

A Simple Synthesis of [^{11}C]Methyl Triflate

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[^{11}C]Methyl triflate ([^{11}C]methyl trifluoromethanesulfonate) was formed in high yield when [^{11}C]methyl iodide in a nitrogen carrier was passed at 200°C through a column containing graphitized carbon impregnated with 50% by weight of silver triflate.

Introduction

[^{11}C]Methyl iodide (Marazano *et al.*, 1976; Långström and Lundqvist, 1977) is a principal intermediate for the introduction of ^{11}C into radiopharmaceuticals. While CH_3I is highly reactive by the standards of preparative organic chemistry, for ^{11}C radioalkylations it is often necessary to heat the components under confinement, and to use a large excess of substrate to cope with the limitation of a 20-min half-life. Forcing conditions may result in the formation of side-products which must be removed from the product radiopharmaceutical, and some sensitive substrates such as norscopolamine may be destroyed completely (Vora *et al.*, 1983; Mulholland *et al.*, 1988). Methyl triflate (CH_3OTf) is far more reactive than CH_3I in most systems (Lewis *et al.*, 1983, 1985; Matyjaszewski, 1984; Hanson, 1965). It is less volatile and thus more easily trapped and confined in small reactors. It is probable that [^{11}C]CH $_3$ OTf would offer a favorable alternative to [^{11}C]CH $_3$ I for many radiomethylations. Below, a simple synthesis of [^{11}C]CH $_3$ OTf from [^{11}C]CH $_3$ I is described. [^{11}C]CH $_3$ I is passed at 200°C over a column of graphitized carbon impregnated with silver triflate (Booth *et al.*, 1980). It reacts instantaneously and essentially completely. No significant complexity is introduced into an existing system for producing [^{11}C]CH $_3$ I, and no additional time is required for the conversion.

Materials and Methods

Colorimetric assay for methyl triflate

A N_2 carrier stream containing CH_3OTf to be assayed (on the order of 20 μg) was passed into

1.0 mL of reagent grade acetone containing 1% 4-(4-nitrobenzyl)pyridine (NBP). At 20°C the CH_3OTf reacted immediately with the reagent. After removal of most of the acetone under a stream of N_2 the NBP residue was diluted with fresh acetone to a volume of 3 mL. Triethylamine, 40 μL , was added. The optical density of the resulting magenta chromophore was measured at 565 nm and compared to a standard. The latter consisted of 5–20 μL of dry CH_2Cl_2 containing a measured amount of CH_3OTf . CH_3I was unreactive under the conditions of the assay. This provided a convenient way to distinguish between CH_3I and CH_3OTf .

Silver triflate-impregnated graphitized carbon

The preparation was done in a dry atmosphere away from strong light. Silver triflate (Aldrich), 1.0 g, was ground with a spatula in a 3 mL V-vial to break up coarse particles. Graphpac GC, 80–100 mesh (Alltech) 2.0 g was added. The vial was sealed with a Teflon-faced septum stopper and shaken gently to mix the two solids. The vial was evacuated and placed for 5 min in an aluminum block maintained at 300°C.

Reaction column

A Pyrex tube (6 mm o.d. \times 23 cm) was equipped with a ring of three small indentations 13 cm from the upstream end. The tube was constricted to an o.d. of 4 mm at the ends to allow Viton tubing to be fitted over the ends during synthesis. Fine silver wire was rolled into a loose ball, inserted into the upstream end of the column and pressed against the ring of indentations to form a coarse frit capable of restraining the AgOTf-impregnated carbon packing. The latter (about 600 mg) was poured into the column to a depth of 2.5 cm. During operation the column was maintained in a vertical position with downward flow to keep the packing in place. Before synthesis the column was connected to the system by 0.8 mm i.d. Teflon tubing via short sleeves of Viton tubing.

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Before and during synthesis a slow N₂ purge flowed through the column to exclude air. The column was inserted through a longitudinal hole (6.3 mm i.d.) in a thermally-insulated aluminum cylinder 18 cm long by 2.5 cm o.d. During the synthesis the cylinder was heated to 200°C by an imbedded cartridge heater.

Synthesis of [¹¹C]methyl triflate

[¹¹C]Methyl iodide was synthesized essentially as reported by Marazano *et al.* (1977). The N₂ carrier (50 mL/min) containing the [¹¹C]CH₃I was passed through a column (25 mm × 5 mm) of dry 40–60 mesh soda lime to remove traces of HI and reduce the amount of water before passing over the AgOTf-impregnated carbon at 200°C, in the reaction column described above. The [¹¹C]CH₃OTf eluting with the N₂ carrier was trapped in 2 mL of acetone containing 1% NBP. The effluent from the acetone was passed through two traps in series (4 cm × 9 cm) packed with 20-mesh activated charcoal at 0°C to catch any unreacted [¹¹C]CH₃I.

Radioassay of [¹¹C]methyl triflate and [¹¹C]methyl iodide

After all [¹¹C]CH₃I had been distilled and converted (2–3 min) the acetone was evaporated from the NBP solution into the downstream charcoal trap. Any unreacted [¹¹C]CH₃I remaining was transferred along with the acetone into the charcoal trap, whereas the radioactivity from the [¹¹C]CH₃OTf was rendered non-volatile by instantaneous reaction with the NBP. At the end of the synthesis the radioactivities of the NBP and charcoal traps were measured in an ionization counter to determine the relative amounts of [¹¹C]CH₃OTf and [¹¹C]CH₃I.

Preparative synthesis of methyl triflate from methyl iodide

To obtain sufficient CH₃OTf for NMR analysis, 100 mg CH₃I in about 200 mL N₂ was passed over 2.5 g of AgOTf-impregnated carbon in a 10 mm × 70 mm glass column at 213°C. The effluent was condensed directly in an NMR sample tube and diluted with deuterated benzene containing 1% TMS as a standard.

