

## Note

# Preparation of [ $^{11}\text{C}$ ]methyl nona-fluorobutyl-1-sulfonate ([ $^{11}\text{C}$ ]MeONf) and its use in the synthesis of [ $^{11}\text{C}$ ]-6-OH-BTA-1

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**Abstract:** The rapid, simple and high-yield synthesis of the extraordinarily reactive  $^{11}\text{C}$ -methylating agent, [ $^{11}\text{C}$ ]methyl nona-fluorobutyl-1-sulfonate ([ $^{11}\text{C}$ ]MeONf), and its use in the synthesis of the promising  $\beta$ -amyloid imaging agent, [ $^{11}\text{C}$ ]-6-OH-BTA-1, is reported. In terms of radioactive methylation yields, [ $^{11}\text{C}$ ]MeONf seems to surpass [ $^{11}\text{C}$ ]methyl trifluoromethanesulfonate ([ $^{11}\text{C}$ ]MeOTf) as a methylating agent in this particular case giving the  $^{11}\text{C}$ -labelled compound in high-preparative radiochemical yields between 27 and 29% EOS with a minimum formation of radioactive by-products. Copyright © 2007 John Wiley & Sons, Ltd.

**Keywords:**  $^{11}\text{C}$ -methylation; nonaflate; Pittsburgh compound

## Introduction

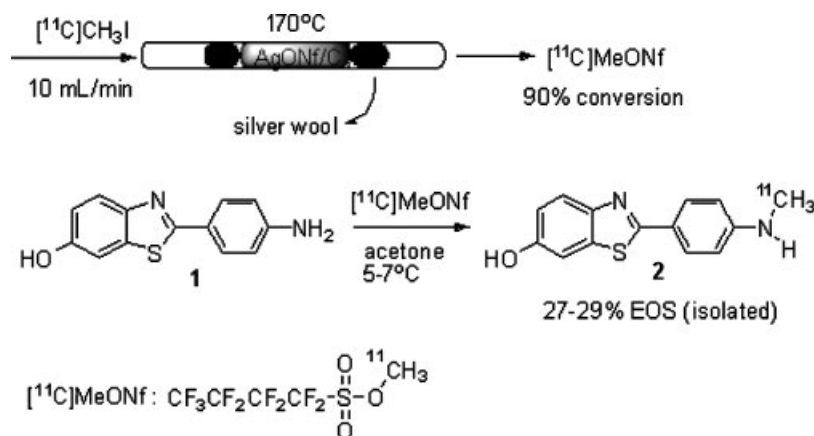
The synthesis of  $^{11}\text{C}$ -labelled compounds is based predominantly on the use of [ $^{11}\text{C}$ ]methyl iodide ([ $^{11}\text{C}$ ]CH<sub>3</sub>I),<sup>1</sup> a labelling precursor routinely produced by commercially available synthesis modules for simple methylation reactions of desmethyl precursors. Despite its straightforward synthesis, in some cases the reactivity of [ $^{11}\text{C}$ ]CH<sub>3</sub>I is not high enough to guarantee high radiochemical yields (RCYs) of the labelled compound and more reactive methylating agents are therefore needed. Especially, the  $^{11}\text{C}$ -methylation of an aniline structure element, which is e.g. present in 2-(4'-aminophenyl)-6-hydroxybenzothiazole (**1**) used as a precursor for the synthesis of the  $\beta$ -amyloid imaging compound [ $^{11}\text{C}$ ]-6-OH-BTA-1 (**2**),<sup>2</sup> has been proven to be difficult as a result of its low reactivity towards alkylation. Harsh reaction conditions such as high temperatures and the use of potassium hydroxide are

