Tetrahedron Letters 51 (2010) 313–316

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A simplified [^{11}C]phosgene synthesis

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ARTICLE INFO

Article history:
Received 23 September 2009
Revised 27 October 2009
Accepted 3 November 2009
Available online 10 November 2009

Keywords:
Phosgene
Carbon-11
Radiolabelling

ABSTRACT

A new flow-through system for the production of [^{11}C]phosgene, a versatile labelling agent in radiochemistry for PET, is described. Cyclotron-produced [^{11}C]CH_4 is mixed with Cl_2 and converted into [^{11}C]CCl_4 by passing the mixture through an empty quartz tube at 510 °C. The outflow is directed through a Sb-filled guard that takes out Cl_2 and then, without intentional O_2 addition, through a second empty quartz tube at 750 °C, giving rise to [^{11}C]phosgene in 30–35% radiochemical yield.

Positron emission tomography (PET) is a medical imaging technique that traces quantitatively substances, radiolabelled with a short-lived positron-emitting radioisotope, administered to the patient.[1] Carbon-11 (20.4 min half-life) is one of the more important radioisotopes in PET and [^{11}C]phosgene has been for long a well-recognized tool in radiochemical carbon-11 incorporation. It is particularly useful in the generation of carbonyl-labelled cyclic and linear carbamates and ureas. Its high chemical reactivity, which often ensures almost instantaneous reaction, is an advantage in view of the 20.4 min half-life of carbon-11.

Since its first introduction in 1978 [^{11}C]phosgene has been used in a number of laboratories for the radiosynthesis of many tracers for biomedical investigations, for example, the β-adrenoceptor ligand [^{11}C]CGP-12177,[2–4] the acetylcholinesterase inhibitor [^{11}C]physostigmine,[5] the MAO-A inhibitor [^{11}C]befloxatone[6,7] (Fig. 1) and many others.[8–35] Recently some nonphosgene methods for [^{11}C]ureas and [^{11}C]carbamates from [^{11}C]CO_2 and [^{11}C]CO have been proposed[36,37] which may become more important in the future although they may not have the same scope that offers phosgene chemistry.

Our original procedures of [^{11}C]phosgene production based on [^{11}C]carbon monoxide[38,39] were replaced in 1987 by a method also developed in our laboratory by Landais and Crouzel.[40] In this procedure [^{11}C]methane and chlorine gas are passed by way of a vector gas through hot cupric chloride on pumice stone giving [^{11}C]tetrachloromethane which is then converted into [^{11}C]phosgene by passage through hot iron filings. Some dioxygen, added to the inert vector gas, serves as an oxygen source for the latter reaction (Scheme 1A). In 1997 we adopted a modification proposed by Link et al. which replaces the cupric chloride catalyst by an empty quartz tube at 560 °C (Scheme 1B).[41] In our experience and in that of others,[42] however, the iron catalyst can give rise to

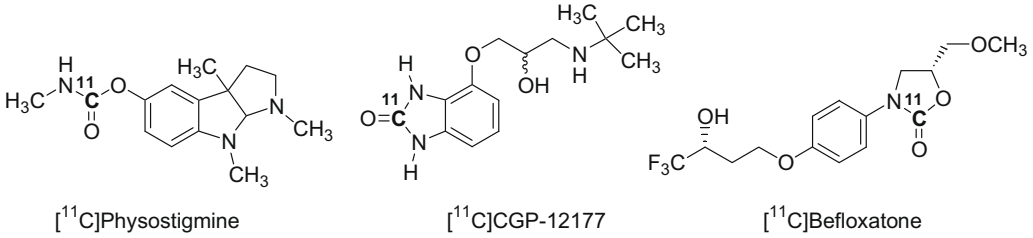

Figure 1. Three selected structures labelled with carbon-11 using [^{11}C]phosgene.

