not take place as expected. The reaction of dimethylamine with **7** did not yield the desired 5-dimethylamino-3-methoxy-penta-2,4-dien-1-al but 4-dimethylaminopyridine (**9**) according to Scheme 6. In this case the pyridinium salt **7** was decomposed in its components by substitution of the dimethylamino group for the 4-methoxy group. **9** was obtained even at room temperature by conversion in ethanol as well as in water with or without subsequent addition of aqueous NaOH.



7 **9** Scheme 6

4. Synthesis of the final precursor

Conversion of 5-dimethylamino-2-methoxy-penta-2,4-dien-1-al (**8**) with dimethylamine perchlorate or tetrafluoroborate according to Scheme 7 leads to the desired pentamethinium salt **2**, the 5-dimethylamino-2-methoxy-penta-2,4-dienylidene-1-dimethylammonium perchlorate (**2a**; yield: 18 %) or tetrafluoroborate (**2b**; yield: 46 %), by elimination of water:



8 **2** Scheme 7

2a: X = ClO_4
2b: X = BF_4

These pentamethinium salts, which were purified by recrystallization from n-propanol, are stable crystalline compounds with yellowish colour.

Synthesis of 3-nitro-[3-^{11}C]anisole

The results of the ring closure experiments for preparing 3-nitro-[3-^{11}C]anisole (**3**) are listed in Table 1. Initial attempts to synthesize **3** were carried out according to the procedure for synthesizing nitro-[1-^{11}C]benzene [1]. A mixture of 8 mg (30 µmol) 5-dimethylamino-2-methoxy-penta-2,4-dienylidene-1-dimethyl-ammonium tetrafluoroborate (**2b**), 3.5 mg (30 µmol) solid t-BuOK, 250 µl HMPT and [^{11}C]nitromethane (**1**) was heated in a well-sealed vessel at 170 °C for 7 min. Unfortunately, only small amounts of **3** (13.2 %) as well as unconverted **1** (76.1 %) were found by HPLC investigations. The reaction conditions therefore had to be optimized by varying the bases, their amounts and the reaction times.

Similar shares of **3** (17.6 %) were obtained using 1.3 mg NaH, a 60 % dispersion in mineral oil (30 µmol) instead of t-BuOK. But in this way an undesired isomerization reaction took place: **1** was converted into [^{11}C]methyl nitrite (24.9 %). With 130 µmol NaH this conversion was the main reaction (83.0 % [^{11}C]methyl nitrite).

The shares of **3** (21.9 %) as well as of [^{11}C]methyl nitrite (31.4 %) were increased by extension of the reaction time to 20 min, using 30 µmol t-BuOK. A further increase in **3** (49.0 %) was obtained by using 7 mg (60 µmol) t-BuOK and 20 min reaction time. With 14 mg (120 µmol) t-BuOK and 20 min reaction time a decrease in **3** to 25.4 % as well as an increase in [^{11}C]methyl nitrite (68.1 %) was found.

By varying the HPLC eluents and their gradients in the course of the experiments (see footnotes [c), d), e)] of Table 1) it was found that the above-mentioned percentage of **3** is a sum of an unidentified ^{11}C-labelled product and **3**. We suppose that the unidentified product is 1-dimethylamino-4-methoxy-6-nitro-[6-^{11}C]hexatriene (**IA**) which was not isomerized into the appropriate **IB** and that a complete cyclization/ aromatization was not possible. Steric reasons could be responsible for this phenomenon. A further indication of this assumption is the fact that the reducing power of sodium sulphide is not strong enough for the reduction of the aliphatic nitro group of **IA** (see Table 2 and Fig. 2).

Table 1: Product distribution of the ^{11}C-labelled compounds after ring closure experiments, preparing **3** under various conditions. General conditions: 30 µmol precursor **2b**, [^{11}C]CH_3NO_2 [6] from [^{11}C]CH_3I [7], reaction in HMPT at 170 °C; HPLC with RP-18 at a flow rate of 0.5 ml/min