necessary to label **1** with [ $^{11}\text{C}$ ]CH<sub>3</sub>I. Furthermore, the phenolic hydroxy group present in the molecule has to be protected in advance to avoid unwanted *O*-methylation. Despite the inconvenient and time-consuming deprotection step and the insufficient reactivity of [ $^{11}\text{C}$ ]CH<sub>3</sub>I, compound **2** was obtained in RCYs of 12%. To circumvent these difficulties, Wilson *et al.* as well as Solbach *et al.* independently reported the rapid one-step radiosynthesis of [ $^{11}\text{C}$ ]-6-OH-BTA-1 using the far more reactive labelling agent [ $^{11}\text{C}$ ]MeOTf and the unprotected phenolic benzothiazole labelling precursor 6-HO-BTA-0.<sup>3,4</sup> RCYs of 11–16% (Wilson *et al.*, preparative RCY at EOS, uncorrected for radioactive decay) and 58% (Solbach *et al.*, RCYs based on integration of the radio-high-performance liquid chromatography (HPLC) chromatogram) of [ $^{11}\text{C}$ ]-6-OH-BTA-1 have been reported after a synthesis time of 22 and 33 min, respectively, which is a great improvement when compared with the original labelling procedure using [ $^{11}\text{C}$ ]CH<sub>3</sub>I. A significant difference between these two procedures is the used reaction temperature (Wilson *et al.* used 20°C, Solbach *et al.* used 80°C) as well as the applied amount of precursor (Wilson *et al.* applied 0.4 mg, Solbach *et al.* applied between 4 and 8 mg). The corresponding HPLC chromatogram (Wilson *et al.*) of the crude reaction mixture showed still large

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**Figure 1** Top: Synthesis of [ $^{11}\text{C}$ ]MeONf via online conversion of [ $^{11}\text{C}$ ]CH<sub>3</sub>I using a AgONf/C filled glass column at 170°C and a flow rate of 10 mL/min. Bottom: Reaction of **1** with [ $^{11}\text{C}$ ]MeONf at 5–7°C within 2 min in acetone.

amounts of radioactive by-products. Between 2 and 4 min large amounts of unspecified by-products were observed and the formation of the unwanted *O*-methylated compound was low but still observable (<5%). We here report the synthesis of the homologous  $^{11}\text{C}$ -labelling agent [ $^{11}\text{C}$ ]MeONf starting from [ $^{11}\text{C}$ ]CH<sub>3</sub>I. We successfully applied [ $^{11}\text{C}$ ]MeONf to the synthesis of [ $^{11}\text{C}$ ]-6-OH-BTA-1 (Figure 1). RCYs of [ $^{11}\text{C}$ ]-6-OH-BTA-1 could be enhanced by further minimizing the formation of uncharacterized by-products as well as completely avoiding the formation of *O*-[ $^{11}\text{C}$ ]methylated compound (Figure 2).

## Experimental

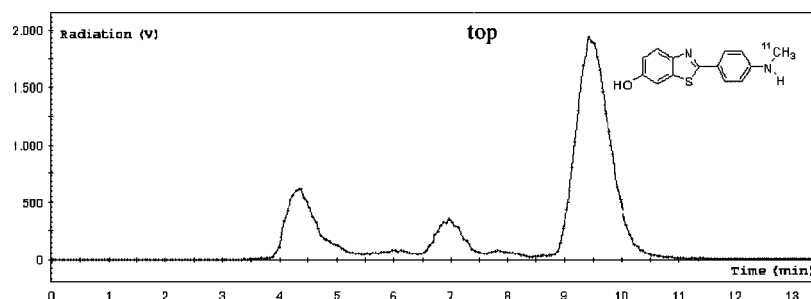
Authentic 6-HO-BTA-0, 6-OH-BTA-1 and 6-OCH<sub>3</sub>-BTA-1 were purchased from ABX (Germany). Graphitized carbon (Carbograph 1 60/80) was purchased from Alltech. Silvercarbonate, 4-(4'-nitrobenzyl)pyridine (NBP) and nona-fluorobutane-1-sulfonic acid were available from Sigma Aldrich.

### Synthesis of nona-fluorobutane-1-sulfonic acid silver salt (AgONf)

The synthesis based on a procedure published by Frasch *et al.* was simplified as a result of available starting material of higher quality.<sup>5</sup> In brief, to a stirred solution of nona-fluorobutane-1-sulfonic acid (2.5 g, 8.3 mmol) in water (5 mL), Ag<sub>2</sub>CO<sub>3</sub> (1.14 g, 4.15 mmol) was carefully added in small portions until a clear solution was obtained. The solution was filtered and freeze dried under light exclusion to obtain AgONf as a white solid (3 g, 7.4 mmol, 90%).