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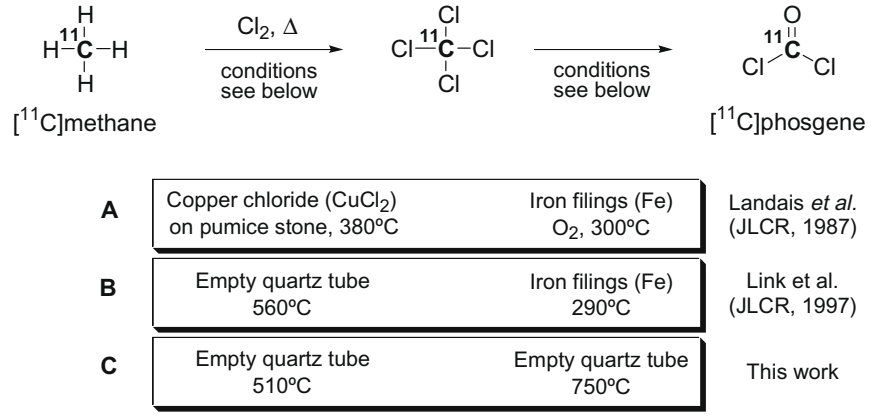
doi:10.1016/j.tetlet.2009.11.011



Scheme 1. Conversion of [^{11}C]methane into [^{11}C]phosgene with reaction conditions of the various methods.

reproducibility problems related to the state of the iron. In the present Letter we report on an innovation that disposes of the iron catalyst in the second step and replaces it by an empty quartz tube at 750 °C (Scheme 1C).

The new manually remote-controlled flow-through system for [^{11}C]phosgene synthesis, placed in a 5 cm-lead shielded hot cell, comprises three stages arranged in series (stages 1–3, Fig. 2). The vector gas for taking the radioactivity through the system is helium. [^{11}C]Methane is directly produced in a dedicated cyclotron target holder.[43]

The first stage aims at the isolation of cyclotron-produced no-carrier-added [^{11}C]methane from the irradiated matrix gases N_2 and H_2. It features an empty stainless steel coil (T_0), a glass tube filled with phosphorus pentoxide, a U-shaped copper tube (T_1), filled with Porapak-Q, a second phosphorus pentoxide guard and a second smaller U-shaped copper tube (T_2) with Porapak-Q. The units T_0, T_1 and T_2 are cooled in liquid-argon bath (−186 °C). The irradiated pressurized target gas is expanded through traps T_0/T_1 (maximum flow rate: ~500 mL/min). The [^{11}C]methane (<1 μmol) is retained on T_1. Apart from [^{11}C]methane the irradiation gives rise to considerable amounts of ammonia comprising radioactive [^{13}N]ammonia as well. Ammonia would interfere with the formation of [^{11}C]phosgene and therefore trap T_0 freezes it out with the phosphorus pentoxide guard as a backup.[44] Any traces of water are also intercepted by this system. [^{13}N]Dinitrogen that is also formed in the target in large quantities, is not retained and ends

