

# Microwave-enhanced radiochemistry

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The application of microwaves to synthetic organic chemistry is currently experiencing considerable growth. Here we show how the area of radiochemistry, with particular reference to the synthesis of <sup>3</sup>H-

(or T-), <sup>11</sup>C- and <sup>18</sup>F-labelled compounds, can benefit. Faster, cleaner, more selective reactions are possible with the formation of much reduced levels of radioactive waste.

Nils Elander was born in Orebro, Sweden in 1945. He obtained his B.S. in 1969 and his PhD in Physics in 1977, both at Stockholm University. He then spent a postdoctoral period during 1977–1978 at the Quantum Theory Project at the University of Florida, Gainesville, FL, USA. Returning to Stockholm, he obtained a research position and later a senior research position in 1979 at the Research Institute of Physics. He is Professor in theoretical molecular physics at Stockholm University. He currently has two main areas of research in (i) theoretical modelling of primary chemical reactions and (ii) microwave induced chemical reactions.

John R. Jones was born in London but spent his formative years in Wales, being educated at the University College of Wales, Aberystwyth (BSc, 1958; PhD, 1961). Apart from a sabbatical at the University of British Columbia (1966–1967) he has spent all of his academic career at the University of Surrey and its precursor (Battersea College of Technology). His early work on the ionisation of carbon acids was followed by the co-development of <sup>3</sup>H NMR spectroscopy and a number of radio-chromatographic methods before moving on to sol-gel based scintillators and microwave-enhanced tritiation procedures. He is currently Professor of Radiochemistry and editor of the *Journal of Labelled Compounds and Radiopharmaceuticals*.

Shui-Yu Lu was born in the Suzhou countryside, China. He received his BSc in Organic Chemistry at Nanjing University in 1983, his MSc in Applied Chemistry at Changsha Institute of Technology in 1988 and his PhD at the University of

Manchester with Drs C. Booth and P. Quayle in 1991. From 1983–1989, he was an Assistant Professor in the Department of Materials Science and Applied Chemistry, Changsha Institute of Technology. He was a postdoctoral research fellow at the University of Edinburgh with Dr R. M. Paton (1992–1993) before joining Professor J. R. Jones' group at the University of Surrey in 1994. His research interests include the synthesis of isotopically labelled compounds and their application in materials chemistry, sol-gel technology as applied to radio-analytical chemistry and the development of microwave-enhanced deuteriation/tritiation methodology.

Sharon Stone-Elander was born in Bassett, VA, USA and received her B.S. from Emory and Henry College, Emory, VA in 1973. Studying the mechanisms of cyclopolymerization reactions in the solid state and in solution, she earned a PhD in Organic Chemistry at the University of Florida, Gainesville, FL, USA in 1978. She was a visiting scientist at the Royal Institute of Technology in Stockholm, Sweden for one year before joining the Positron Emission Tomography research group at the Karolinska Pharmacy in late 1979. Since 1992 she has also been Professor of Medicinal Radiochemistry in the Department of Clinical Neuroscience of the Karolinska Hospital/Institute in Stockholm. Her research interests centre around the development, validation and application of positron emitting radiopharmaceuticals for tracing biochemical processes in vivo. Since 1989 she and Nils and their research groups have been developing and applying monomodal microwave devices in accelerating syntheses involving the short-lived positron emitters.



Nils Elander



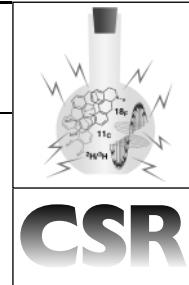
John R. Jones



Shui-Yu Lu



Sharon Stone-Elander



## 1 Introduction

The radionuclides formed as a result of fission in a nuclear reactor are, in the words of Gordon Dean, sometime Chairman of the US Atomic Energy Commission, 'used to treat the sick, to learn more about disease, to improve manufacturing processes, to increase the productivity of crops and livestock, and to help man to understand the basic processes of his body, the living things around him, and the physical world in which he exists.' In addition there is another group of radioactive nuclides that are produced in accelerators (cyclotrons). Many of these are positron ( $\beta^+$ ) emitters, which form the basis of an increasingly important technique, Positron Emission Tomography (PET),<sup>1</sup> which enables one to study the physiological, biochemical and pharmacological functions of man at the molecular level, either in health or in a diseased state. This is a rapidly expanding area which has seen in recent times the opening of close on 300 PET centres worldwide, approximately 20% of which are located in western Europe.

All of the known elements have radioactive isotopes. These differ widely in their properties and there is no way that one can do justice to all of them within the confines of a short article such as the present one. Consequently it is necessary to restrict our choice and here we will concentrate on those that find most use on the organic side of chemistry (Table 1). The very short half-lives of the positron emitters have meant that a good deal of time and effort have been spent in developing synthetic methods that are both rapid and easily automated. With the current interest in combinatorial chemistry and the need for chemists, be they in academia or industry, to be able to carry out their syntheses more efficiently and selectively, there is much to be gained from a technology transfer, not least to the area of labelled compounds containing longer-lived radionuclides, such as tritium. Legislative issues (e.g. tighter controls on how much radioactivity can be released to the atmosphere) together with commercial considerations (e.g. the increasing cost associated with the storage of radioactive waste) are additional factors which will help the move towards a more environmentally acceptable approach to radiosynthesis, and in due course contribute to an improved image for the chemical industry.

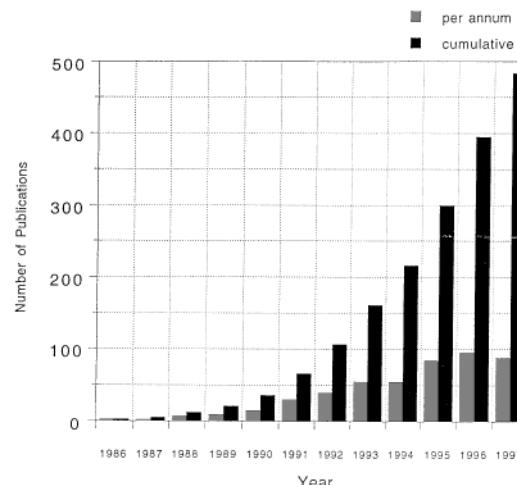
Many of the important developments that have taken place in catalysis over the last 10–20 years (Table 2) have benefited the radiosynthesis area. Certainly the one with the longest history relates to energy-enhanced procedures. Of these microwave dielectric heating offers the greatest potential but, as Fig. 1 shows, the number of research papers in this area, whilst increasing rapidly, is still at a low level.

