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[^{11}C]Carbon Disulfide: A Versatile Reagent for PET Radiolabelling

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Positron emission tomography (PET) is an important imaging modality for the clinical diagnosis and staging of a wide range of conditions such as cancer, neurodegenerative illnesses and cardiovascular diseases.[1] The preparation of radiotracers necessary for PET imaging is an exceptionally challenging area of chemistry principally because of the short half-lives of the commonly used positron emitting radioisotopes (^{11}C $t_{1/2}$ = 20.4 min, ^{18}F = 109 min, ^{13}N = 9.96 min, ^{15}O = 2.04 min).[2] Typically, only one or two discrete chemical transformations can ever be performed, which can limit the complexity of the desired tracer molecule. The key challenge in PET radiochemistry is to convert basic cyclotron-generated precursors into suitably complex molecules for imaging studies within a timeframe of minutes.

Carbon-11 is one of the most widely used PET radioisotopes because of its favourable physical and biological characteristics, however, its short 20 min half-life necessitates extremely rapid chemistry.[3] Currently, [^{11}C]methyl iodide is the most widely used reactive precursor for ^{11}C radiolabelling, with ^{11}C-methylation reactions accounting for the vast majority of labelled ^{11}C PET tracers. ^{11}C-methylation reactions are, in general, technically straight forward to perform, are typically fast reactions and can be used to access a wide variety of ^{11}C-labelled tracer molecules. However, there are inherent limitations to ^{11}C-methylation chemistry that restricts the range and diversity of tracer molecules that can ever be labelled using this method. ^{11}C-methylation reactions are always restricted to labelling the periphery of the target molecule, which can be a disadvantage in terms of metabolism of the molecule. Consequently, new labelling protocols and methods are required to expand the types of labelled molecules used for PET imaging. In recent years the use of ^{11}CO[4] and ^{11}CO$_2$[5] have become more important as alternative reagents for the synthesis of ^{11}C tracers, especially for radiolabelling within the core of a molecule. However, despite these newer chemical labelling techniques and the application of technologies such as microfluidics[6] and microwave reactors,[7] there is still an enormous desire to develop new and innovative chemical methods to radiolabel tracer molecules.

Carbon disulfide, the sulfur analogue of carbon dioxide, is a commonly used reagent and solvent in the chemical industry for the production of materials such as rayon and cellophane and for the synthesis of a wide range of organosulfur compounds including dithiocarbamates, xanthates and thioureas.[8] There are obvious parallels between CS_2 and its isoelectronic partner CO_2, however, CS_2 has distinctly different physical and chemical properties. Notably, CS_2 is a volatile and flammable liquid at room temperature (b.p. = 46 °C) and is considered to be more reactive owing to the weaker C=S double bond. Considering the now widespread use of small and reactive ^{11}C molecules, such as CO, CO_2, HCN, $COCl_2$, CH_3OTf and CH_3I, in the PET field it is surprising that there has only been one previous report of $^{11}CS_2$, obtained in low radiochemical yields,[9] even though it has enormous potential to form a wide range of organic molecules that may hold promise for potential applications in PET imaging. Herein, we report a new method for the rapid and high yielding synthesis of $^{11}CS_2$ and demonstrate its reactivity for the first time as an effective route to ^{11}C-labelled organosulfur compounds.

$^{11}CS_2$ was efficiently produced by the gas phase reaction of the widely used ^{11}C precursor $^{11}CH_3I$ and the thionating agent P_2S_5. In a typical reaction, a gas stream of $^{11}CH_3I$, produced using a commercial GE TRACERlab fx module, was passed through a small glass column packed with a mixture of P_2S_5 and sand, in a 1:2 ratio, and heated to 380 °C. The gases were vented into a collection vial containing acetonitrile at room temperature, which conveniently trapped $^{11}CS_2$ in solution. A small activated charcoal trap was placed at the vent of this vial to trap any radioactivity that passed though the solution. The conversion of $^{11}CH_3I$ was instantaneous, and high radiochemical yields (>85 %) and high specific radioactivities (100 GBq μmol^{-1}) of $^{11}CS_2$ were obtained as determined by radio-HPLC analysis (Figure 1 and Table 1). The only major contaminant was a small amount of unreacted $^{11}CH_3I$. The conversion of $^{11}CH_3I$ to $^{11}CS_2$ was found to be dependent on both the oven temperature and gas flow rate through the column. Reactions at lower temperatures of 150 °C failed to give any conversion of $^{11}CH_3I$, whereas raising the oven temperature to 380 °C was found to give highly efficient conversions. The gas flow rate of

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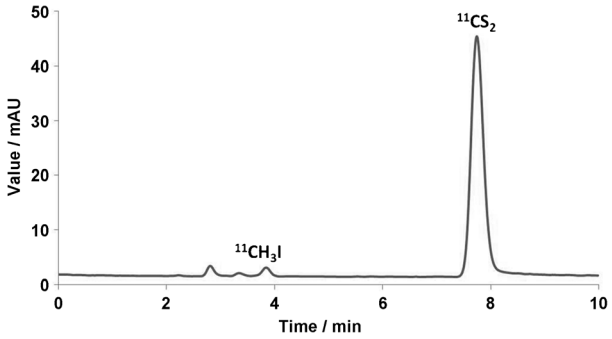


Figure 1. Radio-HPLC trace of a typical $^{11}CS_2$ production reaction.

