Journal of Labelled Compounds and Radiopharmaceuticals
J Label Compd Radiopharm 2007; **50**: 1230–1233.
Published online 2 August 2007 in Wiley InterScience
(www.interscience.wiley.com). DOI: 10.1002/jlcr.1432

JLCR

Note

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

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Received 30 April 2007; Revised 11 June 2007; Accepted 12 June 2007

Abstract: The rapid, simple and high-yield synthesis of the extraordinarily reactive ^{11}C-methylating agent, [^{11}C]methyl nona-fluorobutyl-1-sulfonate ([^{11}C]MeONf), and its use in the synthesis of the promising β-amyloid imaging agent, [^{11}C]-6-OH-BTA-1, is reported. In terms of radioactive methylation yields, [^{11}C]MeONf seems to surpass [^{11}C]methyl trifluoromethansulfonate ([^{11}C]MeOTf) as a methylating agent in this particular case giving the ^{11}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}C-methylation; nonaflate; Pittsburgh compound

Introduction

The synthesis of ^{11}C-labelled compounds is based predominantly on the use of [^{11}C]methyliodide ([^{11}C]CH_3I),[1] 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}C]CH_3I 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}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 β-amyloid imaging compound [^{11}C]-6-OH-BTA-1 (**2**),[2] 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}C]CH_3I. 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}C]CH_3I, 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}C]-6-OH-BTA-1 using the far more reactive labelling agent [^{11}C]MeOTf and the unprotected phenolic benzothiazole labelling precursor 6-HO-BTA-0.[3,4] 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}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}C]CH_3I. 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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Contract/grant sponsor: CIHR
Contract/grant sponsor: Fonds de la Recherche en Santé du Québec (FRSQ)

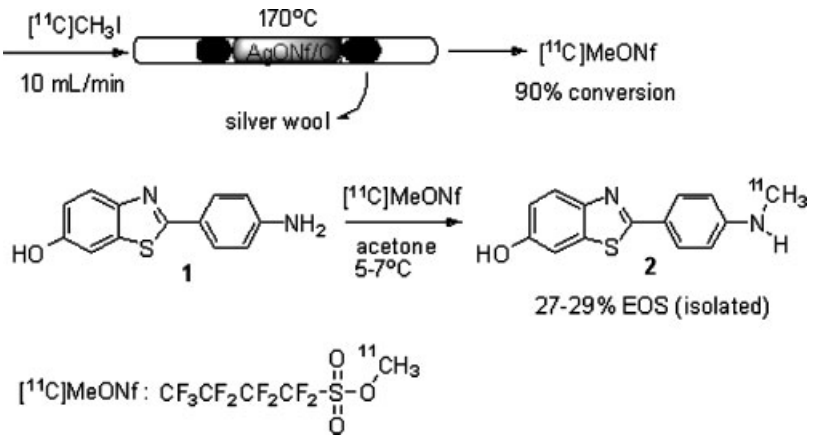

Figure 1 Top: Synthesis of [11C]MeONf via online conversion of [11C]CH_3I using a AgONf/C filled glass column at 170°C and a flow rate of 10 mL/min. Bottom: Reaction of **1** with [11C]MeONf at 5–7°C within 2 min in acetone.

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}C-labelling agent [11C]MeONf starting from [11C]CH_3I. We successfully applied [11C]MeONf to the synthesis of [11C]-6-OH-BTA-1 (Figure 1). RCYs of [11C]-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*-[11C]methylated compound (Figure 2).

Experimental

Authentic 6-HO-BTA-0, 6-OH-BTA-1 and 6-OCH_3-BTA-1 were purchased from ABX (Germany). Graphitized carbon (Carbograph1 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.[5] In brief, to a stirred solution of nona-fluorobutane-1-sulfonic acid (2.5 g, 8.3 mmol) in water (5 mL), Ag_2CO_3 (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 [11C]MeONf and [11C]-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, [11C]CH_3I is produced by conversion of [11C]CO_2 with $LiAlH_4$ and HI) for the preparation of [11C]CH_3I and [11C]MeOTf and heated up to 170°C in a stream of nitrogen for 5 min. [11C]CH_3I 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_2 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.*[3] using slightly different HPLC conditions (HPLC column: Phenomenex Prodigy 10 μ (250 × 10 mm), eluent: acetonitrile/0.1 N NH_4HCO_3 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_4HCO_3 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®) were added and the mixture was passed through a sterile filter (MILLEX®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