### Synthesis of [ $^{11}\text{C}$ ]MeONf and [ $^{11}\text{C}$ ]-6-OH-BTA-1

A short glass column (4 mm ID × 95 mm) was partially filled (approximately one-third its volume) with a mixture of AgONf (200 mg, 0.49 mmol) and graphitized carbon (200 mg), prepared by simply mixing the compounds in a mortar with a spatula according to Figure 1. The prepared column was placed in a commercially available synthesis unit (MEI plus by Bioscan, [ $^{11}\text{C}$ ]CH<sub>3</sub>I is produced by conversion of [ $^{11}\text{C}$ ]CO<sub>2</sub> with LiAlH<sub>4</sub> and HI) for the preparation of [ $^{11}\text{C}$ ]CH<sub>3</sub>I and [ $^{11}\text{C}$ ]MeOTf and heated up to 170°C in a stream of nitrogen for 5 min. [ $^{11}\text{C}$ ]CH<sub>3</sub>I from the module, which was previously passed over a short drying column (5.0 g NaOH), was streamed through the AgONf/C column and was bubbled (N<sub>2</sub> sweep flow of 10 mL/min) into a solution of **1** (0.8–2 mg, 3.3–8.2 μmol) dissolved in acetone (0.5 mL) at 5–7°C for 2 min. Purification was performed according to Wilson *et al.*<sup>3</sup> using slightly different HPLC conditions (HPLC column: Phenomenex Prodigy 10 μ (250 × 10 mm), eluent: acetonitrile/0.1 N NH<sub>4</sub>HCO<sub>3</sub> 50/50, flow: 3 mL/min). Before the reaction mixture was subjected to the HPLC, 1.5 mL of HPLC solvent (acetonitrile/0.1 N NH<sub>4</sub>HCO<sub>3</sub> 50/50) was added. After collection of the peak corresponding to **2**, the HPLC solvent was removed by using a vacuum evaporator at 80°C. To the dried compound, ethanol (0.5 mL) and sterile phosphate buffer (10 mL, pH 7, SABEX<sup>®</sup>) were added and the mixture was passed through a sterile filter (MILLEX<sup>®</sup> GV) to obtain the final injectable solution. The overall synthesis time was between 25 and 27 min. For quality control of the final sterile product, we used a Prodigy 5 μ 250 × 4.6 mm HPLC column and an Agilent 1200 HPLC system equipped with a UV-detector (Agilent 1200 series) and a radioactivity



**Figure 2** Radio-HPLC chromatogram of the crude reaction mixture of the reaction between **1** and [ $^{11}\text{C}$ ]MeONf showing high RCYs of **2** and decreased formation of radioactive by-products. No formation of *O*-[ $^{11}\text{C}$ ]methylated product (retention time: 12 min) was observed.

detector (Raytest, Germany). The following conditions for quality control were applied: HPLC-solvent: acetonitrile/0.1  $\text{NH}_4\text{HCO}_3$  50/50; flow: 0.7 mL/min;  $R_t$  **2**: 9.5 min. The purity of the final sterile compound was determined to be >95%.

## Results and discussion

The higher homolog of [ $^{11}\text{C}$ ]MeOTf, [ $^{11}\text{C}$ ]MeONf could be synthesized in high RCYs (90% based on [ $^{11}\text{C}$ ]CH $_3\text{I}$ ) from [ $^{11}\text{C}$ ]CH $_3\text{I}$ , which was converted to the [ $^{11}\text{C}$ ]methyl-sulfonate using a AgONf-graphitized carbon column. Non-radioactive MeONf has been reported to be a more reactive methylation agent than MeOTf.<sup>6,7</sup> For the synthesis of [ $^{11}\text{C}$ ]MeONf, a commercially available synthesis unit for [ $^{11}\text{C}$ ]CH $_3\text{I}$  was used, which already contains a compartment for the synthesis of [ $^{11}\text{C}$ ]MeOTf and could therefore be used for the production of [ $^{11}\text{C}$ ]MeONf without modification. The [ $^{11}\text{C}$ ]CH $_3\text{I}$  was streamed over the pre-heated column (170°C) using a flow rate of 10 mL/min according to Jewett's procedure for the synthesis of [ $^{11}\text{C}$ ]MeOTf.<sup>8</sup> Higher flow rates resulted in a dramatically decreased RCY of [ $^{11}\text{C}$ ]MeONf. When a flow rate of 15 mL/min was used, the conversion rate dropped to 3% only. The conversion of [ $^{11}\text{C}$ ]CH $_3\text{I}$  could be easily monitored by the reaction of [ $^{11}\text{C}$ ]MeONf with NBP which does not react with unconverted [ $^{11}\text{C}$ ]CH $_3\text{I}$ .<sup>8</sup> In order to maximize the RCY of the reaction with **1** and [ $^{11}\text{C}$ ]MeONf in acetone, the temperature dependency of the reaction was investigated. Best results were obtained between 5 and 7°C giving compound **2** in preparative RCYs between 27 and 29% at EOS (obtaining the final injectable solution is defined as EOS) as a sterile injectable solution (based on production of 5 GBq of [ $^{11}\text{C}$ ]CO $_2$ ) which almost doubles the previously published amount using [ $^{11}\text{C}$ ]MeOTf. The specific activity of **2** was determined using a UV-calibration curve and was found to be between 40 and 50 GBq/ $\mu\text{mol}$ . This is

