POLYMER-SUPPORTED NUCLEOPHILIC RADIOLABELING REACTIONS WITH [$^{18}$F]FLUORIDE AND [$^{11}$C]CYANIDE ION ON QUATERNARY AMMONIUM RESINS.

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Polymeric reagents are particularly valuable aids in radiopharmaceutical synthesis where fast, simple and easily automated chemical operations are necessary. Nucleophilic radiofluorination is an operation which could be simplified through use of polymeric reagents. Existing procedures require several steps to convert aqueous [$^{18}$F]fluoride form the target to an organic soluble "activated" form suitable for nucleophilic displacement reactions. The steps include addition of base and solubilizing agent and azeotropic removal of water. The procedure is time consuming and can result in significant contamination or loss of expensive $^{18}$O target water. Furthermore, after the labeling reaction is complete an additional step is usually necessary for removal of base and solubilizing agent prior to HPLC purification of the reaction mixture.

In an effort to simplify these operations we explored the use of polymeric quaternary ammonium hydroxide resin for both trapping and nucleophilic activation of [$^{18}$F]fluoride from target water. Ion exchange resins of this class previously have been used to separate [$^{18}$F]fluoride ion from [$^{18}$O]target water (1) but efforts to conduct $^{18}$F labeling reactions on the surfaces of resins at the no-carrier-added level previously have been unsuccessful (2). We attempted to do this using commercial Dowex 1 and Amberlite resins with unsatisfactory results. However, 4-aminopyridinium resin which we prepared based upon a report of heat-stable phase transfer catalysts (3), gave very encouraging results. The resins were easily synthesized (Fig. 1) by heating 4-(N,N-dialkyl)aminopyridines with chloromethylated polystyrene (Merrifield's resin) in acetonitrile. Conversion to hydroxide form was achieved by rinsing with 2N NaOH. The $OH^-$ forms of the resins appear to be stable and active for at least several months. Most of the work described here has employed resin 1 although resin 2 appears to be equivalent in the cases examined so far.

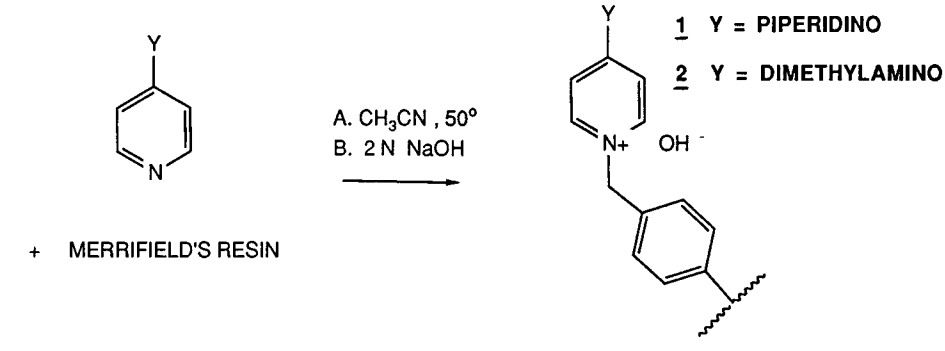


**Figure 1. Resin Synthesis**

[$^{18}$F]Fluoride ion was prepared by proton irradiation of $H_2{}^{18}O$ in an all-silver target (4). A single pass of target water (1 mL) through a 5-10 mg bed of this resin is sufficient to capture 75-90% of the total $^{18}$F activity present. Target $^{18}$O water is recovered for reuse. Drying and activation of the retained [$^{18}$F]fluoride are achieved without application of heat simply by passing 2-3 mL of dry acetonitrile or DMSO through the resin bed. [$^{18}$F]Fluoride ion remains fixed to the resin during this process and cannot be significantly removed even by extended flushing with organic solvent alone. Radiofluorination reactions are conducted by passing an acetonitrile or DMSO solution of substrate back and forth through the heated $^{18}$F resin bed with alternating syringe pumps at each end of the bed. As the reaction proceeds, radioactivity leaves the resin and appears in solution, and thus the progress of a radiolabeling reaction is very easily determined by monitoring the radioactivity in one of the syringes at the end of a stroke. Contact with the heated resin is intermittent and brief; we have observed that several difficult base-sensitive substrates are $^{18}$F labeled in respectable yield by this method. Some example n.c.a. radiofluorinations are shown in Table 1. Yields are based on total $^{18}$F applied to the resin column.

In the course of this work we have found the same resin 1 also promotes n.c.a. radiocyanations. The method and apparatus are identical to that used for radiofluorination. Aqueous [$^{11}$C]$CN^-$(pH~5) is quantitatively trapped on ~ 10 mg of resin. Resin bound [$^{11}$C]$CN^-$ appears to be significantly more nucleophilic than resin bound [$^{18}$F]fluoride and [$^{11}$C] cyanations proceed rapidly at lower temperature. Furthermore, we have found that using resin-[$^{11}$C]CN certain aromatic [$^{11}$C]cyanodenitrations can be carried out rapidly. To our knowledge it is the first application of this reaction to $^{11}$C radiolabeling. Some example n.c.a. radiocyanations are shown in Table 2.

Table 1. Radiofluorinations

| Substrate | Conditions (solvent/resin temp/min) | [$^{18}$F] Product | Decay Corrected Yield % |
|---|---|---|---|
| 2-triflylmannose-$Ac_4$ | $CH_3CN$/130°/4 | FDG-$Ac_4$ | 40-65 |
| 2-bromomethylnaphthalene | $CH_3CN$/130°/4 | 2-fluoromethylnaphthalene | 50 |
| 1,3 diiodopropane | $CH_3CN$/130°/10 | fluoroiodopropane | 30 |
| 3-Br-diazepam | $CH_3CN$/130°/6 | 3-F-diazepam | 30 |
| 4-$NO_2$-$C_6H_4$-CN | DMSO/170°/15 | 4-F-$C_6H_4$-CN | 35 |
| 4-$NO_2$-$C_6H_4COCH_3$ | DMSO/170°/15 | 4-F-$C_6H_4COCH_3$ | 20-30 |
| 4-$NO_2$-$C_6H_4COcycC_3H_5$ | DMSO/170/15 | 4-F-$C_6H_4COcycC_3H_5$ | 25 |

Table 2. [$^{11}$C]Cyanations

| Substrate | Conditions solvent/temp/min | [$^{11}$C]Product | Decay Corrected Yield % |
|---|---|---|---|
| $C_6H_5CH_2Br$ | $CH_3CN/40^o/4$ | $C_6H_5CH_2CN$ | 75 |
| 1-Bromomethylnaphthalene | $CH_3CN/40^o/6$ | $C_{10}H_9CH_2CN$ | 70 |
| 1,2 dinitrobenzene | $DMSO/100^o/9$ | $C_6H_4NO_2CN$ | 40 |

In summary, we have developed a new approach for the preparation of reactive [$^{18}$F]fluoride ion and [$^{11}$C]$CN^-$ for radiopharmaceutical syntheses. The advantages of this approach include speed, simplicity and versatility. Labeling of sensitive substrates is feasible because of reduced contact time with base and heat. There is no need for separation of base or solubilizing agent from final radiolabeled products. Finally, in the case of $^{18}$F reactions, expensive $^{18}$O target water is easily recovered.

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