## 2 Microwaves and microwave activation

Although microwave dielectric heating has been used in areas as divergent as meal preparation and industrial processing,<sup>2</sup> the benefits of its use in performing chemical transformations has only emerged within the last 14 years.<sup>3,4</sup> The mechanisms

**Table 2** Important developments in catalysis

(a)	Phase transfer catalysis
(b)	Supercritical fluids
(c)	Sol-gel technology
(d)	Ionic liquids
(e)	Solid state reactions
(f)	Energy-enhanced reactions
(g)	New reagents



**Fig. 1** Refereed papers on microwave-enhanced organic chemistry in recent years.

behind and the factors determining the successful application of microwave heating are still not widely familiar to chemists, possibly because electric field theory is generally taught in engineering/physics rather than in chemistry. The basic understanding of macroscopic microwave interactions with matter was formulated by von Hippel.<sup>5</sup> In this section we give a very brief presentation of the current understanding of microwaves and their interactions with matter as well as factors to be considered in choosing suitable microwave devices for chemistry applications. For more in depth presentations, the reader is referred to recent reviews<sup>6–8</sup>.

Microwaves are electromagnetic waves in the frequency region 0.3 to 300 GHz. Electromagnetic field theory generally regards matter as charges, electric or magnetic dipoles or combinations thereof. The interaction of the electromagnetic field with matter is described by the Lorentz force

$$\mathbf{F} = q\mathbf{E} + \mu q\mathbf{v} \times \mathbf{H} \quad (1)$$

with the first and second terms describing the electric and magnetic interactions, respectively. From first principles, it can be shown that only the electric factor of the Lorentz force is active in the energy transfer between the field and non-ferromagnetic matter.<sup>9</sup> However, microscopic, non-heating, magnetic effects may possibly also contribute to enhancements

**Table 1** Physical properties of some important radionuclides

Radionuclide	Half-life	Decay mode (%)	Maximum energy/MeV	Maximum specific activity/Ci mol <sup>-1</sup>	NMR Characteristics
<sup>3</sup> H	12.3 y	$\beta^-$	0.0186	$2.9 \times 10^4$	Spin $\frac{1}{2}$ , most sensitive of all NMR active nuclei, low ( $< 10^{-16}\%$ ) natural abundance
<sup>11</sup> C	20.3 m	$\beta^+$ (99.8) EC (0.2)	0.96	$9.2 \times 10^9$	
<sup>14</sup> C	5730 y	$\beta^-$	0.155	62.4	
<sup>13</sup> N	9.96 m	$\beta^+$ (100)	1.19	$1.89 \times 10^{10}$	Spin zero
<sup>15</sup> O	2.05 m	$\beta^+$ (99.9) EC (0.1)	1.72	$8.9 \times 10^{10}$	
<sup>18</sup> F	109.7 m	$\beta^+$ (97.0) EC (3.0)	0.635	$1.71 \times 10^9$	

observed when performing chemical reactions with the aid of dielectric heating.<sup>10</sup>

If free electric charges are not present, then the interaction between a microwave field and the sample can be described as an interaction between the electric field and a set of electric dipoles. The polarisation,  $\mathbf{P}$ , is the response of a sample to an electric field  $\mathbf{E}$

$$\mathbf{P} = \epsilon_0 \chi_e \mathbf{E} \quad (2)$$

where  $\chi_e$  is the electric susceptibility of the sample. It, in turn, is related to the electric permittivity of the sample through

$$\epsilon = \epsilon_0 (1 + \chi_e) \quad (3)$$

where  $\epsilon_0$  is the electric permittivity in vacuum. The applied field creates a current in the sample which can be expressed as a vector sum of the polarisation current (describing the fast alternating charge transport due to motions of dipoles) and the conduction current (describing the transport of ions or electrons). At high frequencies the inertia of the molecular system causes the polarisation vector  $\mathbf{P}$  to lag behind the applied field  $\mathbf{E}$ . This implies that the variation with time of the effective current in the sample is out of phase with that of the applied field by an effective difference  $\delta$ , which defines the tangent loss factor,  $\tan \delta$ . The average microwave power converted into heat per unit volume is given by eqn. (4),

$$P_{\text{ave}} = \pi v \epsilon \tan \delta |\mathbf{E}|^2 \quad (4)$$

where  $v$  is the microwave frequency and  $\epsilon$  is the relative electric permittivity. The tangent loss factor is dependent on and proportional to the electric conductivity and the polarisability of the chemical sample, which is why polar or ionically conducting chemical samples are required for chemistry performed in microwave fields. The strong electric field component of the microwave field may also create microscopic displacements of the electrons within a molecule. Such displacements have a time scale of  $10^{-14}$  s or less while the time scale of the microwave field is around  $10^{-10}$  s and rotational motion of molecules in a solution has a time scale of about  $10^{-9}$  to  $10^{-11}$  s. A polarisable molecule thus may first become polarised and then begin to be rotated by the action of the applied electric field. While the electronic motion within a molecule does not create significant heat, the rotation of a dipole surrounded by other molecules will. Gabriel *et al.*<sup>6</sup> discuss in detail the rotation of permanent and induced dipoles, both formally and for various solute—solution mixtures.