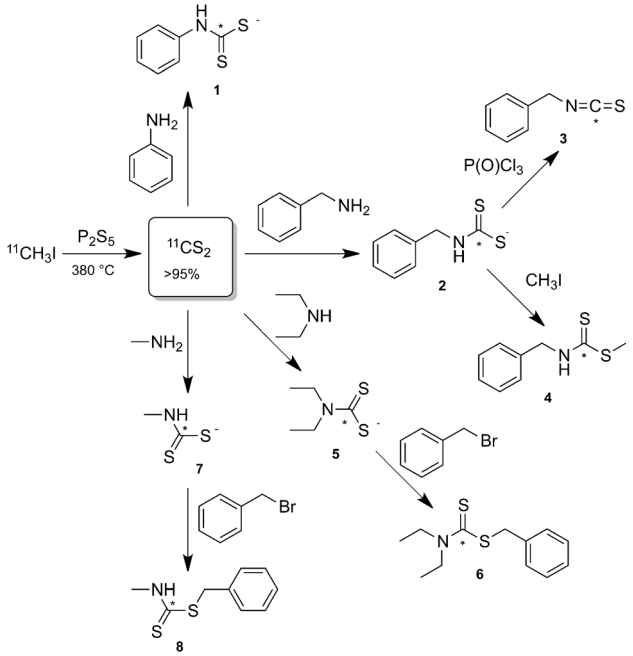
Table 1. Results of $^{11}CS_2$ production runs by reaction of thionating agents $^{11}CH_3I$.

Entry	Thionating agent	T [°C]	RTE[a]	RCP[b]	RCY[c]
1	P_2S_5	150	85 ($n=2$)	–	–
2	P_2S_5	380	91 ($n=6$)	93 ± 2	87 ± 3
3	Lawesson's reagent	380	5 ($n=1$)	–	–

[a] RTE (radioactive trapping efficiency) is based on activity trapped in the collection vial expressed as a fraction of total of radioactivity measured in the system from the end of $^{11}CH_3I$ production. [b] RCP (radiochemical purity) is based on the integration of radioactive peaks from the radio-HPLC trace. [c] RCY (radiochemical yield) is decay corrected based on total radioactivity in the system corrected for RCP. n = number of runs.

methyl iodide through the P_2S_5 column also had a significant impact on conversions, higher gas flow rates of 15–20 mL min^{-1} resulted in decreased conversions, whereas an optimum gas flow rate of 5–6 mL min^{-1} resulted in good conversions with an acceptable processing time of <10 min from the end of $^{11}CH_3I$ production. We also investigated the effect of other thionating agents to further improve $^{11}CS_2$ production. A mixture of the commonly used thionating agent, the Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide), and sand (1:2 ratio) was packed into a glass column and the reaction of $^{11}CH_3I$ performed under the previously determined optimised conditions. Disappointingly however, no $^{11}CS_2$ was formed under these conditions. The vast majority of radioactivity was found to be retained on the column which appeared blackened as a result of the decomposition of the Lawesson's reagent. Only a small fraction of radioactivity ($<5\%$) was trapped in the acetonitrile solution. Subsequent radio-HPLC analysis revealed a complex mixture of radioactive peaks.

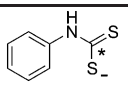
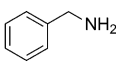
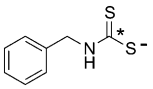
Carbon disulfide is a small electrophilic molecule that has found numerous uses in organic synthesis as a one-carbon building block primarily for the preparation of organosulfur compounds. Our initial experiments have focused on the reaction of nucleophilic amines with $^{11}CS_2$. This is a well-known and widely used reaction for the high yielding formation of dithiocarbamate compounds.[10] A range of primary and secondary amines were selected for reaction with $^{11}CS_2$, and included aniline, benzylamine, diethylamine and methylamine. In a typical experiment a small aliquot (200 μL) of the $^{11}CS_2$ solution in acetonitrile was added to an amine solution and the reaction mixture was allowed to stand at room temperature for 5 min prior to radio-HPLC analysis. All the amines tested were found to react cleanly and efficiently with $^{11}CS_2$ to give the corresponding dithiocarbamate salts **1**, **2**, **5** and **7** (Scheme 1) in almost quantitative yield



Scheme 1. Production and reaction of $^{11}CS_2$.

(Table 2). The radio-HPLC trace of [^{11}C]benzylamine dithiocarbamate (**2**) showed quantitative conversion and complete reaction of $^{11}CS_2$ with benzylamine (see the Supporting Information). The only observed radioactive by-product from these reactions was the corresponding ^{11}C methylated quaternary ammonium salt, which is a result of the slight contamination of the $^{11}CS_2$ solution with $^{11}CH_3I$. In most cases,

Table 2. Reaction of $^{11}CS_2$ with amines to form dithiocarbamate salts.