Results and Discussion

Table 1 shows the ¹¹C radioactivity distribution for a series of preparations of [¹¹C]methyl triflate. The product is taken to be the radioactivity rendered non-volatile by reaction with NBP in acetone. While the synthesis of [¹¹C]CH₃I was quite variable, conversion of the latter to a species capable of reacting with NBP was always near 100%. In experiments 5–7 the [¹¹C]methoxyaluminate intermediate from the reaction of [¹¹C]CO₂ with LiAlH₄ was decomposed with 56% aqueous HI (Dannals and Lågström, 1985) instead of 85% H₃PO₄. This tended to increase the overall yield of [¹¹C]CH₃OTf by improving the conversion of [¹¹C]CH₃OH to [¹¹C]CH₃I. The synthesis from end of beam until maximum [¹¹C]CH₃OTf activity was trapped, required 7 min. The amount of [¹²C]CH₃OTf associated with the radioactivity reacting as [¹¹C]CH₃OTf was determined spectrophotometrically from the NBP residue in the trap. The AgOTf column did not appear to introduce any additional reactive ¹²C to the product (Table 1). In experiments 2 and 8 (Table 1) the AgOTf-carbon column was omitted from the system to demonstrate the markedly different behavior of [¹¹C]CH₃I with respect to trapping in charcoal vs NBP-acetone. The same gas-phase reaction was done on a 100 mg scale with a larger AgOTf-carbon column to permit analysis by ¹H-NMR. The ¹H-NMR spectrum for the product in deuterobenzene was identical to that for a CH₃OTf reference (methyl singlet, δ_{TMS} 3.3 ppm) and distinct from that for CH₃I (δ_{TMS} 1.5 ppm).

Figure 1 shows the effect of temperature on the conversion of CH₃I to CH₃OTf as determined spectrophotometrically after reaction with NBP. The variability was characteristic of the spectrophotometric assay itself and was not apparent in the radiochemical experiments. No change in the yield occurred when the carrier flow rate was varied from 20 to 100 mL/min at 190°C. Further, coinjection of water vapor with the CH₃I did not reduce the yield. The apparent lack of critical variables should permit the reaction to be readily adapted to a variety of existing systems for making [¹¹C]CH₃I.

No extraordinary precautions were observed in the preparation of the AgOTf-impregnated carbon. Heating of the components was done in a vacuum

Table 1. Summary of radiochemical yields and conversion efficiencies for the synthesis of [¹¹C]methyl triflate

Expt. No.	Radioactivity balance corrected to end of synthesis (mCi)						Radiochem. yield CH ₃ OTf (%)	Conversion of MeI (%)	CH ₃ OTf (μmol)
	LiAlH ₄	HI	Soda lime	AgOTf column	Charcoal trap	NBP trap (CH ₃ OTf)			
1	0.9	2.1	5.6	—	0.5	69.1	86	99	—
2	0.83	0.44	0.57	(none)	1.77	0.04	—	—	—
3	1.2	32.4	30.0	1.8	3.2	118.4	63	97	—
4	0.5	29.4	22.3	1.4	4.2	86.4	60	95	—
5	2.8	1.8	8.5	7.5	4.9	317.6	93	98	0.49
6	0.4	0.5	1.1	0.7	1.2	76.5	95	98	0.20
7	0.5	0.5	2.6	1.0	0.9	31.5	85	97	0.15
8	0.82	0.45	0.32	(none)	34.7	2.2	—	—	—

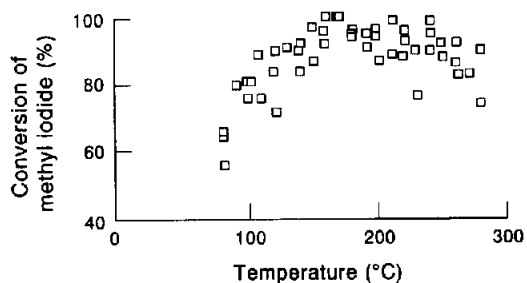


Fig. 1. Effect of column temperature on the conversion of methyl iodide to methyl triflate by silver triflate-impregnated carbon.

and in the absence of bright light to avoid possible side-reactions. AgOTf alone tended to sinter in the column and was difficult to pack uniformly. For this reason an inert carrier was selected. A graphitized carbon for gas chromatography proved satisfactory. A less expensive graphitized carbon (Graphpac GB, Alltech) also appeared to be adequate, but no quantitative study was carried out with the latter. Columns were reused several times without apparent loss of efficiency. The columns used for the radiosyntheses (Table 1) had previously been exposed to small amounts of unlabeled CH_3I in other experiments.

Methyl bromide and methyl chloride were also converted by AgOTf in the gas phase to MeOTf. This may permit access to $[^{11}\text{C}]\text{MeOTf}$ directly from $[^{11}\text{C}]\text{methane}$ via methyl halides (Prenant and Crouzel, 1991).

The above method should provide ready access to $[^3\text{H}]\text{CH}_3\text{OTf}$ and $[^{14}\text{C}]\text{CH}_3\text{OTf}$ as well as $[^{11}\text{C}]\text{CH}_3\text{OTf}$. The availability of $[^{11}\text{C}]\text{CH}_3\text{OTf}$ should offer an additional degree of freedom in developing new ^{11}C radiomethylations, and may possibly, by its unique reactivity, suggest new routes to useful radiopharmaceuticals. Conversely, adoption of $[^{11}\text{C}]\text{CH}_3\text{OTf}$ for radiopharmaceutical research may lead to the discovery of new preparative applications of this remarkable reagent.

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