DOI: 10.1002.jlcr

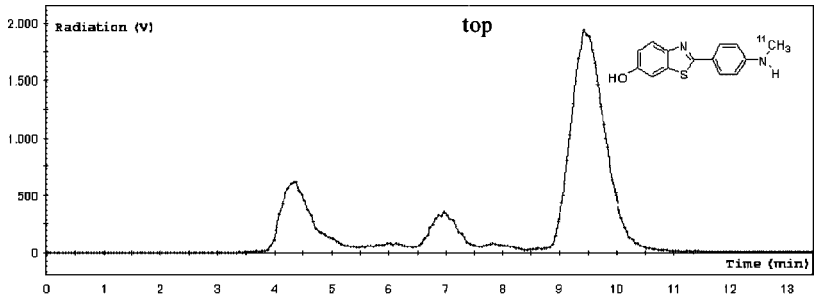

Figure 2 Radio-HPLC chromatogram of the crude reaction mixture of the reaction between **1** and [^{11}C]MeONf showing high RCYs of **2** and decreased formation of radioactive by-products. No formation of *O*-[^{11}C]methylated product (retention time: 12 min) was observed.

detector (Raytest, Germany). The following conditions for quality control were applied: HPLC-solvent: acetonitrile/0.1 NH_4HCO_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}C]MeOTf, [^{11}C]MeONf could be synthesized in high RCYs (90% based on [^{11}C]CH_3I) from [^{11}C]CH_3I, which was converted to the [^{11}C]methyl-sulfonate using a AgONf–graphitized carbon column. Non-radioactive MeONf has been reported to be a more reactive methylation agent than MeOTf.[6,7] For the synthesis of [^{11}C]MeONf, a commercially available synthesis unit for [^{11}C]CH_3I was used, which already contains a compartment for the synthesis of [^{11}C]MeOTf and could therefore be used for the production of [^{11}C]MeONf without modification. The [^{11}C]CH_3I 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}C]MeOTf.[8] Higher flow rates resulted in a dramatically decreased RCY of [^{11}C]MeONf. When a flow rate of 15 mL/min was used, the conversion rate dropped to 3% only. The conversion of [^{11}C]CH_3I could be easily monitored by the reaction of [^{11}C]MeONf with NBP which does not react with unconverted [^{11}C]CH_3I.[8] In order to maximize the RCY of the reaction with **1** and [^{11}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}C]CO_2) which almost doubles the previously published amount using [^{11}C]MeOTf. The specific activity of **2** was determined using a UV-calibration curve and was found to be between 40 and 50 GBq/μmol. 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_f: 4.5 min) in the radio-HPLC chromatogram, which we assume corresponds to hydrolyzed un-reacted [^{11}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_f: 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}C]MeONf. In order to trap most of the [^{11}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}C]MeONf and [^{11}C]MeOTf at our individual laboratory conditions, the methylation of **1** was performed with [^{11}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}C]methylated product could not be observed in any case using [^{11}C]MeONf, giving rise to

DOI: 10.1002.jlcr

speculations whether it is true that [^{11}C]methyl-sulfonates such as [^{11}C]MeOTf and [^{11}C]MeONf are less discriminative methylating agents in comparison to [^{11}C]CH_3I. According to our observations, [^{11}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}C]MeOTf[3] 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}C]MeONf is applicable to the selective ^{11}C-methylation of bi- or multifunctional compounds in general. Furthermore, it would be worthwhile to introduce ^{11}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.

Acknowledgements

The authors would like to thank Dr Esther Schirrmacher for the determination of specific activity and Dr Mirko Diksic for discussions. This study was supported in part by operating grants from the CIHR and the Fonds de la Recherche en Santé du Québec (FRSQ) awarded to H. C. H. C. is a chercheur national of the FRSQ (Fonds de la Recherche en Santé du Québec).

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DOI: 10.1002.jlcr