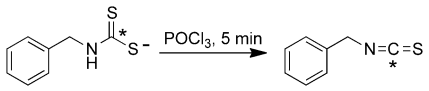
Entry	Amine	[^{11}C]dithiocarbamate	RCY[a]
1			99 ($n=2$)
2			99 ($n=4$)
3			69 ($n=2$)[b]
4	H_3C-NH_2		98 ($n=2$)

[a] RCY is based on the conversion of $^{11}CS_2$ to [^{11}C]dithiocarbamate and measured using integration of radioactive peaks from the radio-HPLC trace. (*) indicates ^{11}C labelling position. n = number of runs.[b] Average yield is lower due to contamination with $^{11}CH_3I$.

however, this accounted for <5% of radioactivity on the radio-HPLC trace. Interestingly, when an approximate 50:50 mixture of $^{11}CH_3I$ and $^{11}CS_2$ in acetonitrile was added to a benzylamine solution (5 μL in 300 μL) and allowed to stand at room temperature for 5 min the complete reaction of $^{11}CS_2$ was observed within this time while $^{11}CH_3I$ remained unreacted, which indicated that $^{11}CS_2$ is a more potent electrophile than $^{11}CH_3I$. A significant decrease in the $^{11}CH_3I$ peak on the radio-HPLC trace was only observed after a 10 min reaction time and only after all the $^{11}CS_2$ had reacted.

Dithiocarbamates have found many uses as chelating ligands for the formation of a very wide range of metal complexes within the field of inorganic chemistry.[11] They are also commonly used precursors for a range of organosulfur-containing compounds and have found large-scale agricultural uses as herbicides and pesticides.[12] Dithiocarbamates, such as diethyldithiocarbamate (**5**), are also finding applications as anticancer agents by acting as zinc and copper chelators.[13] ^{11}C-labelled dithiocarbamates, efficiently prepared by the one-step reaction of $^{11}CS_2$ with amines, are versatile precursors for further reaction. A series of dithiocarbamate alkylation reactions were investigated using either methyl iodide or benzylamine (Scheme 1). In a typical reaction, a small amount of alkylhalide solution (5 μL in 150 μL acetonitrile) was added to the ^{11}C dithiocarbamate and allowed to stand at room temperature for 5 min followed by radio-HPLC analysis. Both the methylation of benzyldithiocarbamate (**2**) and the benzylation reaction of diethyldithiocarbamate (**5**) and methyldithiocarbamate (**7**) were found to be highly efficient and selective resulting in high radiochemical yields of products (see the Supporting Information). Thus ^{11}C dithiocarbamate salts can be efficiently converted into their neutral alkylated forms by the simple and rapid reaction with alkylhalides.

Dithiocarbamates are also precursors to highly reactive isothiocyanates, which can subsequently be converted to important classes of sulfur-containing organic compounds such as thioureas, thiosemicarbazones and sulfur containing heterocyclic rings. It was, therefore, of high interest for us to explore the reactivity of ^{11}C dithiocarbamates for the formation of ^{11}C isothiocyanates owing to their importance as highly reactive intermediates.[14] Dithiocarbamates may be converted to isothiocyanates through a desulfurylating reaction by a variety of techniques.[15] Unfortunately, however, when desulfurylating reactions of [^{11}C]benzyldithiocarbamate were performed using molecular iodine or lead nitrate, decomposition of the dithiocarbamate occurred that resulted in poor radiochemical yields of the labelled isothiocyanate. The use of $POCl_3$ as a desulfurylating agent, however, proved to be more successful in generating [^{11}C]benzylisothiocyanate (**3**) (Scheme 2). When a large excess of $POCl_3$ (100 μL) was added to a solution of [^{11}C]benzyldithiocarbamate, [^{11}C]benzylisothiocyanate was efficiently generated (RCY = 78%). Radio-HPLC of this reaction confirmed the complete conversion of the dithiocarbamate to the [^{11}C]benzyldithiocarbamate after only 5 min (see the Supporting Information).



Scheme 2. Conversion of [^{11}C]benzyldithiocarbamate (**2**) to [^{11}C]benzylisothiocyanate (**3**).

We believe that $^{11}CS_2$ will be an extremely useful addition to the inventory of small and reactive ^{11}C molecules that are currently being used for PET radiotracer synthesis. Both the ease and efficiency with which $^{11}CS_2$ can be formed should prove particularly appealing to the field of PET chemistry and radiotracer development. In addition to investigating further methods to improve $^{11}CS_2$ synthesis, we are currently in the process of exploring the scope of $^{11}CS_2$ labelling reactions for a much wider range of [^{11}C]organosulfur compounds. Of particular interest is the development of methods to produce [^{11}C]isothiocyanates and the subsequent reaction of these compounds to form more complex heterocyclic ring compounds, which could form the basis of new radiotracers for PET imaging applications.

Experimental Section

Detailed experimental procedures for the production and reaction of $^{11}CS_2$ are reported in the Supporting Information.

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Keywords: carbon disulfide · carbon-11 · imaging agents · positron emission tomography · radiochemistry

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