In order to achieve efficient heating with microwaves, eqn. (4) tells us to optimise the electric field component of the microwave field in the sample. This is, however, not the only factor to consider. Most solvent and solute mixtures have, as described above, non-zero electrical conductivities,  $\sigma$ , which contribute to the heating process. Nor can the vessel be arbitrarily chosen since the penetration of the microwave field is geometry—as well as sample—dependent. Electromagnetic field theory defines the skin-depth,  $\Delta$ , that describes how deeply the  $\mathbf{E}$ -field penetrates into a sample before it reaches the strength  $1/e$  ( $\approx 37\%$  of its initial amplitude).

$$\begin{aligned} E(d) &= E_0 \exp(-d/\Delta) \\ \Delta &= (\mu \sigma \pi v)^{-1/2} \end{aligned} \quad (5)$$

where  $E_0$  is the amplitude to the field just inside the surface of the conducting chemical sample,  $d$  is the distance from the surface and  $\mu$  is the magnetic permeability. Therefore the average dissipated power per unit volume follows the relation

$$P_{\text{ave}}(d) \propto \exp(-2d/\Delta) \quad (6)$$

The penetration depth,  $D_P$ , is defined as the distance from the surface of the material at which the power has decreased to  $1/e$  ( $\approx 37\%$ ) of its value at the surface. Measurements of the penetration depths for a number of substances, temperatures and microwave frequencies have been reported by Ohlsson *et al.*<sup>11</sup> When designing experiments the size of the sample is

important. The commonly used domestic oven magnetrons have a frequency of 2.45 GHz corresponding to a vacuum wavelength of 12.25 cm while the penetration depth for that frequency of most solvents ranges from a couple of millimeters up. This implies that it may be helpful to perform initial investigative reactions on a small scale of a few milliliters where the influence of the microwave field is easier to handle than in larger scale systems.

In summary, a microwave device for performing chemical transformations has to be optimised for a range of solvent-solute mixtures and it should have a high and stable  $\mathbf{E}$ -field intensity. This may be achieved by using monomodal cavities or special types of applicators in which the microwave field is controlled at and focused on the sample.<sup>2,9,12,13</sup> These devices give better reproducibility, shorter reaction times and sometimes better chemical yields simply due to the fact that the interaction between the microwave field and the sample is controlled and thereby can be optimised. However, most microwave-induced chemistry is performed using multi-modal microwave ovens. These devices have less well-defined electric fields. Consequently, special measures must often be taken so that the exposure of the sample to the electromagnetic field can be kept constant.

### 3 Microwave-enhanced labeling procedures

#### 3.1 Background

More than forty years ago Wilzbach reported the successful tritiation of a number of organic compounds simply by exposure to tritium gas. Typically 0.5–4.0 g of substrate was exposed to 7–14 curies (1 Ci = 37 GBq) of  $T_2$  gas for between 3 and 10 days, leading to 20–600 mCi incorporation with the specific activities of the pure product being in the 1–100 mCi g<sup>-1</sup> region. Although the hopes of the author that ‘the availability of  $T_2$  gas at low cost and the high levels of activity attainable, even in materials of complex structure, combine to make exposure to tritium gas an attractive method for the preparation of tritium-labeled compounds’ were not fully realised, mainly because of the difficulties in attaining high radiochemical purities and the development of more attractive alternatives, it nevertheless stimulated a great deal of research in allied areas. Wolfgang *et al.* were already using recoil tritons, accelerated to an energy of 100 eV, to induce hydrogen–tritium exchange reactions. The passage of an electric discharge through the tritium gas led to improvements as also did the use of ultra-violet,  $\gamma$  and X-radiation as additional sources of energy. Westermark and colleagues reported on the first use of microwaves in this area. However, more than a decade elapsed before the microwave discharge activation of tritium gas was developed by Hembree *et al.* for labeling peptides and proteins and used by Peng to tritiate a number of steroids. References on these historical findings and subsequent improvements can be found elsewhere.<sup>14</sup> Nevertheless it is generally agreed that it was the two papers<sup>3,4</sup> which appeared in 1986, reporting on the use of microwaves to enhance general synthetic opportunities, which served as the catalyst for the increased activity in this area. The first successful use of microwave techniques to speed up the synthesis of radiopharmaceuticals for PET application was reported shortly afterwards.<sup>15</sup>

#### 3.2 Tritium

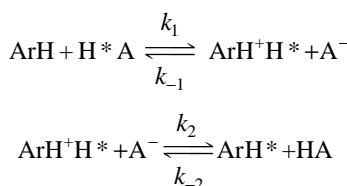
Details of the most widely used tritiation procedures are to be found in Table 3 from which it can be seen that all have one or more disadvantages which may, in some cases, be removed through the use of microwaves. In all cases the reactions can be

**Table 3** Widely used methods for incorporating tritium into organic compounds

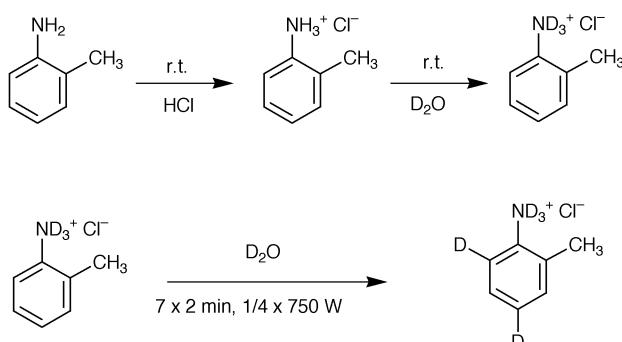
Method	Comments
(a) Hydrogen isotope exchange reactions—catalysed by acids, bases or metals	Specific activity of the product is somewhat limited by the fact that $T_2O$ can not be readily used.
(b) Hydrogenation of an unsaturated precursor using either a homogeneous or heterogeneous catalyst and $T_2$ gas	$T_2$ is sparingly soluble in many common solvents so that the reactions are frequently slow. Separation difficulties sometimes exist. There are also problems in storing excess $T_2$ gas.
(c) Catalytic dehalogenation of aromatic halides using $T_2$ gas	Frequently only one tritium atom is incorporated. Similar problems to hydrogenations encountered.
(d) Reduction of suitable precursors with labelled borohydrides	Not all the tritium is incorporated. Tritiated borohydrides need to be prepared immediately prior to use.
(e) Methylation using e.g. $CT_3I$	Range of compounds that can be tritiated is somewhat restricted. $CT_3I$ is not very stable and easy to use.

greatly accelerated as the following examples illustrate. In some cases further advantages emerge.