an important advancement because the demand for **1** is steadily increasing. When the reaction was performed at 0°C ( $n = 2$ ), according to the HPLC chromatograms, the first peak ( $R_t$ : 4.5 min) in the radio-HPLC chromatogram, which we assume corresponds to hydrolyzed un-reacted [ $^{11}\text{C}$ ]MeONf gets more pronounced and accounts for 40% of the detected radioactivity. When performed at room temperature ( $n = 2$ ), a new radioactive by-product ( $R_t$ : 9 min) occurred, accounting for 25% of the observed radioactivity. As these experiments served the purpose of optimizing the reaction, no isolated uncorrected RCYs were determined. In comparison to Wilson *et al.*, we did not apply the HPLC loop technique for performing the reaction between **1** and [ $^{11}\text{C}$ ]MeONf. In order to trap most of the [ $^{11}\text{C}$ ]MeONf, we used a larger amount of solvent (0.5 mL acetone instead of 0.25 mL methylethylketone) and between 0.8 and 2 mg of **1**. This is a shortcoming in terms of needed precursor material compared with Wilson *et al.*, who used only 0.4 mg of precursor material. In contrast to Solbach *et al.* who used 5–10 times more precursor, the other methods are preferable from an economical point of view. To directly compare [ $^{11}\text{C}$ ]MeONf and [ $^{11}\text{C}$ ]MeOTf at our individual laboratory conditions, the methylation of **1** was performed with [ $^{11}\text{C}$ ]MeOTf either at room temperature or between 5 and 7°C. At room temperature ( $n = 3$ ), we obtained nearly the same results as published by Wilson *et al.* Our isolated yields were between 13 and 17% at EOS (after 22–27 min) and the radio-HPLC chromatogram showed still a large radioactivity peak (ca. 30%) at 4.5 min. This peak was even more pronounced when the reaction was performed at 5–7°C ( $n = 2$ ) and accounted for more than 40% of the detected radioactivity. Furthermore, the increased formation of radioactive by-products was observed. In this case no isolated yields were determined. Interestingly, the formation of the *O*-[ $^{11}\text{C}$ ]methylated product could not be observed in any case using [ $^{11}\text{C}$ ]MeONf, giving rise to

speculations whether it is true that [ $^{11}\text{C}$ ]methyl-sulfonates such as [ $^{11}\text{C}$ ]MeOTf and [ $^{11}\text{C}$ ]MeONf are less discriminative methylating agents in comparison to [ $^{11}\text{C}$ ]CH<sub>3</sub>I. According to our observations, [ $^{11}\text{C}$ ]MeONf obviously seems to distinguish between the aromatic amino moiety and the phenolic hydroxy function to 100% at the temperatures we investigated. Wilson *et al.* reported the formation of small amounts of *O*-methylated product using [ $^{11}\text{C}$ ]MeOTf<sup>3</sup> at 20°C, but Solbach *et al.* who performed the synthesis at 80°C for 1 min did not confirm this observation. We are currently investigating whether [ $^{11}\text{C}$ ]MeONf is applicable to the selective  $^{11}\text{C}$ -methylation of bi- or multifunctional compounds in general. Furthermore, it would be worthwhile to introduce  $^{11}\text{C}$ -methylating agents covering a wider spectrum of reactivity to thoroughly investigate the dependency of discrimination of methylation and leaving group in complex multifunctional molecules.

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