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Research Article

Synthesis of no-carrier-added [^{11}C]methanesulfonyl chloride as a new labeling agent for PET radiopharmaceutical development

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Summary

Three methods are described for labeling methanesulfonyl (mesyl) chloride with no-carrier-added (NCA) carbon-11 ($t_{1/2} = 20.4$ min; $\beta^+ = 99.8\%$) to provide a new labeling agent of potential value in radiopharmaceutical development for positron emission tomography (PET). Each method uses NCA [^{11}C]iodomethane, which is readily prepared from cyclotron-produced [^{11}C]carbon dioxide or [^{11}C]methane by known procedures. The first method (route 1) consisted of converting [^{11}C]iodomethane into [^{11}C]methyllithium and then treatment with sulfuryl chloride. NCA [^{11}C]mesyl chloride was obtained in 78% decay-corrected radiochemical yield (RCY) from [^{11}C]iodomethane at 30 min from the end of radionuclide production (ERP). However, co-production of *n*-butanesulfonyl chloride limited the extent of reaction of this labeling agent with 1,2,3,4-tetrahydroisoquinoline (THIQ). Two new syntheses were devised, based on converting [^{11}C]iodomethane into [^{11}C]methanethiol by passage over heated sodium hydrogen sulfide for subsequent treatment with either chlorinated water (route 2) or over heated manganese(IV) oxide and then calcium hypochlorite (route 3). These procedures gave NCA [^{11}C]mesyl

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chloride in 77% (route 2) and 28% (route 3) RCYs from [^{11}C]iodomethane at about 20 min from ERP. Crude [^{11}C]mesyl chloride, produced by route 2 or 3, reacted rapidly with THIQ to give the corresponding NCA [^{11}C]methanesulfonamide in 49 or 74% RCY, respectively. Phenol was also converted rapidly with [^{11}C]mesyl chloride into the corresponding [^{11}C]mesylate (>90% RCY).

Key Words: Carbon-11; labeling agent; PET; [^{11}C]mesyl chloride; [^{11}C]methanesulfonamide; [^{11}C]mesylate

Introduction

The development of new labeling agents is fundamentally important to the search for new radiopharmaceuticals in the field of positron emission tomography (PET),[1–3] an important biomedical imaging modality that finds increasingly widespread application in clinical research,[1–3] clinical diagnosis,[4] drug development[5–7] and biological investigations in small animals.[8,9] Methanesulfonyl (mesyl) groups are present in several drugs and potential PET radiopharmaceuticals.[10] Mesyl chloride is well known to be reactive towards amines, alcohols and phenols,[11] and hence, no-carrier-added (NCA) [^{11}C]mesyl chloride could have widespread use for labeling with the short-lived positron-emitter, carbon-11 ($t_{1/2} = 20.4$ min; $\beta^+ = 99.8\%$), if a rapid and effective radiosynthesis could be developed. Following our earlier brief reports,[12,13] we describe three methods for the radiosynthesis of [^{11}C]mesyl chloride in full detail, one based on treatment of [^{11}C]methyllithium with sulfuryl chloride and two others that each use [^{11}C]methanethiol as an intermediate for oxidation and chlorination. One of these is a complete 'on-line' gas phase process from [^{11}C]iodomethane and especially suited to future easy automation.

Results and discussion

NCA [^{11}C]iodomethane can be readily prepared from cyclotron-produced [^{11}C]carbon dioxide[14–16] or [^{11}C]methane[17–19] in high radioactivity and high specific radioactivity, and has the potential to serve as a useful substrate for the preparation of [^{11}C]mesyl chloride. Initially, we explored the preparation of NCA [^{11}C]mesyl chloride by treating

[^{11}C]iodomethane with *n*-butyllithium and the resultant [^{11}C]methyllithium[20,21] with sulfuryl chloride (Figure 1; route 1). This procedure gave [^{11}C]mesyl chloride in 78% RCY (decay-corrected radiochemical yield) within 12 min from the production of [^{11}C]iodomethane. Reaction of NCA [^{11}C]mesyl chloride with 1,2,3,4-tetrahydroisoquinoline (THIQ; 51 mg) gave [^{11}C]*N*-mesyl-THIQ in 61% RCY.

