

## Novel Solid-state Support for Rapid Synthesis of Radiopharmaceuticals Labelled with [ $^{11}\text{C}$ ]-Cyanide

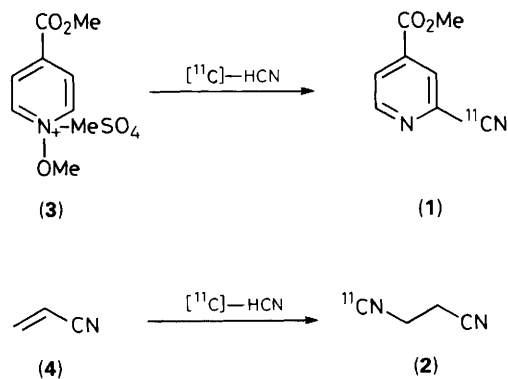
Chandrasiri W. Somawardhana, Munawwar Sajjad, and Richard M. Lambrecht\*

Radionuclide & Cyclotron Operations Department, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Kingdom of Saudi Arabia

A silica gel solid-state support was used to trap [ $^{11}\text{C}$ ]-HCN for the synthesis of  $^{11}\text{C}$ -labelled compounds including base sensitive compounds; examples of the Reissert-Kaufmann type reaction and Michael addition are given.

There is great potential for  $^{11}\text{C}$ -labelled compounds ( $t_{1/2}$  20.4 min)<sup>1</sup> in diagnostic nuclear medicine and biomedical research.<sup>2,3</sup> L-Methyl-[ $^{11}\text{C}$ ]-methionine,<sup>4</sup> 1-[ $^{11}\text{C}$ ]-palmitic acid,<sup>5</sup> [ $^{11}\text{C}$ -methyl]-thymidine,<sup>6</sup> etc., have been synthesized and used to resolve various biomedical and health related problems. The gases [ $^{11}\text{C}$ ]-CO, [ $^{11}\text{C}$ ]-CO<sub>2</sub>,<sup>7</sup> and [ $^{11}\text{C}$ ]-HCN play a major role in the synthesis of  $^{11}\text{C}$ -labelled organic compounds because of their availability as the primary precursor of carbon-11. When [ $^{11}\text{C}$ ]-HCN is used as the precursor for the synthesis of  $^{11}\text{C}$ -labelled organic compounds, the tracer gas is usually trapped in a small volume of NaOH or KOH solution (0.5 M).<sup>8</sup> This basic [ $^{11}\text{C}$ ]-HCN solution can be used for labelling base resistant organic compounds; however, it is not useful in labelling base sensitive compounds such as esters, amides, etc. In this communication, we report a novel method of trapping  $^{11}\text{C}$ -HCN and its incorporation into organic compounds through two different types of reaction. Scheme 1 shows the two reactions studied. This method is used to synthesize methyl 2-[ $^{11}\text{C}$ ]-cyanoisonicotinate (**1**) by a Reissert-Kaufmann<sup>9-11</sup> type reaction and 1-[ $^{11}\text{C}$ ]-succinonitrile (**2**) by Michael addition. These two reactions need cyanide ions in neutral and basic media, respectively.

[ $^{11}\text{C}$ ]-HCN was prepared by the previously reported method<sup>12</sup> via the  $^{14}\text{N}(\text{p},\alpha)^{11}\text{C}$  reaction. A N<sub>2</sub>:H<sub>2</sub> gas mixture (95:5) was used as the target gas at 4.5 bar. After irradiation the gas was passed over a platinum catalyst maintained at 1000 °C at a flow rate of 200 ml min<sup>-1</sup>. The [ $^{11}\text{C}$ ]-HCN gas was trapped on a small column made of a Pasteur pipette (9 × 0.25 in.) containing silica gel (200 mg; 70–230 mesh, 60 Å, Aldrich) coated with the substrate or the base. The trapping efficiency was measured by bubbling the effluent from the silica gel column, through a NaOH solution (0.5 M) and measuring the activity trapped in the silica gel column and in the solution. The [ $^{11}\text{C}$ ]-HCN trapping efficiency was increased from 51% to almost 100% by drying the coated silica gel overnight under high vacuum. The dependency of the radioactivity trapping efficiency on the weight of silica gel in the column and the duration of target gas flow is shown in Figures 1 and 2.



Compound (**1**) is the precursor of 2-[ $^{11}\text{C}$ ]-cyanoisonicotinic acid hydrazide, which is a possible radiotracer for tuberculosis. 1-Methoxy-4-methoxycarbonyl pyridinium methylsulphate (**3**) (~17 μmol) in water (9 μl) was added to a round bottom flask and diluted with ethanol (2 ml). Silica gel (200 mg) was transferred into this flask and the solvents were slowly evaporated to obtain evenly coated silica gel particles, which were dried overnight under high vacuum to remove

