Studies on the No-carrier-added Synthesis and Chemistry of ^{11}C Labelled Methyl Hypofluorite

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A novel method for the introduction of the short-lived positron emitting radionuclide, ^{11}C, into an organic molecule is described.

We report the first observation of ^{11}C-labelled methyl hypofluorite and application of its chemistry as a novel method for the introduction of a ^{11}C label to an organic substrate. We also describe the potential of this reagent for the synthesis of new radiopharmaceuticals for use in positron emission tomography (PET).

PET is an important method for the *in vivo* study of biochemical processes and consequently has become a valuable diagnostic tool in medicine.[1] This method requires the labelling[2] of a drug or ligand with a short-lived positron-emitting radionuclide such as ^{18}F or ^{11}C. The half-life of ^{11}C is 20 min; this imposes major constraints on the synthesis time, and so methods for the incorporation of this isotope tend to be limited to those based on a few readily prepared synthetic intermediates.[3] Therfore we are constantly searching for new chemistry that will satisfy these special criteria and will increase the scope for labelling radiopharmaceuticals with ^{11}C.

Recent reports have described the generation of methyl hypofluorite (MeOF) from the treatment of methanol with fluorine gas.[4] This has proved to be the only source of the novel electrophilic methoxylium moiety 'MeO^+'.[5] Methyl hypofluorite can be generated quickly as a 0.1–0.15 mol l^{-1} solution in acetonitrile and has been found to react with various types of C–C double bonds at low temperatures. Of interest to us is the reaction of methyl hypofluorite with various types of methyl enol ethers, which rapidly produces the corresponding α-methoxy ketones (Scheme 1) in good to excellent yields.[6]

We envisaged that by being able to synthesize tracer levels of ^{11}C labelled methyl hypofluorite, we would be able to trap this species with methyl enol ethers and thereby have access to a new class of radiolabelled compounds. In order to achieve this goal we would need to be able to produce anhydrous ^{11}C labelled methanol of extremely high purity, so that no side reactions would occur when it was exposed to fluorine.

Carbon-11 is a cyclotron-generated isotope produced by the $^{14}N(p,\alpha)^{11}C$ nuclear reaction. It is conveniently removed from the target, at the end of bombardment, as $^{11}CO_2$. Previous research[7] has shown that reduction to the corresponding alkoxide can be accomplished with lithium aluminium hydride (LAH). We reduced the $^{11}CO_2$ with LAH, but chose to use a non-volatile solvent, bis-(2-ethoxyethyl) ether. By addition of anhydrous citric acid in the same solvent we were able to destroy the alkoxide and could collect the resultant no-carrier-added anhydrous $^{11}CH_3OH$ by distillation into cooled (−20 °C) acetonitrile. These unusual conditions allowed us to obtain the methanol in the desired purity, in approximately 10 min and in greater than 50% yield (non decay corrected, NDC). Manipulation of the $^{11}CO_2$ in this way is conveniently achieved by use of a remotely controlled system, which allows for shielding of the operator from the radioactivity.

Generation of $^{11}CH_3OF$ was simply accomplished by cooling to −40 °C and passing fluorine[8] gas (20% in Ne) through the solution for 5 min. We initially attempted this conversion with more dilute fluorine (0.5, 1 and 5% in Ne), but found that the most efficient transformation in such a short time was best accomplished with the higher concentration. At this point the solution was purged briefly with nitrogen (5 s) and then a solution of the methyl enol ether (10 mg) in dichloromethane (0.2 ml) was added. The mixture was allowed to warm to room temperature and then quenched by the addition of saturated aqueous sodium hydrogen carbonate and passed through a silica cartridge before being finally purified *via* reversed phase semi-preparative HPLC. With the methyl enol ether of 1-tetralone as our model compound (Scheme 2), we have been able to obtain the corresponding 2-[^{11}C]methoxy-1-tetralone in 10% overall radiochemical yield (NDC), with a total synthesis time from the end of bombardment of around 50 min.

The excess, unreacted enol ether was hydrolysed *in situ*, so that the final reaction mixture was composed of radiolabelled product, tetralone, unreacted ^{11}C labelled methanol and traces of other, unidentified, nonradioactive products. Interestingly, we are able to increase our radiochemical yield to 50% (NDC) when the reaction was conducted in the presence of nonradioactive methanol (30 μl), indicating that $^{11}CH_3OF$ may be volatilized out of the reaction mixture in the stream of unreacted fluorine and neon. The structures of ^{11}C labelled products were confirmed by comparison of HPLC and TLC retention times with those of non-radioactive standards. For the no-carrier-added studies, the HPLC trace (measured at 254 nm) showed no peak corresponding to non-radioactive product, indicating that the specific activity of the radiotracer was high.

We are now studying the potential and scope of this novel radiolabelling reaction. A major interest is its use to furnish a novel class of ^{11}C labelled estrogens[9] for evaluation as PET imaging radiopharmaceuticals.

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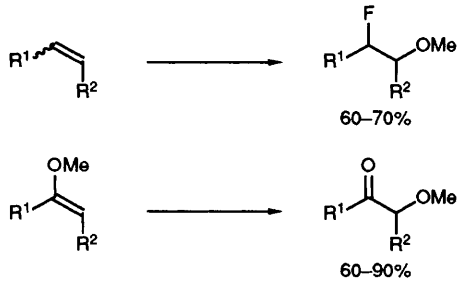
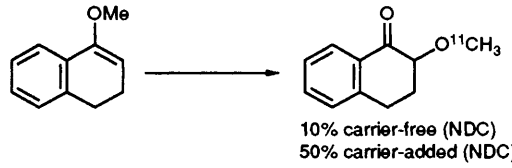


Scheme 1 *Conditions*: MeOF, MeCN, −40 °C to room temp.; R^1 = alkyl or aryl; R^2 = H or alkyl



Scheme 2 *Conditions*: $^{11}CH_3OF$, MeCN, −40 °C to room temp.

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