However, when reactions were performed with the amount of THIQ reduced to 26 and 13 mg, the RCYs of the [^{11}C]*N*-mesyl-THIQ were reduced to 50 and 26%, respectively. This effect is probably due to competition for reaction with THIQ by the substantial quantity of *n*-butanesulfonyl chloride that is expected to be co-produced with the labeling agent. This route was therefore considered impractical for application in cases where it might be necessary to use a small amount of precursor in the labeling reaction. Examples would be cases where there is a need to conserve precious precursor material or to enable effective single pass HPLC separation of the radiopharmaceutical. Use of the more sterically hindered *t*-butyllithium[22] in place of *n*-butyllithium was not effective in eliminating competing reaction with THIQ.

We examined a second approach, whereby NCA [^{11}C]iodomethane might be converted into [^{11}C]methanethiol, which might then be oxidized and chlorinated to [^{11}C]mesyl chloride. It has been reported that [^{11}C]methanethiol may be prepared almost instantaneously and quantitatively by dispensing NCA [^{11}C]iodomethane into a solution of sodium hydrogen sulfide in anhydrous *N*,*N*-dimethylformamide.[23] We prepared [^{11}C]methanethiol satisfactorily by this procedure. Since [^{11}C]methanethiol is gaseous (b.pt.: 6°C), simple nitrogen purge of the reaction mixture enabled transfer of this product to a collection vessel

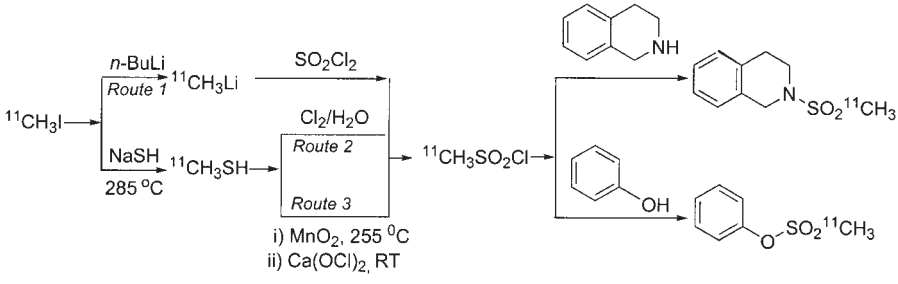

Figure 1. Routes to NCA [^{11}C]mesyl chloride from NCA [^{11}C]iodomethane and its use for labeling a methanesulfonamide and mesylate

that contained reagent for further transformation. Chlorine-saturated water at 0°C has been used to prepare fluoromesyl chloride from 4-chlorobenzyl fluoromethyl sulfide.[24] We found that this reagent would also convert [^{11}C]methanethiol into [^{11}C]mesyl chloride. Thus, after such a reaction, analysis of the aqueous medium revealed that greater than 90% of the trapped radioactivity was [^{11}C]mesyl chloride. However, only about 60% of the initial radioactivity, presumed to be [^{11}C]methanethiol, was successfully transferred over a period of 10 min; a significant proportion of radioactivity, of undetermined chemical form, remained in the reaction vessel that was used to produce the [^{11}C]methanethiol.

This experience prompted us to explore the development of an 'on-line' process for the preparation of [^{11}C]methanethiol. Such a procedure would also be attractive for ease of future radiosynthesis automation and operation with high radioactivity levels. We investigated passage of [^{11}C]iodomethane over anhydrous solid sodium hydrogen sulfide† contained in a silica tube placed within a furnace, with any generated [^{11}C]methanethiol collected in chlorine-saturated water (Figure 1, route 2). The formation of [^{11}C]methanethiol by this method was found to be temperature-dependent. At room temperature (RT), no [^{11}C]mesyl chloride was detected in the chlorinated water. By increasing the furnace temperature to 150°C and then 210°C there was 3 and 15% radiochemical conversion, respectively. At 285°C, 60–80% of the collected radioactivity was found to be [^{11}C]mesyl chloride by HPLC (Figure 2). Byproducts accounted for the remaining radioactivity.

