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Note

A rapid one-step radiosynthesis of the β-amyloid imaging radiotracer *N*-methyl-[^{11}C]2-(4′-methylaminophenyl)-6-hydroxybenzothiazole ([^{11}C]-6-OH-BTA-1)

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Summary

The promising β-amyloid PET imaging agent, [^{11}C]-6-OH-BTA-1, has been radiolabelled in one step using [^{11}C]-methyl triflate. No protection of the 6-hydroxy group is required, greatly simplifying the synthetic method. The reaction may be carried out in solution or by the captive solvent 'loop' method. Copyright © 2004 John Wiley & Sons, Ltd.

Key Words: Amyloid; PET; carbon-11; methyl triflate; Alzheimer's

Introduction

The radiotracer, *N*-methyl-[^{11}C]2-(4′-methylaminophenyl)-6-hydroxybenzothiazole (**1**), has recently been introduced as a highly promising radiotracer for imaging amyloid plaques using positron emission tomography (PET).[1] Benzothiazole (**1**), also known as 6-OH-BTA-1, and PIB, binds with nanomolar affinity to aggregated synthetic Aβ(1-40) fibrils and to postmortem homogenates of cortical tissue from Alzheimer's disease (AD) patients.[1] Initial PET imaging trials of AD subjects and controls show preferential uptake in cortical areas of AD subjects compared to controls.[2,3] These results have generated much interest in this and related radiotracers for imaging plaques.[4,5]

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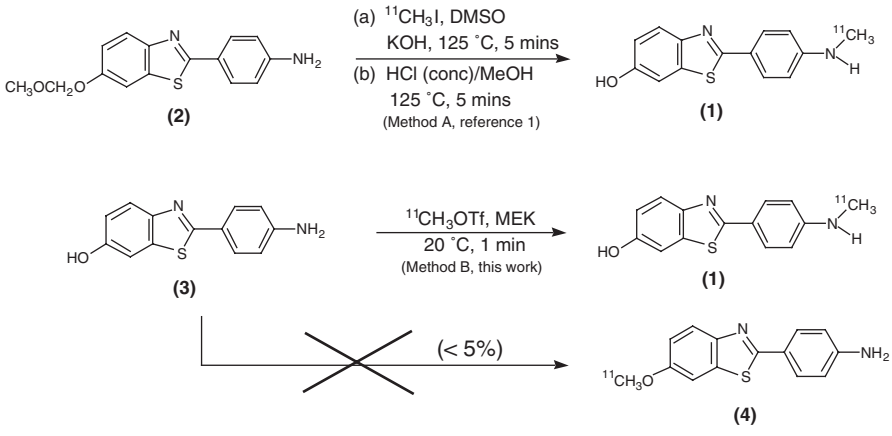

Scheme 1. Radiosynthesis of [^{11}C]-(1) by two different methods

The original radiosynthesis of [^{11}C]-(**1**) utilized the methoxymethyl (MOM) protected phenol (**2**) as precursor and consisted of labelling of the aniline nitrogen with [^{11}C]-iodomethane under forcing (125°C, KOH) conditions, followed by deprotection of the intermediate MOM ether with hot acid (Scheme 1, method A). We report here that a more direct, simpler radiosynthesis of [^{11}C]-(**1**) is possible. Direct radiolabelling of the aniline nitrogen of the unprotected precursor (**3**) with [^{11}C]-methyl triflate results in [^{11}C]-(**1**) in good yields with minimal formation of the undesired [O-methyl-^{11}C] by-product (**4**) (Scheme 1, method B).

Experimental

Authentic (**1**), (**3**), and (**4**) were prepared by literature methods.[1,6] NMR spectra, mass spectra, and melting points were in agreement with the literature.