Experiment No.	Base	Amount of base [µmol]	Reaction time [min]	Product distribution (radioactivity [%] is decay-corrected)			
				[^{11}C]methyl nitrite	nitro-[^{11}C]-methane (**1**)	unidentified ^{11}C-labelled product[a]	3-nitro-[3-^{11}C]anisole (**3**)
1	t-BuOK	30	7	10.7	76.1	13.2[c]	
2	t-BuOK	30	20	31.4	43.4	21.9[c]	
3	t-BuOK	60	20	24.7	24.0	49.0[c]	
4[b]	t-BuOK	60	20	35.4	13.2	41.3[c]	
5	t-BuOK	120	20	68.1	-	25.4[c]	
6	NaH	30	7	24.9	57.5	17.6[c]	
7	NaH	130	7	83.0	-	-	
8	BuLi	30	20	8.3	0.7	89.0[c]	
9	BuLi	30	10	5.3	0.3	27.2[d]	65.1
10	BuLi	40	10	9.7	-	18.9[d]	70.3
11	BuLi	40	10	12.6	-	23.2[e]	61.5[e]
12	BuLi	50	10	14.2	-	24.5[d]	56.6
13	BuLi	60	10	40.0	-	-	50.9

[a] Probably 1-dimethylamino-4-methoxy-6-nitro-[6-^{11}C]hexatriene (**IA**)

[b] Use of 28 µmol (8 mg) precursor **2a**

[c] This peak is the sum of the unidentified ^{11}C-labelled product and **3**, because the following linear gradient of the eluents was not able to separate these two compounds: 0 min - 70 % water/ 30 % MeCN; 10 min - 0 % water/ 100% MeCN; 20 min - 0 % water/ 100 % MeCN

[d] Shoulder of the unidentified ^{11}C-labelled product at the peak of **3**, because the following linear gradient of the eluents is not able to completely separate these two peaks: 0 min - 70 % buffer/ 30 % MeCN; 10 min - 0 % buffer/ 100% MeCN; 20 min - 0 % buffer/ 100 % MeCN; buffer = phosphate buffer pH 7 ($c[NaH_2PO_4]$ = 2.6 mM; $c[Na_2HPO_4]$ = 5.1 mM)

[e] Efficient and complete separation of the peaks of the unidentified ^{11}C-labelled product and **3** was possible by using the following suitable linear gradient of the eluents: 0 min - 70 % buffer/ 30 % MeCN; 20 min - 0 % buffer/ 100 % MeCN; buffer = phosphate buffer pH 7 ($c[NaH_2PO_4]$ = 0.26 mM; $c[Na_2HPO_4]$ = 0.51 mM)

Butyllithium proved to be the suitable base for the desired ring closure reaction. The best results for synthesis of **3** were obtained using precursor **2b** and BuLi in a molar ratio of 1:1 to 3:4 and

a reaction time of 10 min. In this way **3** of a radiochemical purity of 65±5 % and a mean specific radioactivity of 1 Ci/μmol was obtained. The reproducible radiochemical yield of **3** (decay-corrected) in relation to **1** was in the range of 60±5 %. An HPLC radiogram of unpurified **3** from such an experiment is shown in Fig. 1.

A greater excess of BuLi in proportion to **2b** should be avoided because of the increasing isomerization rate of $[^{11}C]CH_3NO_2$ into $[^{11}C]CH_3ONO$.

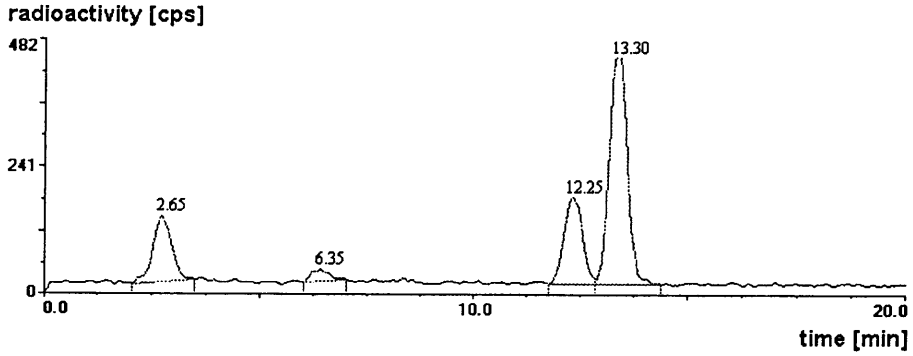
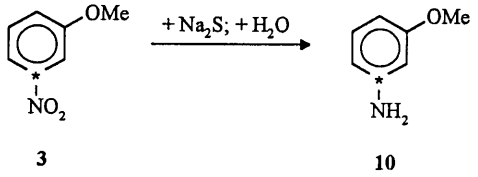