Although [^{11}C]mesyl chloride, generated by this method, is obtained in chlorine-saturated water, it was found possible to prepare [^{11}C]*N*-mesyl-THIQ rapidly in 40% overall RCY from [^{11}C]iodomethane by the addition of THIQ in dichloromethane, containing triethylamine (TEA), to the aqueous mixture. It was also found that [^{11}C]mesyl chloride could be isolated from the reaction mixture in which it was generated with a silica Sep-pak® cartridge that had been pre-activated with chloroform. The reaction mixture was injected onto the cartridge and the [^{11}C]mesyl chloride eluted with chloroform. About 30% of the radioactivity eluted from the cartridge under these conditions. It was further found that an equal mixture of chloroform and dioxane gave improved elution of the labeling agent, equivalent to about 50% of the radioactivity loaded onto the cartridge.

†Potassium hydrogen sulfide was also used satisfactorily until its commercial availability ceased.

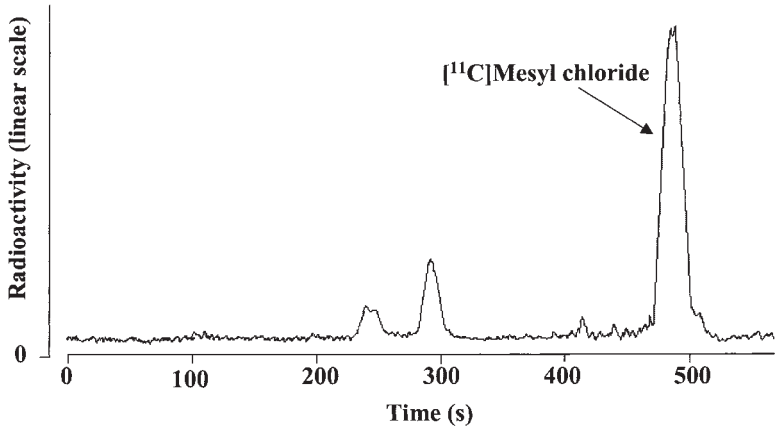

Figure 2. HPLC analysis (system A) of crude NCA [^{11}C]mesyl chloride produced by route 2

We directed further effort towards developing a complete 'on-line' method for producing [^{11}C]mesyl chloride from [^{11}C]iodomethane. The first attempt produced [^{11}C]methanethiol as before and passed that over solid calcium hypochlorite at RT. However, only unreacted [^{11}C]methanethiol was present in the effluent. Passage of [^{11}C]methanethiol over a combination of pyridinium dichromate and calcium hypochlorite at RT produced [^{11}C]mesyl chloride in 10% RCY from [^{11}C]iodomethane. Pyridinium dichromate was replaced with potassium permanganate with no resulting increase in RCY. A variety of other oxidizing agents were tried in the furnace at 255°C with the effluent passed over calcium hypochlorite at RT. These oxidants included potassium dichromate, chromium(III) oxide and manganese(IV) oxide. The last oxidant was the most successful; about 35% of the radioactivity passed into the furnace tubes as [^{11}C]iodomethane was recovered in acetonitrile and 87% of this radioactivity was found to be [^{11}C]mesyl chloride by HPLC (Figure 3). Hence, gas phase [^{11}C]iodomethane was successfully and rapidly converted into [^{11}C]mesyl chloride by a succession of solid reagents (Figure 4). We expect that a similar approach might be adopted for the radiosynthesis of potentially useful higher [^{11}C]alkanesulfonyl chlorides from the known corresponding [^{11}C]iodoalkanes,[25,26] though we have not yet explored this possibility.

In other experiments, [^{11}C]mesyl chloride from route 3 was trapped in a vial containing THIQ (4–8 mg) and TEA in THF. The reaction