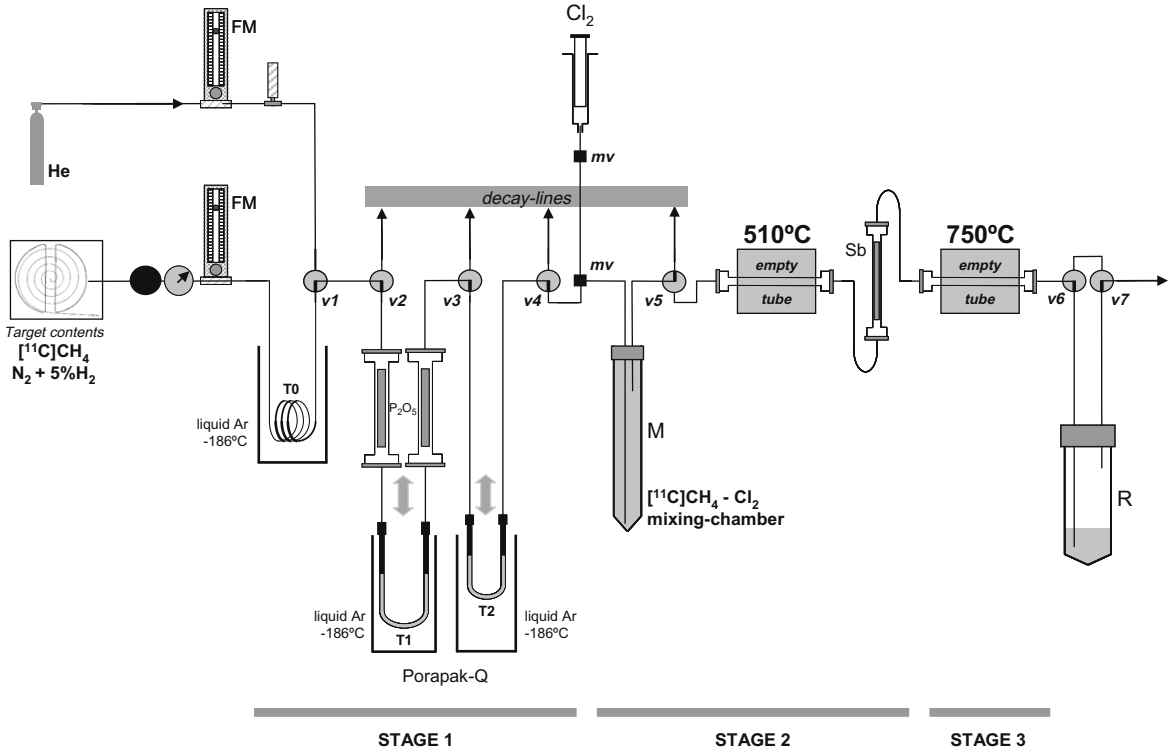


Figure 2. Schematic outline of the [^{11}C]phosgene synthesis apparatus. The components are interconnected by Teflon tubing (id: 1/16″) via three-way valves (v1–v7, Rheodyne 5301 and 5302; mv: manual valve). T_0: 50 cm empty coil, 4 mm id; P_2O_5-filled guards: 3 cm pathway, 10 mm id; T_1: 15 cm tube filled with Porapak-Q (80–100 mesh, Waters), 4 mm id; T_2: 15 cm Porapak-Q-filled tube, 2 mm id; M: Vessel with screw-cap and septum with in- and outlet needles (h: 4.5 cm, V: 1.6 cm^3); Heated quartz tubes: (16.5 cm heated length, 7 mm id, 13 mm od); 13 cm Sb-filled tube, 8 mm id: 4 g of a 60/40 (w/w) mixture of Sb powder (Riedel-de-Haën) and 1 mm glass beads (Aldrich); R: Reaction vessel. Radioactivity is monitored with appropriately positioned miniature ionisation chamber probes.

up as waste gas. Liquid-argon cooled Porapak-Q has a limited capacity of methane retention; the [^{11}C]methane progresses through the tube as in a gas chromatographic system. Therefore our system has a relatively large trap T_1 to initially collect [^{11}C]methane at high flow rate and a second smaller trap T_2 to concentrate it in a small volume, which is important for an efficient mixing with the chlorine in vessel M. Thus T_2 is switched in series with T_1 and the vector gas (40 mL/min) is directed through the two traps (outlet to waste at v4). T_1 is lifted out of its cooling bath and heated with a hot air jet which causes the [^{11}C]methane to migrate to T_2. The helium flow is now reduced to 15 mL/min and T_2 is lifted out of the cooling bath. The very moment that radioactivity begins to leave T_2, the parts of the flow system representing the second and third stage are switched in line.

The second stage oxidizes [^{11}C]methane with chlorine gas to [^{11}C]tetrachloromethane and follows the procedure described by Link and Krohn[41] with a slight modification. The [^{11}C]methane arrives in a chlorine-filled vessel where it mixes with the chlorine. Next a heated horizontal quartz tube assures the chlorination. In our hands the method worked best with the tube at 510 °C, a temperature we maintained in the present work. Like in Link's procedure, dioxygen is not added intentionally. Probably traces of air sneaking in during the filling of M with chlorine gas suffice as an oxygen source or otherwise the hot quartz surface has also oxygen atoms available. Before entering stage three the gases pass through a vertical tube containing a mixture of antimony powder and 1 mm glass beads (Aldrich), which eliminates excess of chlorine transforming it into antimony tri- or pentachloride. The material, like in all other tubes, is kept in place by quartz-wool plugs on either side.

