The Synthesis, Characterization and Chemistry of [Methyl-^{14}C] Methyl Nosylate

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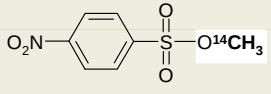
1 Introduction

The use of substances labeled with carbon-14 has been extraordinarily valuable in many aspects of the life sciences for over half a century. One of the most versatile and simple ways to install carbon-14 in many compounds of interest is by methylating available heteroatoms like nitrogen, oxygen and sulfur to afford corresponding methyl-^{14}C analogues. Over the years, [^{14}C] methyl iodide has been a convenient electrophilic reagent of choice to employ in this regard. However safety regulations have restricted the shipment of [^{14}C] methyl iodide by air and its limited stability has made other forms of prolonged transportation impractical and inadvisable. For that reason we decided to explore the synthesis, characterization and chemistry of [methyl-^{14}C] methyl nosylate (**1**) as a useful alternative carbon-14 radiomethylating reagent



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2 Results and Discussion

The synthesis of **1** is analogous to that of the corresponding tritiated reagent first reported by Pounds and is described in the experimental section. It's methylation chemistry is similar to and equally straightforward as that of the tritiated analogue and is illustrated in Section 4. Using **1**, estrone (**2**) could easily be converted to **3** in approximately 95% radiochemical yield, while [methyl-^{14}C] caffeine (**5**) and [methyl-^{14}C] yohimbine (**7**) were correspondingly prepared from their respective desmethyl analogues in about 50% radiochemical yield. Employing **1** also permitted its safe addition to reaction vessels without concern for volatile carbon-14 contamination as is the case with [^{14}C] methyl iodide. Also, subsequent portions of **1**, needed to drive a radiomethylation reaction to completion, could also be easily added.

Besides solving a transportation and regulatory challenge, the availability of reagent **1** has also been accompanied by another valuable benefit; namely, significantly enhanced shelf life over that of [^{14}C] methyl iodide. Preliminary studies have shown that the stability of **1** when stored in a solution of hexane:ethyl acetate (4:1) at – 20 ^{o}C is at least nine months before needing repurification. In contrast, [^{14}C] methyl iodide is well known to be stable for only a few weeks at best.

3 Experimental

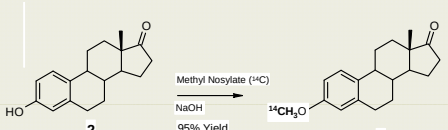
All nonradioactive reagents and solvents were purchased from Sigma-Aldrich Chemical Company. Proton NMR spectra were recorded on a Bruker 300 MHz spectrometer with internal TMS as reference standard.

[Methyl-^{14}C] Methyl Nosylate (1)

Silver nosylate was freshly prepared in the following manner in the dark: Silver carbonate (2.08 g, 7.56 mmol) was placed in a round bottom flask and suspended in 10 mL of acetonitrile under nitrogen. To the flask was then added 3.6 g (15.1 mmol) of 4-nitrobenzenesulfonic acid (85% pure) in 40 mL of acetonitrile with stirring over the course of 20 min. After the addition the dark green opaque solution was heated to 60^{0} C for 1 h. The reaction was then cooled and filtered free of fine black solids. The filtrate was rotary evaporated and the resulting tan colored solid was crushed in a mortar and pestle in the dark. The silver nosylate was transferred to a breakseal flask fitted with a septum and vacuum attachment followed by the addition of 65 mL of dry acetonitrile. [^{14}C] Methyl iodide (12.6 mmol at 51 mCi/mmol) was then added via syringe to the pre-evacuated reaction vessel and the syringe side arm was flame sealed. The reaction was heated to 80^{0} C overnight and cooled to ambient temperature the next morning. The reaction vessel was then attached to a vacuum line and the acetonitrile was distilled away leaving a residue which was dissolved in a minimum amount of ethyl acetate. Silica gel flash chromatography purification using hexane:ethyl acetate (4:1) and pooling appropriate fractions afforded 501 mCi (a 78% radiochemical yield) of **1** that was homogeneous on silica gel TLC (hexane:ethyl acetate (10:3)) and provided a proton NMR ($CDCl_3$) that was in concert with that of unlabelled methyl nosylate; ∂ 8.35 (d, 2), 8.05 (d, 2), 3.80 ppm (s, 3)

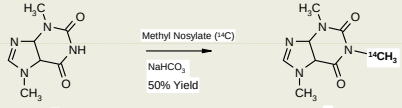
4 Reaction Examples

[Methyl-^{14}C] Estrone 3-methyl ether



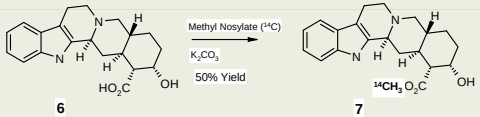
2 **3**

[Methyl-^{14}C] Caffeine



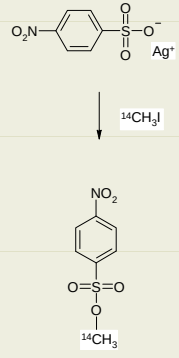
4 **5**

[Methyl-^{14}C] Yohimbine



6 **7**

5 [Methyl-^{14}C] Methyl Nosylate Synthesis



6 Summary

We have demonstrated that [methyl-^{14}C] methyl nosylate, NEC820*, is a useful carbon-14 radiomethylating reagent for several reasons:

1. Stability: [methyl-^{14}C] methyl nosylate is stable for more than nine months whereas [^{14}C] methyl iodide is well known to be stable for only a few weeks at best.
2. Ease of use: [methyl-^{14}C] methyl nosylate can safely be transferred to reaction vessels without concern for volatile carbon-14 releases and contamination as is the case with [^{14}C] methyl iodide. This is very useful for small scale reactions.
3. Safety regulations: [methyl-^{14}C] methyl nosylate solves a transportation and regulatory challenge

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