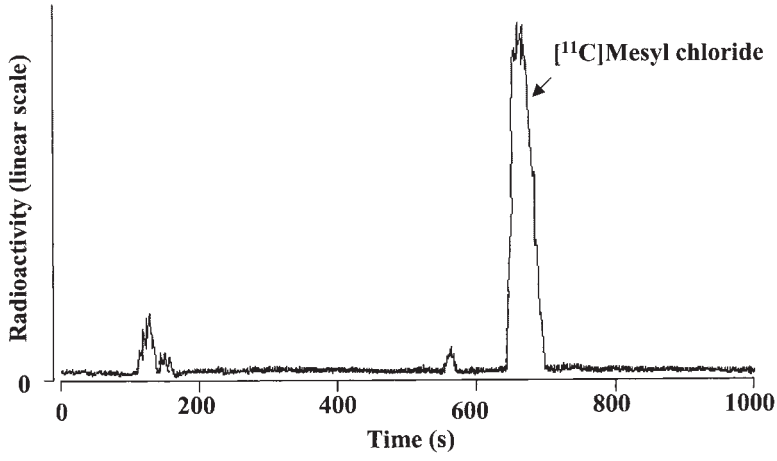

Figure 3. HPLC analysis (system B) of crude NCA [^{11}C]mesyl chloride produced by route 3

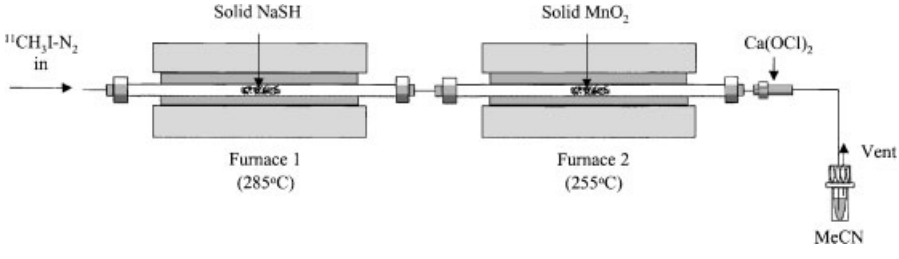

Figure 4. Diagram of apparatus for the 'on-line' conversion (route 3) of NCA [^{11}C]iodomethane into [^{11}C]mesyl chloride

mixture was stirred at RT for 5 min and then analyzed by HPLC. The major radioactive fraction (74%) eluted with the same retention time as authentic *N*-mesyl-THIQ. This demonstrates the potential of [^{11}C]mesyl chloride for the preparation of ^{11}C-labeled methanesulfonamides from small amounts of precursor. [^{11}C]Mesyl chloride is also potentially applicable to the introduction of [^{11}C]mesyl groups at other nucleophilic sites (e.g., hydroxyl, carboxyl and phenolic oxygens). We were able to demonstrate that [^{11}C]mesyl chloride reacts rapidly with phenol to give the corresponding [^{11}C]mesylate in 90% RCY.

The radiochemical yields of [^{11}C]mesyl chloride from repeated use of this 'on-line' production method were found to be quite variable,

indicating that the procedure will require some further optimization before possible inclusion in a system for PET radiopharmaceutical production. It is expected that this process will be particularly sensitive to trace oxygen (with risk of oxidation of the heated sodium hydrogen sulfide). Our limited experience with this new process indicates that results are optimal when great care is taken to purge the apparatus with dry nitrogen before use. Each charge of sodium hydrogen sulfide could be used for three productions.

Conclusion

Three methods produced NCA [^{11}C]mesyl chloride, which was shown to react with a secondary amine precursor and phenol so demonstrating its potential application in PET radiopharmaceutical development. Two of the methods (2 and 3), which use [^{11}C]methanethiol as an intermediate, are especially useful. Route 2 gives moderate and reliable radiochemical yields and would be easily automated for use in routine PET radiopharmaceutical productions. Route 3 is an 'on-line' method that produces [^{11}C]mesyl chloride in the gas phase within 2 min from the production of [^{11}C]iodomethane ($\sim$15 min from ERP), ready for collection in a solvent of choice for further reaction. This method is very promising and needs further optimization for consistent radiochemical yield and utility in PET radiopharmaceutical production.

Experimental

Materials

Anhydrous sodium hydrogen sulfide (m.p.: 350°C) was purchased from Alfa Chemicals. Hydrated sodium hydrogen sulfide ($NaSH \times H_2O$; m.p.: 52–54°C), mesyl chloride, anhydrous sulfuryl chloride (2.0 M in diethyl ether), 1,2,3,4-tetrahydroisoquinoline (THIQ), *n*-butyllithium (1.6 M in hexanes), *n*-butyllithium (1.6 M in hexanes), triethylamine (TEA), chlorine and other commonly used reagents and solvents were purchased from Aldrich Chemical Co. Ltd. μ-Bondapak® HPLC columns (300 × 7.8 mm i.d.) and silica Sep-pak® cartridges were purchased from Waters Associates Inc.