The third stage converts [^{11}C]tetrachloromethane into [^{11}C]phosgene in an empty horizontal quartz tube, identical to the first, heated at 750 °C. The outlet of the system can be connected to a reaction vessel (R) in which the [^{11}C]phosgene is passed through a solution for further reaction and/or analyses.

All experiments were performed, after appropriate system preparation,[48] with a starting amount of [^{11}C]methane of about 1.85 GBq. The outflow of the first quartz tube was analyzed separately (second oven off) with gas chromatography.[49] The radiochemical yield of [^{11}C]tetrachloromethane is around 60%. With both ovens on, the final gaseous radioactive reaction mixture was analyzed as follows: The outflow of the system is passed successively through a solution of aniline (10 μL) in dichloromethane (300 μL) at room temperature,[30] a solution of 0.45 M cuprous chloride in 6.5 N hydrogen chloride (33 mL) at room temperature and a soda lime trap. The first solution converts [^{11}C]phosgene into a mixture of phenyl [^{11}C]isocyanate and *N,N′*-diphenyl[^{11}C]urea and traps all [^{11}C]chloromethanes. It is analyzed with HPLC.[50] The CuCl/HCl solution traps [^{11}C]carbon monoxide and the soda lime intercepts any [^{11}C]carbon dioxide.

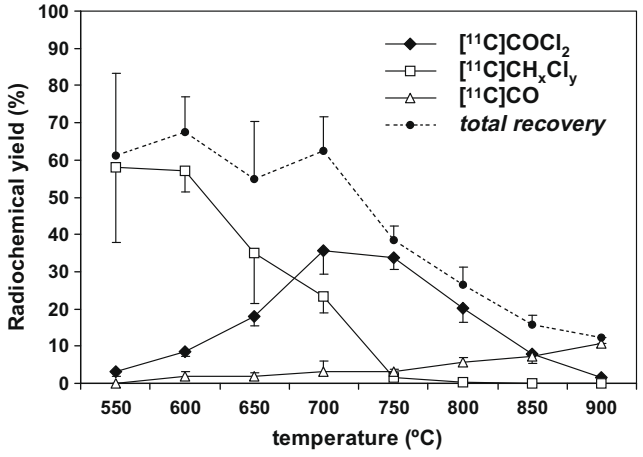


Figure 3. Formation of [^{11}C]phosgene, [^{11}C]chloromethanes and [^{11}C]carbon monoxide and total recovered radioactivity relative to starting [^{11}C]methane as a function of temperature (n = 3 for each point).

Figure 3 shows the results of the experiments aimed at optimization of the temperature of the second quartz tube. At the lowest temperature of this series, 550 °C, most of the recovered radioactivity is [^{11}C]tetrachloromethane (84%, confirmed by GC; [^{11}C]trichloromethane: 12%, [^{11}C]dichloromethane: 4%). The radiochemical yield of [^{11}C]phosgene relative to [^{11}C]methane has a maximum of 30–35% between 700 and 750 °C. With increasing temperature from 700 °C on, the amount of recovered radioactivity, all products included, declines rapidly to reach only 12% at 900 °C. This decline could possibly be due to carbonization on the hot quartz surface on which the elemental carbon-11 would be retained. Above 600 °C the amount of surviving [^{11}C]chloromethanes (mainly [^{11}C]tetrachloromethane) falls rapidly to reach practically zero at 750 °C. Around 750–800 °C [^{11}C]phosgene, although declining in absolute terms, accounts for 80% of the recovered activity. At 900 °C [^{11}C]carbon monoxide, which is mounting gradually all along the temperature stretch and possibly formed by [^{11}C]phosgene decomposition, is the only product present. Practically no [^{11}C]carbon dioxide is found in the soda lime trap. The antimony guard is placed in between the two tubes and not at the end because the presence of Cl_2 in the second tube results in practically no [^{11}C]phosgene and lots of [^{11}C]carbon monoxide.