Fig. 1: HPLC radiogram obtained from the reaction mixture of the 3-nitro-[3-^{11}C]anisole (**3**) synthesis of experiment 11 (Table 1)
2.65 min: $[^{11}C]CH_3ONO$; 12.6 %
6.35 min: 3-amino-[3-^{11}C]anisole (**10**); 2.6 %
12.25 min: unidentified product, probably **IA**; 23.2 %
13.30 min: 3-nitro-[3-^{11}C]anisole (**3**); 61.5 %
(radioactivity [%] is decay-corrected)

Synthesis of 3-amino-[3-^{11}C]anisole

3-Amino-[3-^{11}C]anisole (m-[1-^{11}C]anisidine (**10**)) was synthesized analogously to the synthesis of [1-^{11}C]aniline [1] by reduction of **3** with aqueous Na_2S according to Scheme 8:



3 **10** Scheme 8

Starting from the reaction mixture of the synthesis of **3** mentioned above, the following reduction was carried out by adding an aqueous Na_2S solution (8 mg $Na_2S \cdot 5H_2O$ (50 μmol) in 100 μl

water) and subsequent heating at 170 °C in a one-pot process. The results of the experiments to reduce **3** to **10** are listed in Table 2.

10 could be prepared from **3** in a radiochemical purity of 49 ± 4 % when **3** was synthesized by using 30...40 µmol BuLi. The reproducible radiochemical yield of **10** (decay-corrected) in relation to **1** was in the range of 45±5 %, within a synthesis time from [^{11}C]CH_3NO_2 of 16 min. An HPLC radiogram of unpurified **10** is shown in Fig. 2.

The reduction of **3** with Na_2S led to an apparently increased amount of [^{11}C]methyl nitrite (Fig. 2: peak at 2.60 min; 19.5 %) in comparison with that amount after the ring closure reaction

Table 2: Product distribution of the ^{11}C-labelled products after reduction of several batches of 3-nitro-[3-^{11}C]anisole (**3**) with aqueous sodium sulphide (50 µmol $Na_2S{\cdot}5H_2O$ in 100 µl water) at 170 °C; HPLC with RP-18 at a flow rate of 0.5 ml/min

Experiment No.[a]	[%] of radioactivity of **3** in the starting reaction mixture	Reaction time [min]	Product distribution (radioactivity [%] is decay-corrected)			
			[^{11}C]methyl nitrite + by-product(s)[b]	3-amino-[3-^{11}C]anisole (**10**)	unidentified ^{11}C-labelled product[c]	3-nitro-[3-^{11}C]anisole (**3**)
9[d]	65.1	10	11.6	48.5	37.7	-
10[d]	70.3	5	23.0	53.0	23.5	-
11[e]	61.5	5	19.5	45.2	24.7	8.5
13[d]	50.9	10	58.1	32.2	-	-

[a] In accordance with the experiment no. in Table 1

[b] An increase in the amount of [^{11}C]methyl nitrite after reduction (compare with Table 1) indicates that the peak at 2.60 min (Fig. 2) additionally contains a by-product or by-products of reduction.

[c] Probably 1-dimethylamino-4-methoxy-6-nitro-[6-^{11}C]hexatriene (**IA**)

[d] Linear gradient of the eluents for HPLC: 0 min - 70 % buffer/ 30 % MeCN; 10 min - 0 % buffer/ 100 % MeCN; 20 min - 0 % buffer/ 100 % MeCN; buffer = phosphate buffer pH 7 (c[NaH_2PO_4] = 2.6 mM; c[Na_2HPO_4] = 5.1 mM)

[e] Linear gradient of the eluents for HPLC: 0 min - 70 % buffer/ 30 % MeCN; 20 min - 0 % buffer/ 100 % MeCN; buffer = phosphate buffer pH 7 (c[NaH_2PO_4] = 0.26 mM; c[Na_2HPO_4] = 0.51 mM)

(Fig. 1: peak at 2.65 min; 12.6 %). This fact was observed in all reduction experiments. We assume that this peak also includes ^{11}C-labelled ionic compounds caused by SO_3^{2-} impurities in the Na_2S ("Piria" reaction [8]). Such possible by-products could be N-[^{11}C]phenylsulphamic acids and sulphamidic [^{11}C]benzenesulphonic acids.