Acid catalysed hydrogen isotope exchange has long been used as a method of incorporating tritium (and deuterium) into aromatic compounds, the generally accepted mechanism being of the A-SE2 type:



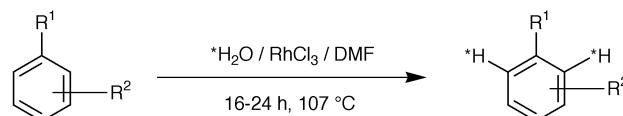
Werstiuk<sup>16</sup> devised conditions—dilute acid at elevated temperatures—in which a large range of aromatics (benzene derivatives, amines, acids, halides, polynuclear hydrocarbons, heteroaromatics as well as some biologically active compounds and naturally occurring insecticides) could be per-deuteriated and by implication tritiated. The conditions employed, however, were very harsh, frequently requiring 24–48 h at temperatures as high as 250 °C. Such conditions were used for the deuteration of aniline hydrochloride whereas under microwave enhanced conditions the deuteration of the structurally similar *o*-toluidine hydrochloride was complete in 14 min<sup>15</sup> (Scheme 1).

**Scheme 1** Acid catalysed deuteration of *o*-toluidine hydrochloride.

The same benefits are to be obtained for tritium although the specific activities are only in the mCi mmol<sup>-1</sup> range. Acids can

of course be used as solids, e.g. Nafion, in which case the rapid hydrogen isotope exchange process induced by the microwaves is coupled to the ease of separation of the labeled product. Similar comments apply to solid bases.

One of the important consequences of the development of <sup>3</sup>H NMR spectroscopy<sup>17</sup> is that it has made it much easier to test the regiospecificity of metal-catalysed hydrogen exchange procedures and ultimately assist the design of new and improved catalysts. Of the many transition metal catalysts that have been used  $RhCl_3$  has been shown to be amongst the best, with a wide range of compounds, including many drug molecules, being tritiated regiospecifically in a one-step catalytic procedure<sup>18</sup> (Scheme 2).

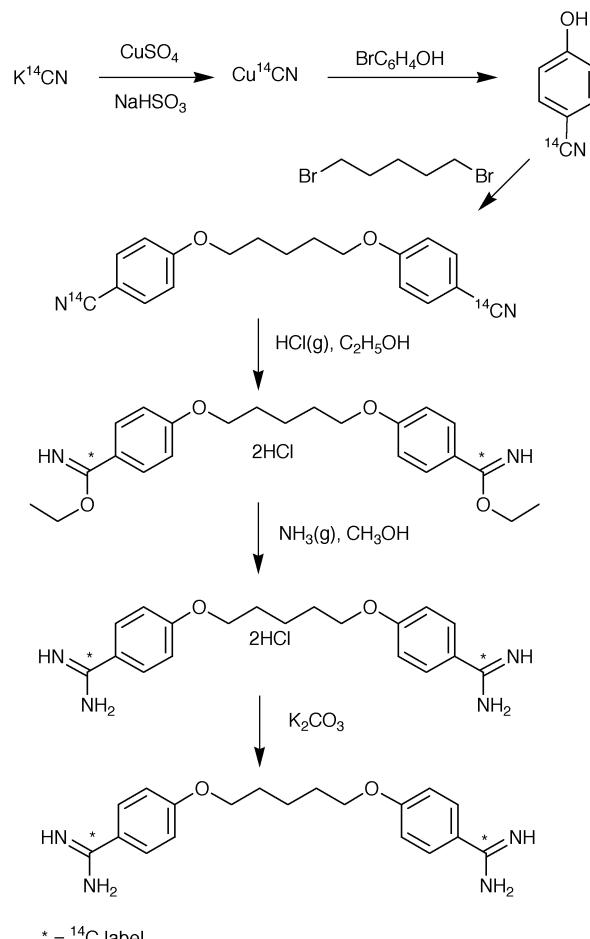


$R^1 = COOH, COONa, CONH_2, CONHR', CH_2NH_2, CH_2NHR', CHMeNH_2, NHCOR'$

$R^2 = \text{many other substituent groups}$

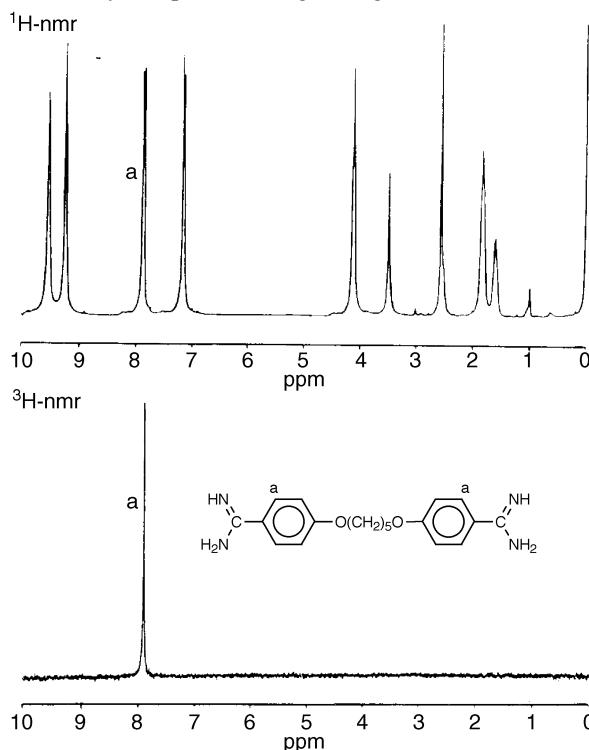
**Scheme 2** Metal catalysed hydrogen isotope exchange reaction.

The contrast between this reaction and the time-consuming nature of <sup>14</sup>C-synthesis is well illustrated by the case of pentamidine, a drug that has been widely used to treat protozoal disease such as malaria as well as to assist AIDS sufferers. A six-step synthesis<sup>19</sup> (Scheme 3) produced pentamidine labelled

**Scheme 3** Synthesis of <sup>14</sup>C labelled pentamidine.

with <sup>14</sup>C in the amidine groups. The overall yield was 19% and the specific activity 24 mCi mmol<sup>-1</sup> whereas the one-step

catalytic procedure gave a tritium labelled product at 90 mCi mmol<sup>-1</sup>. Comparison of the <sup>1</sup>H and <sup>3</sup>H NMR spectra showed that the tritium had been incorporated regiospecifically into metabolically safe positions (Fig. 2). Again, under the influence

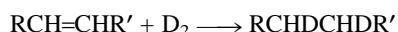


**Fig. 2** <sup>1</sup>H and <sup>3</sup>H NMR spectra of <sup>[3]H</sup>-pentamidine. (Reproduced with permission from ref. 19.)