This new method of [^{11}C]phosgene production has been used now for some time in our laboratory in the radiosynthesis of [^{11}C]befloxatone with yields and specific radioactivities (40–110 GBq/μmol, EOB decay corrected) comparable with the previous method[6,7] and with good reproducibility. The main advantage of the method is a gain in simplicity, as no catalyst at all is used, avoiding at the same time potential problems related to this catalyst. The whole process takes 12–13 min from the end of carbon-11 production.

Acknowledgements

The authors wish to thank the cyclotron operators Mr Daniel Gouel, Mr. Christophe Peronne and Mr. Christophe Lechêne for performing the irradiations. This work was supported in part by the EC—FP6-project DiMI (LSHB-CT-2005-512146) and EMIL (LSH-2004-503569).

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43. *Radioisotope production*: No-carrier-added [^{11}C]methane ([^{11}C]CH_4) was produced on an IBA Cyclone-18/9 cyclotron (18 MeV proton beam, IBA, Louvain-la-Neuve, Belgium) *via* the [^{14}N(p,α)^{11}C] nuclear reaction by irradiation of a target consisting of an ultrapure mixture of dinitrogen and dihydrogen (N_2/H_2, 95/5 (v:v), Air Liquide). The dedicated aluminium target holder (IBA, Louvain-la-Neuve, Belgium) contains the gas mixture at 20 bar (beam off) in a volume of 50 mL. Typical production for the present work: ~1.85 GBq of [^{11}C]CH_4 at the end of bombardment for a 5 μA, 5 min irradiation.
44. To avoid [^{13}N]ammonia one could make [^{11}C]methane from [^{11}C]carbon dioxide ([^{14}N(p,α)^{11}C, N_2/O_2 target) and dihydrogen catalyzed by nickel.[45–47] This dispenses from [^{11}C]methane dedicated cyclotron targetry and the trap T_0 as no ammonia is produced. Also, [^{11}C]carbon dioxide usually can be produced in larger quantities than [^{11}C]methane. On the other hand it introduces an additional radiochemical transformation requiring an additional oven and hydrogen gas manipulation. [^{11}C]Methane often has a somewhat higher specific radioactivity than [^{11}C]carbon dioxide.
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48. *System preparation before [^{11}C]phosgene synthesis*: Phosphorus pentoxide (1.5 g) and antimony (4 g of a 60/40 (w/w) mixture of antimony powder and 1 mm glass beads) fillings are renewed before each synthesis. The Porapak-Q in T_1 and T_2 can be reused an indefinite number of times. The system is thoroughly flushed with helium while the ovens are heating the quartz tubes. The helium flow is finally stopped and the helium in vessel M is replaced by chlorine gas (99.99%, Air Liquide) by way of a 3 mL syringe. Vessel M is isolated from the rest of the system by valves as is the system as a whole from the exterior.
49. Gas chromatography was performed using a Delsi-Nermag DN 200 MC apparatus; column: Hayesep-Q 80/100 mesh (2 m × 1/8″); helium (15 mL/min); catharometer and radioactivity detection. The retention times of the various radioactive products were as follows: [^{11}C]CO: 0.9 min, [^{11}C]CH_4: 1.5 min, [^{11}C]CO_2: 2.8 min, [^{11}C]CH_2Cl_2: 8.5 min, [^{11}C]$CHCl_3$: 10.8 min and [^{11}C]CCl_4: 14.0 min.
50. High performance liquid chromatography (HPLC) was performed using a Waters 510 pump, a Shimadzu SPD10-AVP UV-multi-wavelength spectrometer and a Geiger–Müller detector; column: semi-preparative Lichrosorb® SiO_2, Merck (250 × 10 mm; porosity: 7 μm); solvents and conditions: isocratic elution with CH_2Cl_2/EtOH/H_2O/$EtNH_2$: 990/9.6/0.2/0.2 (v:v:v:v); flow rate: 8.0 mL/min; temperature: rt; absorbance detection at $\lambda = 254$ nm. Capacity factors: phenyl isocyanate: 6.45, *N,N′*-diphenylurea: 1.73, chloromethanes: 1.00.