Loop Method of Radiosynthesis of [^{11}*C*]-(***1***). [^{11}C]-methylations with [^{11}C]-methyl triflate[7] were carried out inside an HPLC sample loop[8] following a previously described method[9] in all respects except for the use of (**3**) as precursor and different HPLC purification conditions to remove excess unreacted (**3**) and other impurities. Conditions were: Phemomenex Luna (2) C18 10 μ (250 × 10 mm), 40%CH_3CN:60% H_2O + 0.1N NH_4HCO_2, 9 ml/min. Formulation of [^{11}C]-(**1**) was carried out as described previously.[9] *V-Vial Method of Radiosynthesis of* [^{11}*C*]-(**1**). [^{11}C]-methyl triflate was bubbled (N_2 sweep flow of 25 ml/min) into a solution of (**3**) (0.4 mg in 250 μl methylethyl ketone) at 20°C. Upon maximal trapping of radioactivity, the reaction was immediately quenched with HPLC buffer (0.6 ml) and injected onto the HPLC column for purification as described above.

Results and discussion

Reaction of the unprotected benzothiazole (**3**) (Scheme 1) with [^{11}C]-methyl triflate in methylethyl ketone, either in solution or in an HPLC loop, was

complete after less than one min at room temperature. Radiosynthesis results including incorporation of radioactivity into [^{11}C]-(**1**) were similar for both methods (50–60% by HPLC analysis). Isolated radiochemical yields of the final, formulated, sterile, and pyrogen-free product were 11–16% (uncorrected for decay, based on production of 35 GBq of [^{11}C]CO_2) in a synthesis time of 22 mins. Specific radioactivities were 30–60 GBq/μmol (end-of-synthesis) and the radiochemical purity was >95% (see below). Formation of the [*O*-methyl-^{11}C]benzothiazole (**4**) was less than 5% in all cases and was easily removed in the HPLC purification step (Figure 1). In some cases a small amount of radiolysis product was observed in the final formulated product (<5%). This could be suppressed by the addition of 0.1% ascorbic acid to the HPLC mobile phase.

In their seminal paper[1] on the preparation and evaluation of [^{11}C]-(**1**), the authors note that in the presence of base the hydroxyl group of (**3**) is preferentially and efficiently attacked by [^{11}C]-iodomethane and concluded that protection at this site would be required for successful *N*-[^{11}C]-methylation (which was also carried out in the presence of strong base). However (**3**) is quite capable of acting as its own base, especially when present in excess over the alkylating agent. Even with the highly reactive, and ostensibly less discriminating [^{11}C]-methyl triflate, *N*-alkylation strongly predominates over O-alkylation.

This is a general observation, not limited to benzothiazoles such as (**3**). We carried out competitive alkylation experiments reacting [^{11}C]-methyl triflate with an equimolar solution of aniline and phenol in methylethyl ketone in the absence of added base. Exclusively, alkylation occurred on aniline and no (<0.5%) ^{11}C-labelled anisole could be detected by HPLC.

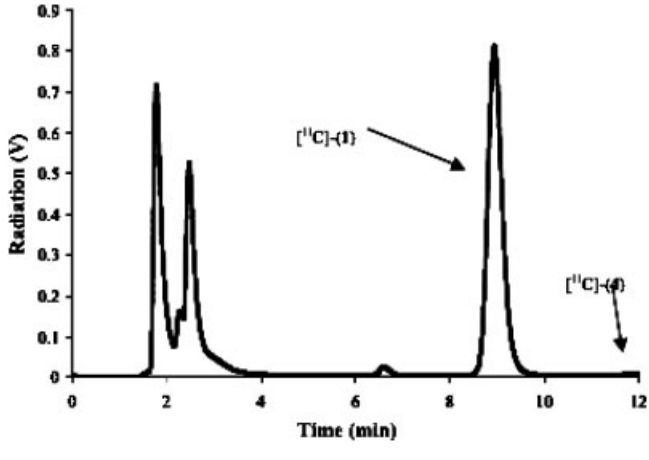

Figure 1. HPLC chromatogram of the purification of [^{11}C]-(1)

Thus (**3**), and presumably most other anilines containing hydroxyphenyl groups, can be directly and efficiently *N*-$^{11}CH_3$ labelled with [^{11}C]-methyl triflate without the need to resort to protecting groups for the phenol moiety.

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