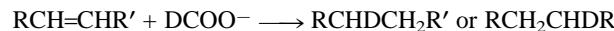
of microwave irradiation, the time required for the tritiation is greatly reduced. Encapsulation of the catalyst can also simplify the isolation of the product.

Other transition metal catalysts<sup>20,21</sup> that have found success in hydrogen isotope exchange reactions under conventional heating conditions and deserve study under microwave enhanced conditions are the two iridium complexes  $[\text{Ir}(\text{COD})(\text{Cy}_3\text{P})(\text{Py})]\text{PF}_6$  and  $[\text{Ir}(\text{H}_2)(\text{Me}_2\text{CO})_2(\text{PPh}_3)_2]\text{BF}_4$ .

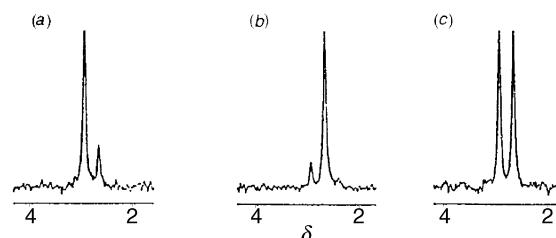
Because T<sub>2</sub> gas is available at 100% isotopic abundance and is relatively inexpensive, hydrogenation in the presence of a heterogeneous catalyst such as Pd/C or a homogeneous catalyst such as Wilkinson's catalyst has constituted one of the most widely used routes to the synthesis of tritiated compounds at high specific activity. Nevertheless the disadvantages referred to in Table 3, particularly the slow rates of reaction and the need to store excess T<sub>2</sub> gas (in the absence of a uranium 'getter') are serious issues which prompted the search for an alternative solution. A special kind of catalytic hydrogenation is catalytic hydrogen transfer<sup>22</sup> in which the T<sub>2</sub> (or D<sub>2</sub>) gas is replaced by a solid, which on heating, either conventionally or through the use of microwaves, gives up its tritium/deuterium. Formates are particularly good in this respect (other known hydrogen donors include hydrazine, cyclohexene, tetralin and triethylsilane) and as they are easily soluble in many solvents, can be readily tritiated (through a one-step metal catalysed hydrogen exchange procedure) and stored for lengthy periods without loss of label, are likely to find increasing use in this area. Furthermore the technology can be readily adapted for deuteration studies and in both cases the pattern of labeling can be easily varied. Thus in the hydrogenation of alkenes, where using D<sub>2</sub> gas and Wilkinson's catalyst, it is customary to obtain very even addition across the double bond, thus:



With DCOO<sup>-</sup> there are two possibilities, with the hydrogen coming from the protic solvent:

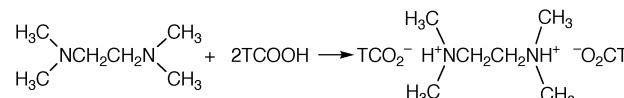


Therefore by using the combinations DCOO<sup>-</sup> + H<sub>2</sub>O, HCOO<sup>-</sup> + D<sub>2</sub>O and DCOO<sup>-</sup> + D<sub>2</sub>O the pattern of labeling can be varied,<sup>23</sup> as was found to be the case in the hydrogenation of

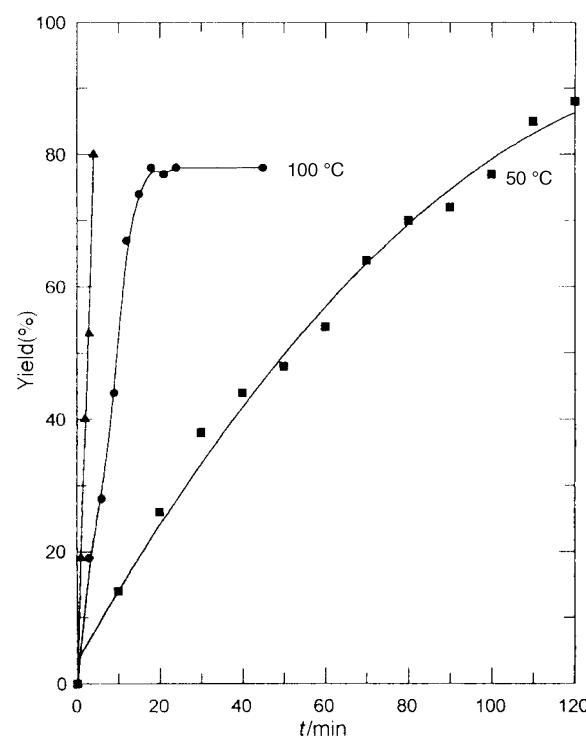


**Fig. 3** <sup>2</sup>H NMR (<sup>1</sup>H decoupled) spectra of dihydrocinnamic acid formed using (a) HCOOK-D<sub>2</sub>O, (b) DCOOK-H<sub>2</sub>O and (c) DCOOK-D<sub>2</sub>O. Reproduced with permission from ref. 23.

cinnamic acid (Fig. 3). In view of the dangers associated with the use of high specific activity tritiated water (5 Ci cm<sup>-3</sup>, amounting to ~0.2% isotopic abundance, is usually the highest that we employ), the preferred solution is to use the diformate salt which is readily synthesised in the following manner:



When the labeled formates are now coupled to the use of microwaves (an option not open to H<sub>2</sub>/T<sub>2</sub>/D<sub>2</sub> gases) hydrogenation is invariably very rapid, frequently being complete