Analytical HPLC

Analytical HPLC was performed on a μ-Bondapak C18 column (300×7.8 mm i.d.) with eluate monitored with detectors for UV absorbance (Model SA 6506; Severn Analytical) and radioactivity (NaI, 20 mm diameter; Bioscan) linked to a computerized data acquisition program (Labview®). The column was eluted with acetonitrile – 0.05 M – potassium dihydrogen orthophosphate (40: 60 v/v) at 2.5 ml/min (system A) (R_t: mesyl chloride, 8.1 min; *N*-mesyl-THIQ, 11.7 min) or acetonitrile – 0.05 M – potassium dihydrogen orthophosphate (20: 80 v/v) at 3.0 ml/min (system B) (R_t: mesyl chloride, 10.4 min). Mesyl chloride was adequately stable to the HPLC conditions at RT ($\sim$20°C; rates of hydrolysis in water and aqueous-organic solvents at 25 and 34.5°C are $<2\%$/min[27]). Radioactive compounds were identified by (i) comparison of R_t with that of authentic non-radioactive standards and (ii) observation of coelution of reference compound by UV absorbance (at 210 nm for aliphatic compounds or 254 nm for aromatic compounds) and radioactivity after spiking the radioactive product with reference compound.

Mass spectrometry

Mass spectrometry (MS) was performed on an analytical quadrupole instrument (R10/10C; Nermag) with a probe interface (Nermag). The spectrometer was calibrated for mass number with residual air and perfluorotributylamine and run in chemical ionization mode (CI +ve), using ammonia or methane as reactant gas.

Gas chromatography–mass spectrometry

Gas chromatography–mass spectrometry (GC–MS) was performed on a Polaris Q instrument (ThermoFinnigan). GC was run on an Rtx capillary column (0.25 mm i.d. $\times$ 30 m; Restek) with a split-less injector at 220°C, transfer-line at 200°C, helium flow at 1 ml/min and temperature program of 60°C for 1 min increased to 180°C at 20°C/min. The MS was run in electron ionization (EI) mode with an ion source temperature of 250°C.

NMR spectroscopy

^{1}H-NMR and proton-decoupled ^{13}C-NMR spectra were recorded with a 400 MHz instrument (Avance 4000; Bruker). Chemical shifts (δ) are reported in ppm from tetramethylsilane as internal standard.

Synthesis of N-mesyl-THIQ[28,29]

A solution of THIQ (940 µl; 7.5 mmol) in anhydrous THF (6.0 ml) was added under nitrogen to a two-necked round-bottom flask. TEA (1.26 ml; 9 mmol) was added and the contents stirred for 5 min at RT. Mesyl chloride (1.036 g; 9 mmol) was then added portionwise. The reaction mixture was stirred overnight at RT, dissolved in dichloromethane (20 ml) and washed with saturated sodium hydrogen carbonate solution (2×20 ml) and brine (2×20 ml). The organic layer was separated, dried over magnesium sulfate, filtered and concentrated under reduced pressure to give a yellow solid (1.14 g; 78%). M.p.: 126–128°C. ^{1}H-NMR ($CDCl_3$; 298 K) δ (ppm): 2.74 (s, 3 H), 2.87 (t, 2 H, $J = 5.9$ Hz), 3.47 (t, 2 H, $J = 5.9$ Hz), 4.36 (s, 2 H), 6.99–7.12 (m, 4 H); cf. Ishibashi *et al.*[30] ^{13}C-NMR ($CDCl_3$; 298 K) δ (ppm): 28.66, 35.76, 43.41, 47.26, 126.34, 126.53, 126.98, 129.03, 131.67, 133.12. MS (CI +ve, NH_3) *m/z*: 212 {$[M+H]^+$, 6.3%}, 229 {$[M+NH_4]^+$, 100%}. HPLC (system A) gave a single peak. TLC (silica gel: CH_2Cl_2-MeOH; 4: 1 v/v), $R_f = 0.69$.