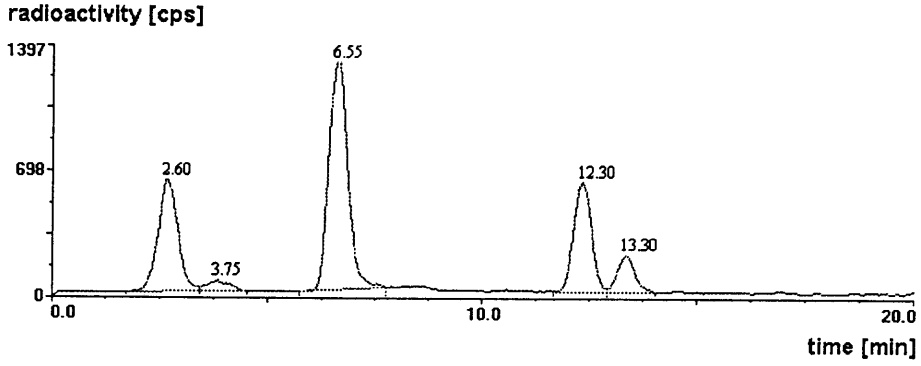


Fig. 2: HPLC radiogram obtained from the reaction mixture of the 3-amino-[3-^{11}C]anisole (**10**) synthesis of experiment 11 (Table 2)
2.60 min: [^{11}C]CH_3ONO + unidentified by-product(s) of reduction; 19.5 %
3.75 min: unidentified product; 2.0 %
6.55 min: 3-amino-[3-^{11}C]anisole (**10**); 45.2 %
12.30 min: unidentified product, probably **IA**; 24.7 %
13.30 min: 3-nitro-[3-^{11}C]anisole (**3**); 8.5 %
(radioactivity [%] is decay-corrected)

EXPERIMENTAL

The ^{13}C NMR spectra were recorded on a Bruker MSL 300 NMR spectrometer at 75.475 MHz or on a DRX 500 (Bruker) at 125.77 MHz, the ^1H-NMR spectra on a Bruker WH 90 DS at 90.02 MHz or on the MSL 300 at 300 MHz.

1-Chloro-2,4-dinitrobenzene, t-BuOK, BuLi (1.6 M in hexane) and HMPT, all of synthesis quality, were purchased from Merck. 3-Hydroxypyridine (distilled, 98 %) and NaH (60 % dispersion in mineral oil) were obtained from Aldrich, 60 % aqueous dimethylamine, $AgNO_2$ and $Na_2S \cdot 5H_2O$ p.a. from Riedel-de Haën, 4-methoxypyridine-N-oxide (97 %) from Janssen Chimica, iron powder "coarse" p.a. (reduced) from Ferak Berlin, Germany, and dimethyl sulphate (for synthesis) from Laborchemie Apolda, Germany. Dimethylamine perchlorate was prepared according to [1]. Dimethylamine tetrafluoroborate was self-made from 60 % aqueous dimethylamine and 40 % tetrafluoroboric acid (purum, Chemiewerk Nünchritz/ BT Dohna,

Germany) in ethanol, followed by evaporation of the solvents. Drying was completed by subsequent addition of n-propanol and repeated evaporation of the solvent.

For HPLC investigations the following reference substances were used: methyl iodide for synthesis (Merck), nitromethane 99 %, 3-nitroanisole 99 %, and m-anisidine 98 % (Fluka).

To determine the extent of the reaction conversion, the radiochemical purity of the reaction products and the specific radioactivity of 3-nitro-[3-^{11}C]anisole, 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 (5 µm, 150 x 3.3 mm, Merck) and a UV detector coupled in series with a radioactivity detector FLO-ONE\Beta A500 (Canberra Packard).

Unless otherwise indicated, the mobile phase consisted of phosphate buffer pH 7 and acetonitrile at a flow rate of 0.5 ml/min (see footnotes of Tables 1 and 2).

Synthesis of the precursors

3-Methoxypyridine (4)

Ethanol (300 ml) was dropped into a flask with pieces of metallic sodium (5.8 g; 0.25 mol). After complete conversion a suspension of 3-hydroxypyridine (23.8 g; 0.25 mol) in ethanol (80 ml) was added while stirring, followed by dropwise addition of dimethyl sulphate (17.6 g; 0.14 mol). Then this mixture was refluxed for 5 h. Removing the solvent under reduced pressure gave a solid residue which was dissolved in aqueous NaOH (5 %, 100 ml). This solution was extracted with methylene chloride (3 x 50 ml), the combined extracts were dried with Na_2SO_4. Evaporation of the filtered extract left a blue fluorescent liquid smelling of pyridine.