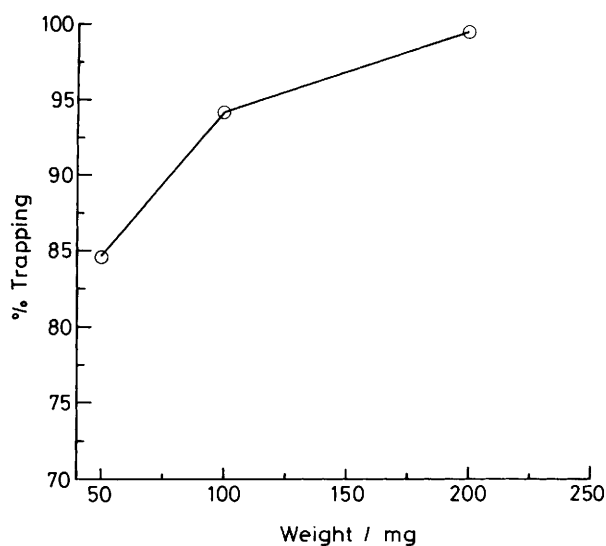


Figure 1. Effect of weight of silica gel on [ $^{11}\text{C}$ ]-HCN trapping efficiency.

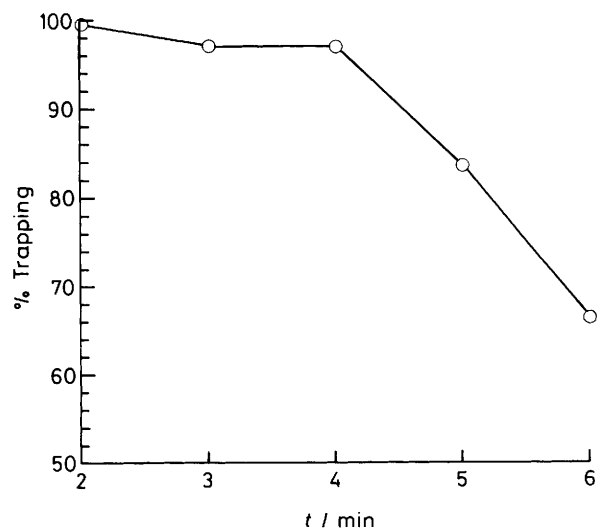


Figure 2. Effect of target gas flow time through the silica gel column on [ $^{11}\text{C}$ ]-HCN trapping efficiency.

moisture. A small column was made out of this coated silica gel support in a Pasteur pipette using a cotton wool plug.  $[^{11}\text{C}]\text{-HCN}$  was passed through this column and the narrow tip was sealed. Water (10  $\mu\text{l}$ ) was added and the top end of the column was sealed also. The tube was placed in a water bath at 40 °C for 5 min, after mixing the contents well, then cut open and eluted with water (1.5 ml). The water eluate was analysed by HPLC (C-18 reverse phase column, 4.6  $\times$  250 mm) with acetonitrile:water (40:60) as the mobile phase (flow rate 1 ml min<sup>-1</sup>). Methyl 2- $[^{11}\text{C}]\text{-cyano-isonicotinate}$  was eluted from the column with a retention time of 6.3 min and all by-products were eluted within 4 min. The average radiochemical yield of eleven experiments was 32.4  $\pm$  12.2%.

We have used our new technique to synthesize compound (2), a precursor of 1- $[^{11}\text{C}]\text{-putrescine}$ , which is a useful PET radiotracer for diagnosis of brain tumours.<sup>13</sup> This new method has the advantages of increased radiochemical yield and a shorter reaction time. Silica gel (200 mg) was placed in a round bottom flask and methanolic KOH solution (1%; 200  $\mu\text{l}$ ) and methanol (2 ml) were added. The solvents were evaporated under vacuum to obtain silica gel particles thinly coated with KOH, which were dried overnight under high vacuum. A column was prepared with this KOH coated silica gel as described earlier and  $[^{11}\text{C}]\text{-HCN}$  was trapped on the support. After the addition of acrylonitrile (0.193  $\mu\text{mol}$ ) both ends of the column were sealed. The sealed column was placed in a boiling water bath for 2 min, then cut open and eluted with ethanol (2 ml). The eluate was chromatographed on silica gel TLC plates with ether:ethyl acetate (9:1) as the eluent. The  $R_f$  value of succinonitrile was 0.6. The average radiochemical yield of six experiments was 84.7  $\pm$  7.3%.

McPherson *et al.*<sup>13,14</sup> have synthesized 1- $[^{11}\text{C}]\text{-succinonitrile}$  (2) using acrylonitrile (4) (500  $\mu\text{l}$ ) in a solvent mixture of tetrahydrofuran (500  $\mu\text{l}$ ) and aqueous potassium hydroxide solution (1%; 200  $\mu\text{l}$ ). The presence of water in the reaction mixture causes the formation of 3-cyanopropan-1-ol as a by-product. At the end of the reaction, water has to be completely removed to perform the next reaction which involves the reduction of cyano to amino groups. Water is completely excluded from our system and compound (2) is supplied in ethanol, which is easily removed. This absence of water prevents the formation of the by-product 3-cyano-

propan-1-ol. The reaction time is reduced from 5 to 2 min and the radiochemical yield is increased<sup>13</sup> from 73.9 to 84.7  $\pm$  7.3%. This method will effectively reduce the total synthesis time of 1- $[^{11}\text{C}]\text{-putrescine}$ , because of the shorter reaction and solvent evaporation time. Time is of the essence due to the short half-life of carbon-11.

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