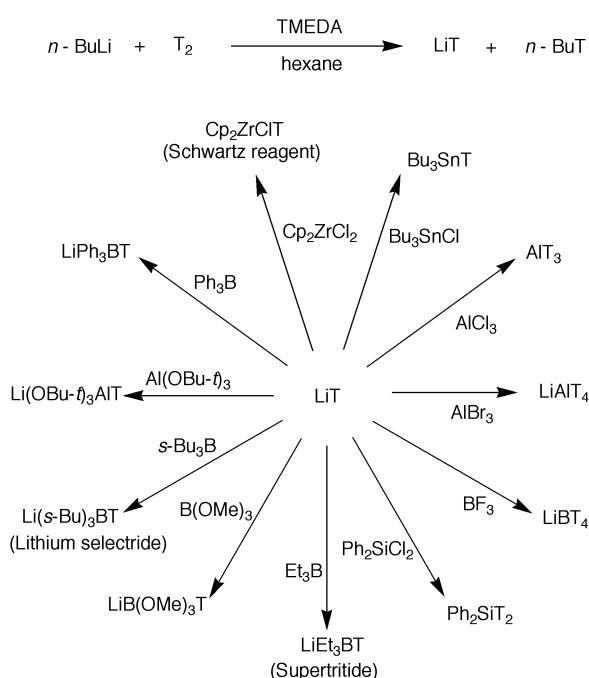


**Fig. 4** Hydrogenation of  $\alpha$ -methylcinnamic acid under various conditions. ■ 50 °C, oil bath; ● 100 °C, oil bath; ▲ Microwave irradiation, 750 W. Reproduced with permission from ref. 23.

within 5 min (Fig. 4) whereas the corresponding reactions in an oil bath take several hours to complete. There are further interesting possibilities in this area as the work of Loupy *et al.*<sup>24</sup> in particular has drawn attention to the fact that many microwave-enhanced reactions can take place entirely in the

solid state. Where problems of radioactive waste are an issue such reactions offer considerable benefits, not least being the fact that one no longer needs to worry about what to do with the large volumes of radioactive solvents.

Another consequence of the development of tritium NMR spectroscopy has been the increased attention paid to the development of new tritiating reagents especially at carrier free level. Until recently tritiated compounds at very high specific activity ( $\text{Ci mmol}^{-1}$ ) could only be obtained by hydrogenation or dehalogenation using  $\text{T}_2$  gas or from the reduction of functional groups with tritide reagents. The latter method suffered from the fact that sodium borotritide ( $\text{NaBT}_4$ ) was the only reducing agent available at close to carrier free level of radioactivity. However the observation that extremely reactive hydrides (much more so than the commercially available forms prepared from the elements at high temperatures) could be prepared from their *n*-butyl compounds and hydrogen under very mild conditions and near ambient temperatures has transformed the situation and been nicely capitalised on, especially by Andres and coworkers.<sup>25</sup> The crucial reaction is the formation of lithium tritide from which a whole range of selective reducing agents can then be synthesised (Scheme 4).



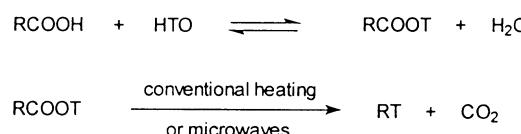
Scheme 4 Preparation of a wide range of tritide reagents from LiT.

This capitalises on the fact that their reactivity can be fine-tuned through the element (*e.g.* B, Al, Si, Sn and Zr) to which the tritium is attached and by the electronic and steric nature of the substituents at the central atom.

Recently it has been shown that the rapid reduction of aldehydes and ketones can be performed in the solid state by using alumina supported  $\text{NaBH}_4$  in the presence of microwaves.<sup>26</sup> Simple mixing of the carbonyl compound with  $\text{NaBH}_4$ -alumina (10%) and irradiating the mixture in a microwave oven for 0.5–2 min produced the desired product in high purity and high yield. Corresponding deutieriations, as a prelude to tritiations, in our laboratory have been equally successful. Synthesis of the labeling reagents can also be enhanced. Together these findings illustrate the potential benefits of using microwaves in this area.

Finally there are some reactions, which in the past were rarely used for tritiating (or deuteriating) compounds but which, because of the benefits of using microwaves, are now much more attractive. Decarboxylations are but one such example. Indole-2-carboxylic acid is usually decarboxylated with difficulty by heating at high temperature in quinoline and the

presence of a copper catalyst. This traditional method is both inefficient and unsuitable environmentally and Strauss<sup>27</sup> has recently shown that simply in water the microwave-enhanced reaction is complete in 20 min with a 100% yield. When the decarboxylation takes place in the presence of tritiated water rapid exchange with the carboxy hydrogen takes place prior to the decarboxylation (Scheme 5). This is now an attractive tritiation procedure and it is interesting to note that in one of his last papers Barton<sup>28</sup> showed how decarboxylation could be used to prepare tritium, as well as deuterium, labeled imines and aldaizines.



Scheme 5 Room temperature hydrogen–tritium exchange and subsequent decarboxylation.

### 3.3 Carbon-11

In radiolabelling with carbon-11 most strategies begin with  $^{11}\text{CO}_2$  itself and usually involve first converting carbon dioxide to other small reactive molecules before coupling with the target molecule (Table 4). For every 10 min that a procedure takes

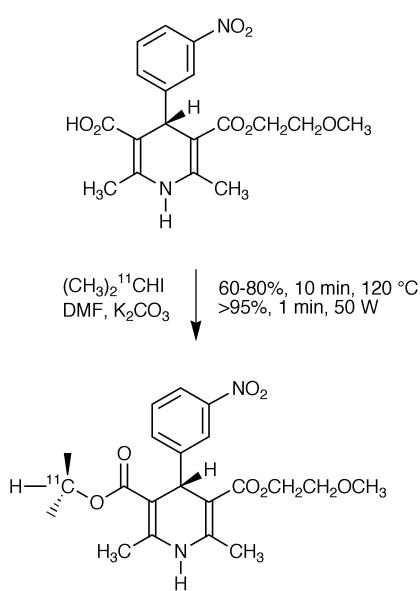
Table 4 Some methods for incorporating carbon-11 into specific positions in organic compounds