Synthesis of phenylmethanesulfonate

A solution of phenol (1.00 g; 10.6 mmol) and TEA (1.2 g; 12.7 mmol) in THF was cooled to 0°C and mesyl chloride (1.45 g; 12.7 mmol) was added dropwise. The reaction mixture was stirred at 0°C for 1 h and then warmed to RT and stirred overnight. The reaction mixture was then poured into water (100 ml) and ethyl acetate (100 ml) added. The organic layer was separated and washed with saturated sodium bicarbonate solution (100 ml) and water (100 ml). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give phenylmethanesulfonate as a white solid (1.64 g; 88%). M.p.: 59–60°C. (Lit. m.p.: 61.5°C;[31] 62–63°C[32]). ^{1}H-NMR ($CDCl_3$; 298 K) δ (ppm): 3.14 (s, 3 H) 7.25–7.6 (m, 5 H); cf. Percec *et al.*[32] ^{13}C-NMR ($CDCl_3$; 298 K) δ (ppm): 37.35, 122.01, 122.33, 127.09, 127.42, 127.65. 129.76, 130.05, 149.33. GC-MS (EI) *m/z*: 172 {$[M]^+$, 11%}, 94 {$[M\text{-}PhH]^+$, 100%}.

Production of [^{11}C]carbon dioxide

No-carrier-added [^{11}C]carbon dioxide was prepared by the $^{14}N(p,\alpha)^{11}C$ nuclear reaction by bombarding nitrogen gas containing 0.1% oxygen

at 1.5 MPa (15 bar) with a beam (30 μA) of 19 MeV protons from a Scanditronix MC40 (Mark II) cyclotron. The [^{11}C]carbon dioxide was transferred in nitrogen from the target to the lead-shielded hot-cell through stainless steel tubing ($\frac{1}{8}$ in o.d.) and passed through a column of magnesium perchlorate before being trapped in a spiral of stainless steel tubing ($\frac{1}{16}$ in o.d.) immersed in liquid argon.

Production of NCA [^{11}C]iodomethane

[^{11}C]Iodomethane was produced in a lead-shielded hot-cell using automated apparatus driven by a programmable logic controller (Toshiba Ltd).[33] Cryogenically trapped [^{11}C]carbon dioxide was warmed to RT and dispensed into a solution of lithium aluminum hydride in THF (0.2 ml; 0.2 M) in a stream of nitrogen (8 ml/min) for 2 min. The solvent was evaporated off at 120°C for 3 min and the reaction pot then cooled to RT by compressed air for 2.5 min. Hydroiodic acid (0.2 ml) was added and the reaction pot heated at 160°C for 2 min. NCA [^{11}C]iodomethane was obtained within 10 min from the end of radionuclide production (ERP) in >90% RCY from [^{11}C]carbon dioxide. Generally, this procedure gave [^{11}C]iodomethane with a specific radioactivity far exceeding 185 GBq/μmol (5 Ci/μmol).

Synthesis of [^{11}C]mesyl chloride from [^{11}C]methyllithium (route 1)

n-Butyllithium (1.6 M in hexanes; 0.1 ml) and anhydrous diethyl ether (0.4 ml) were added to a septum-sealed vial (volume 1 ml; Pierce) under nitrogen and cooled to −78°C (acetone-cardice bath). [^{11}C]Iodomethane (~370 MBq; ~10 mCi) was transferred into the vial in a stream of nitrogen and the sealed contents then stirred vigorously for 5 min. Anhydrous sulfuryl chloride (1.0 M solution in dichloromethane; 0.1 ml) was then added and stirring continued at −78°C for 2 min before the reaction mixture was allowed to warm to RT. The reaction mixture was stirred for a further 8 min. On opening the vial about 20% of the radioactivity was lost as an unknown volatile product. A sample of the reaction mixture (0.1 ml) was diluted with acetonitrile (0.5 ml) and analyzed by HPLC (system A). One major radioactive peak was identified as [^{11}C]mesyl chloride (78% RCY from [^{11}C]iodomethane).