Yield: 5.6 g ≙ 20 %.

^{1}H-NMR: 90 MHz, $CDCl_3$, TMS ≙ 0, δ in ppm

3.58 (s, 3H, OCH_3); 6.97 (m, 2H, H-C(4) and H-C(5)); 7.93 (m, 1H, H-C(6)); 8.04 (m, 1H, H-C(2))

N-(2',4'-Dinitrophenyl)-3-methoxypyridinium chloride (6)

A mixture of 1-chloro-2,4-dinitrobenzene (10 g; 49 mmol) and **4** (5.6 g; 51 mmol) in diethyl ether (150 ml) was refluxed for 18 h. The separated salt was filtered through a frit glass filter, washed with diethyl ether and dried. The beige crystals had m.p. 182-184 °C.

Yield: 4.9 g ≙ 31 %

^{13}C-NMR: 125.77 MHz, CD_3OD, TMS ≙ 0, δ in ppm

58.6 (3-OCH_3); 123.1 (CH, C(3')); 129.9 (CH, C(5)); 131.1 (CH, C(5')); 132.6 (CH, C(6')); 134.7 (CH, C(2)); 135.0 (CH, C(4)); 139.7 (CH, C(6)) 140.1 (C, C(1')); 144.6 (C; C(2')); 151.2 (C, C(4')); 160.4 (C, C(3))

5-Dimethylamino-2-methoxy-penta-2,4-dien-1-al (8)

6 (4.9 g; 15.7 mmol) in ethanol (30 ml) was treated with 40 % aqueous dimethylamine (4.0 ml; 31.5 mmol). The mixture was heated at 70 °C for 30 min, evaporated under reduced pressure, and treated with cold water (50 ml). The precipitated 2,4-dinitroaniline was separated by filtration and the filtrate made alkaline with sodium hydroxide (1 g; 25 mmol) in water (6 ml). As a result the solution turned dark brownish. This mixture was extracted with methylene chloride (4 x 15 ml), the combined extracts were dried with Na_2SO_4. Evaporation of the filtered extract left a dark brownish solid.

Yield: 1.3 g ≙ 53 %.

^{13}C-NMR: 75.475 MHz, $CDCl_3$, TMS ≙ 0, δ in ppm

40.7 (5-$N(CH_3)_2$); 59.1 (2-OCH_3); 92.7 (CH, C(4)); 141.5 (CH, C(3)); 147.7 (C, C(2)); 150.3 (CH, C(5)); 185.0 (CHO, C(1))

5-Dimethylamino-2-methoxy-penta-2,4-dienylidene-1-dimethylammonium perchlorate (2a)

8 (1.3 g; 8.4 mmol), dimethylamine perchlorate (1.8 g; 12.4 mmol), and ethanol (8 ml) were refluxed for 5 h. Then the solvent was evaporated. After washing with n-propanol and diethyl ether, the dried residue was recrystallized from n-propanol. The yellow-orange crystals had m.p. 160 °C. The salt is soluble in water, methanol, chloroform, methylene chloride, acetone, acetonitrile and insoluble in diethyl ether.

Yield: 0.43 g ≙ 18 %.

^{13}C-NMR: 75.475 MHz, $CDCl_3$, TMS ≙ 0, δ in ppm

38.1 and 46.2 (1-=$N(CH_3)_2$); 38.9 broad and 47.9 broad (5-$N(CH_3)_2$); 60.8 (2-OCH_3); 97.8 (CH, C(4)); 136.8 (C, C(2)); 153.4 (CH, C(1)); 156.1 (CH, C(3)); 160.9 (CH, C(5))

Analysis calcd. for $C_{10}H_{19}N_2ClO_5$: C, 42.48; H, 6.73; N, 9.91; Cl, 12.57. Found: C, 42.43; H, 6.63; N, 9.96; Cl, 12.62.

5-Dimethylamino-2-methoxy-penta-2,4-dienylidene-1-dimethylammonium tetrafluoroborate (2b)

8 (1.0 g; 6.4 mmol), dimethylamine tetrafluoroborate (1.0 g; 7.5 mmol), and ethanol (5 ml) were refluxed

for 2 h. Then the solvent was evaporated. The residue was recrystallized from n-propanol. The ochre crystals had m.p. 141-143 °C. The salt is soluble in water, methanol, chloroform, acetone, and insoluble in diethyl ether.

Yield: 0.8 g ≙ 46 %.