Method	Comments
(a) Reaction of organometallics with $^{11}\text{CO}_2$ to give carboxylic acids or, subsequently, alcohols	$^{11}\text{CO}_2$ is available directly from the cyclotron. Rapid reactions at low temperatures, giving label in the terminal position.
(b) <i>N</i> -, <i>O</i> -, <i>S</i> -alkylations using $^{11}\text{RX}$ ( $\text{R} = \text{CH}_3, \text{Et}, n\text{-Pr}, iso\text{-Pr}; \text{X} = \text{I}, \text{OTf}$ )	Widely used method. $\text{CH}_3\text{I}$ and $\text{CH}_3\text{OTf}$ can be rapidly produced in high specific activity. The higher homologs are less easily prepared and react much more slowly.
(c) Substitutions/condensations using $^{11}\text{CN}^-$ to give labelled nitriles and, subsequently, amines, amides, acids, aldehydes, alcohols	Cyanide is the most widely used nucleophilic $^{11}\text{C}$ -reagent. Stringent conditions and lengthy multi-step routes, however, impede full utilisation.
(d) C–C bonds with labelled organometallics, <i>e.g.</i> $^{11}\text{RLi}$ , $^{11}\text{RCuLi}$ , and $^{11}\text{RMgX}$	The reagents, prepared <i>via</i> halides, are moisture-sensitive, which complicates production and use.
(e) Condensations/substitutions using $^{11}\text{C}$ -nitroalkanes	$\text{CH}_2\text{NO}_2^-$ reacts similarly to $\text{CN}^-$ . Used to label aromatics primarily <i>via</i> cyclizations of hexatriene systems and in condensations with pyrylium salts. The higher homologs can be used to introduce branched alkyl groups.
(f) C–C bonds <i>via</i> $^{11}\text{C}$ -ylides or Pd-coupling reactions using $^{11}\text{RX}$	Usage in radiolabeling still being developed. Applications expected to increase in the future.
(g) Insertions with $^{11}\text{C}$ -diazomethane	Difficult to prepare and use the reagent for intended selective insertions.
(h) Condensations with $\text{R}^{11}\text{C}(\text{O})\text{X}$ and $^{11}\text{C}(\text{O})\text{X}_2$	Reagents can be difficult to prepare under labeling conditions.
(i) Condensations/reactions with multi-functional precursors.	Potential route for introducing the label in positions of differing metabolic stability, in heterocycles, etc.

with carbon-11, the amount of radioactive material and the product's specific activity will be decreased by 29% simply due

to the decay of the radionuclide. It is thus a practical reality that, although a radiotracer may be produced in higher chemical yield with longer reaction time, the actual radiochemical yield and specific activity may be so reduced by the time elapsed that the product cannot be used for its planned application. In this field of performing chemistry against the clock, notable gains in synthetic flexibility very much depend on the degree to which new methodological developments (see, for example, Table 2) can be incorporated into production sequences. Experiences from this area of radiochemistry should consequently be of obvious interest for other areas in which microscale organic chemistry is practised (labeling with other radionuclides, teaching laboratories, building libraries in combinatorial approaches to drug development, *etc.*) and for all areas performing microscale exploratory studies prior to scaling-up.

The most commonly used method for introducing a carbon-11 label into an organic molecule is by nucleophilic reaction of an alcohol, amine, amide or thiol with a labelled alkyl halide. Reactions with  $^{11}\text{CH}_3\text{I}$  can generally be accomplished in moderate to good yields in 5–10 min. Mixed bases and/or solvent systems as well as high temperatures are used to drive the reactions and, to even further reduce the alkylation times,  $\text{CH}_3\text{I}$  has been converted to the more reactive methyl triflate ( $\text{CH}_3\text{OTf}$ ). Alternatively, the same or even greater reductions in reaction times have been achieved by the use of mono- and multi-modal microwave techniques as, for example, in alkylation of an amide to give the benzodiazepine receptor antagonist, [*N*-methyl- $^{11}\text{C}$ ]flumazenil,<sup>13</sup> and of an imidazole to yield the  $\beta_1$ -adrenoceptor ligand, [*N*-methyl- $^{11}\text{C}$ ]CGP 20712A.<sup>29</sup> In the latter synthesis, not only the total reaction time was reduced, but also the relative yields of alkylations at other sites in the molecule were affected. The higher homologues ([ $^{11}\text{C}$ ]-ethyl, -*n*-propyl and -isopropyl halides) are more difficult to prepare and the corresponding triflates are not available. Furthermore the alkylation reactions are slower and consequently they have been used less frequently. The monomodal microwave accelerations of alkylations with these less reactive halides [see, for example, the alkylation of a carboxylate salt with [ $^{11}\text{C}$ ]isopropyl iodide<sup>14</sup> (Scheme 6)] have not been achieved with any other technique.

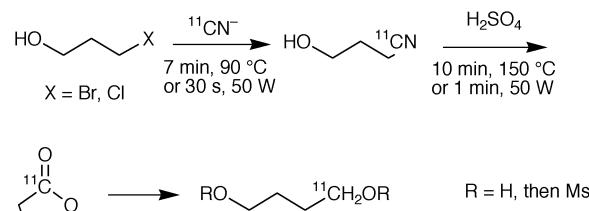


Scheme 6 Esterification of an *in situ* generated carboxylic acid salt by nucleophilic aliphatic substitution on a branched alkyl halide.

Cyanide-based chemistry using carbon-11 parallels the strategies employed for many years in carbon-14 syntheses (see a typical example in Scheme 3), with the basic difference that all the chemical transformations and purifications must be com-

pleted within a total synthesis time of less than one hour. Microwave techniques have achieved dramatic accelerations in some of these reactions which under conventional heating require relatively long times and stringent conditions. In some cases additional advantages of microwave heating have been utilised.