Synthesis of NCA [methyl-^{11}C]N-mesyl-THIQ from [^{11}C]mesyl chloride prepared by route 1

[^{11}C]Mesyl chloride was produced by route 1 as described above and transferred to a Teflon®-sealed reaction vial (volume, 2 ml) containing THIQ (51 mg; 0.38 mmol) and TEA (40 µl; 0.29 mmol) in THF (0.4 ml). The reaction mixture was stirred at 70°C for 10 min. Analysis of the mixture by HPLC (system A) gave one major radioactive peak identified as [*methyl*-^{11}C]*N*-Mesyl-THIQ (61% RCY from trapped [^{11}C]mesyl chloride). Reactions were repeated using 26 and 13 mg of THIQ giving [*methyl*-^{11}C]*N*-mesyl-THIQ in 50 and 26% RCY, respectively.

Synthesis of [^{11}C]mesyl chloride from [^{11}C]iodomethane (route 2)

[^{11}C]Iodomethane (370 MBq; 10 mCi) in nitrogen was slowly (~50 ml/min) passed over heated (285°C) anhydrous sodium hydrogen sulfide (100 mg) in a silica tube (30 cm × 2 mm i.d.) that had been pre-flushed with nitrogen for at least 2 h. The [^{11}C]methanethiol emerging from the furnace was then trapped in cold (0°C) chlorine-saturated water (1 ml). Analysis of the reaction mixture by HPLC (system A) gave one major radioactive peak identified as [^{11}C]mesyl chloride (77% RCY from trapped [^{11}C]iodomethane). Mesyl chloride was stable in this solution for up to 45 min at RT.

Synthesis of NCA [methyl-^{11}C]N-mesyl-THIQ from [^{11}C]mesyl chloride prepared via route 2

[^{11}C]Mesyl chloride was obtained via route 2 in cold (0°C) chlorinated water (1.5 ml), as described above. A solution of THIQ (5 mg; 37 µmol) and TEA (30 µl, 0.22 mmol) in dichloromethane (2 ml) was added and stirred at RT for 3 min. A sample of the organic layer (~60% of the total radioactivity) was analyzed by HPLC (System A). The major radioactive fraction was identified as [*methyl*-^{11}C]*N*-mesyl-THIQ (57% RCY from trapped [^{11}C]mesyl chloride).

Synthesis of [^{11}C]mesyl chloride from [^{11}C]iodomethane (route 3)

The apparatus (Figure 4) was flushed with dry nitrogen for at least 2 h before the start of radiochemistry. [^{11}C]Iodomethane (~1.85 GBq; ~50 mCi) in nitrogen was passed sequentially at 60 ml/min through (i) a silica tube (30 cm × 2 mm i.d.) containing sodium hydrogen sulfide

(100 mg) heated in a furnace to 285°C, (ii) a silica tube (30 cm × 2 mm i.d.) containing manganese(IV) oxide (40 mg) in a furnace heated at 255°C and (iii) a calcium hypochlorite (20 mg) reactor at RT. The radioactivity emerging from the reactor was trapped in acetonitrile (1 ml) and analyzed by HPLC (system B). One major fraction was identified as [^{11}C]mesyl chloride (27% RCY from [^{11}C]iodomethane).

Synthesis of [^{11}C]N-mesyl-THIQ from [^{11}C]mesyl chloride prepared via route 3

Crude [^{11}C]mesyl chloride (~370 MBq; ~10 mCi), prepared via route 3, was dispensed into THF (1.0 ml) containing THIQ (4–8 mg; 30–60 μmol) and TEA (30 μl; 0.22 mmol) in a septum-sealed vial. The contents of the vial were stirred at RT for 5 min and then analyzed by HPLC (system A). One major fraction was identified as [^{11}C]*N*-mesyl-THIQ (74% RCY from crude [^{11}C]mesyl chloride).

Synthesis of [methyl-^{11}C]phenylmesylate from [^{11}C]mesyl chloride prepared via route 2

Crude [^{11}C]mesyl chloride (~370 MBq; ~10 mCi) in diethyl ether (2.0 ml) was added to a vial containing phenol (10 mg; 0.1 mmol) and TEA (40 μl; 0.29 mmol). The reaction mixture was heated to reflux for 8 min and then analyzed by HPLC (system A). One major fraction was identified as [*methyl*-^{11}C]phenyl mesylate (90% RCY from crude [^{11}C]mesyl chloride).

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