^{13}C-NMR: 75.475 MHz, $CDCl_3$, TMS ≙ 0, δ in ppm

38.0 and 46.2 (1-=$N(CH_3)_2$); 39.2 broad and 47.9 broad (5-$N(CH_3)_2$); 60.8 (2-OCH_3); 98.0 (CH, C(4)); 137.1 (C, C(2)); 153.8 (CH, C(1)); 156.7 (CH, C(3)); 161.3 (CH, C(5))

Analysis calcd. for $C_{10}H_{19}N_2OBF_4$: C, 44.48; H, 7.04; N, 10.38. Found: C, 44.23; H, 6.87; N, 10.29.

4-Methoxypyridine (5)

4-Methoxypyridine-N-oxide (12.5 g; 0.1 mol), iron powder (10 g; 0.18 mol) and acetic acid (50 ml; 0.87 mol) were kept at 100 °C for 4 h. Then the mixture was basified with aqueous NaOH (35 g; 0.87 mol in 100 ml H_2O) and filtered through a frit glass filter. The filtration residue was washed with water, the filtrate was extracted with methylene chloride (3 x 50 ml) and the combined extracts were dried with Na_2SO_4. Evaporation of the filtered extract left a light-yellow liquid smelling of pyridine.

Yield: 8.3 g ≙ 76 %.

^{1}H-NMR: 90 MHz, $CDCl_3$, TMS ≙ 0, δ in ppm

3.76 (s, 3H, OCH_3); 6.74 (m, 2H, H-C(3) and H-C(5)); 8.36 (m, 2H, H-C(2) and H-C(6))

N-(2',4'-Dinitrophenyl)-4-methoxypyridinium chloride (7)

A mixture of 1-chloro-2,4-dinitrobenzene (13.5 g; 67 mmol) and **5** (7.3 g; 67 mmol) in diethyl ether (100 ml) was refluxed for 20 h. The separated salt was filtered through a frit glass filter, washed with diethyl ether and dried. The yellow solid had m.p. 137-139 °C.

Yield: 16.0 g ≙ 77 %

^{13}C-NMR: 75.475 MHz, CD_3OD, TMS ≙ 0, δ in ppm

59.8 (4-OCH_3); 114.8 (CH, C(3) and C(5)); 123.1 (CH, C(3')); 131.1 (CH, C(5')); 133.0 (CH, C(6')); 139.9 (C, C(1')); 144.9 (C; C(2')); 148.2 (CH, C(2) and C(6)); 150.8 (C, C(4')); 175.1 (C, C(4))

Reaction of 7 with dimethylamine

Aqueous dimethylamine (0.29 g; 6.4 mmol in 6 ml water) was dropped into an aqueous solution of **7** (1 g; 3.2 mmol in 10 ml water) while stirring. The dark oily residue was separated by filtration, the filtrate was

extracted with CH_2Cl_2 (3 x 10 ml), and the combined extracts were dried with Na_2SO_4. Evaporation of the filtered extract left a dark-brown solid which was identified as 4-dimethylaminopyridine (**9**).

Yield: 0.2 g ≙ 51 %

^{1}H-NMR: 300 MHz, CD_3OD, TMS ≙ 0, δ in ppm

3.10 (s, 6H, $N(CH_3)_2$); 6.69 (m, 2H, H-C(3) and H-C(5)); 8.12 (m, 2H, H-C(2) and H-C(6))

^{13}C-NMR: 75.475 MHz, CD_3OD, TMS ≙ 0, δ in ppm

39.1 (4-$N(CH_3)_2$); 107.8 (CH, C(3) and C(5)); 149.3 (CH, C(2) and C(6)); 156.5 (C, C(4))

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]anisole (3)

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) 5-dimethylamino-2-methoxy-penta-2,4-dienylidene-1-dimethylammonium tetrafluoroborate (**2b**) and 20-25 µl 1.6 M BuLi in hexane (30-40 µmol). Cyclization/ aromatization into 3-nitro-[3-^{11}C]anisole (**3**) was achieved by heating the well-sealed vessel at 170 °C for 10 min.

3-Amino-[3-^{11}C]anisole (10)

The reduction to 3-amino-[3-^{11}C]anisole (**10**) was performed by adding an excess of 8 mg (50 µmol) $Na_2S{\cdot}5H_2O$ in 100 µl water to the above reaction mixture of **3** and heating at 170 °C for 5 min.

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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