Cyanide is widely used in nucleophilic aliphatic substitution reactions to extend the carbon chain by one. In cyano-dehalogenations to yield [ $^{11}\text{C}$ ]-4-hydroxybutyronitrile (Scheme 7), reaction times for 3-bromopropan-1-ol were



Scheme 7 Cyano-dehalogenation and subsequent nitrile hydrolysis with cyclisation in the synthesis of the cytotoxic agent, busulphan.

reduced 15-fold compared to the time required with conventional heating.<sup>30</sup> With the less reactive 3-chloropropan-1-ol and otherwise identical conditions, the yields were lower (10% *vs.* 60%) regardless of whether conventional or microwave heating was used. The yields could, however, be increased by a factor of 3–5 by adding salts to the microwaved samples, while only  $\text{K}_2\text{CO}_3$  had a comparable effect on the conventionally heated samples (Table 5). The coupling of microwaves with a given

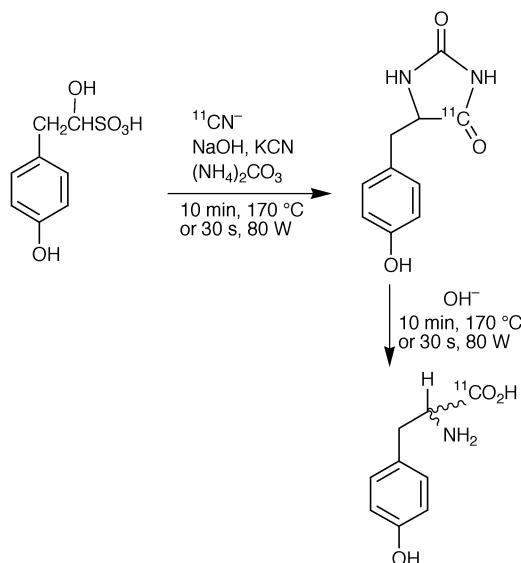
Table 5 Effects of adding salts on the conversions (%) of  $^{11}\text{CN}^-$  to [ $^{11}\text{C}$ ]-4-hydroxybutyronitrile in the cyano-dehalogenation using 3-chloropropan-1-ol

	n.c.a. <sup>a</sup>	KCN	$\text{NH}_4\text{Cl}$	KCl	KBr	$\text{K}_3\text{PO}_4$	$\text{K}_2\text{CO}_3$
90 °C, 7 min	10	14	3	10	1	16	28
70 W, 0.75 min	8	44	8	31	47	27	26

<sup>a</sup> No-carrier added.

sample becomes more favorable as the ionic strength is increased. In closed reaction vessels, the pressure will increase and high temperatures will be achieved more rapidly at a given input power when salts are added.<sup>7,12,31</sup> As a rule of thumb, reaction times may be halved for every 10 °C increase in temperature. Molecules previously disregarded as too unreactive may therefore be reconsidered as feasible alternative substrates in microwave-induced transformations.

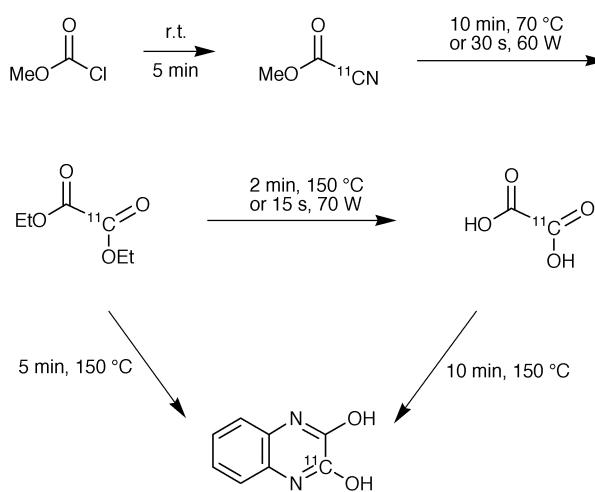
Cyanide adds to carbon–carbon or carbon–hetero multiple bonds to give saturated and unsaturated nitriles or geminal difunctional molecules such as  $\alpha$ -keto,  $\alpha$ -hydroxy or  $\alpha$ -amino nitriles. Since the nitriles can be subsequently converted to a number of other groups, these approaches have been often utilised, for example, to make vicinal difunctional labeling precursors, racemic  $\alpha$ -amino acids, the  $\alpha$ -hydroxy aldehydes of carbohydrate molecules, *etc.* The Bücherer–Strecker synthesis illustrates both the frequent necessity to drive these reactions in order to achieve good yields and the improvements that can be achieved with alternative heating techniques. The two-step method involves the initial condensation of  $\text{CN}^-$  with aldehydes in the presence of ammonium chloride and/or carbonate to form alkyl or aryl hydantoins followed by hydrolysis to give the racemic  $\alpha$ -amino acids. The synthesis of D,L-[ $^{11}\text{C}$ ]-tyrosine starting with the *p*-hydroxyphenylacetaldehyde–bisulfite adduct (Scheme 8) required heating in a steel bomb for 2 × 10 min at 170 °C. Monomodal microwave techniques reduced the total synthesis time to 1 min<sup>30</sup> while maintaining comparable or slightly higher conversions (up to 60%). The



**Scheme 8** Bücherer–Strecker synthesis of  $^{11}\text{C}$ -labelled D,L-tyrosine.

essential amino acids, their analogs, peptides and proteins are important in many pharmaceutical and medical applications. The advantages of implementing these experiences in other fields should be apparent.

Microwave heating may well become a determining factor for the broader utilisation of difunctional building blocks in rapidly and efficiently building complicated molecules. For example, heterocyclic compounds are widely distributed in nature and are also predominant in a large number of pharmaceutical compounds, agrochemicals, dyestuffs, etc. Techniques which facilitate these typically difficult cyclizations are therefore of interest for many fields of chemistry. In radiolabeling, the possibility of incorporating a label in ring positions is particularly attractive since they should be metabolically stable *in vivo*. The advantages and potential problems of using microwaves in this area were demonstrated in the synthesis of the heterocycle, 2,3-dihydroxyquinoxaline<sup>32</sup> (Scheme 9), a basic structural unit in antagonists of the



**Scheme 9** Cyanide-based synthesis of difunctional precursors for heterocyclization reactions.

excitatory amino acid receptor system. Syntheses of the difunctional labeling precursors diethyl [ $^{11}\text{C}$ ]oxalate and [ $^{11}\text{C}$ ]oxalic acid were accelerated when the nitrile hydrolyses could be performed in  $\leq 1$  min in alcoholic and aqueous media, respectively. However, the highly polar, concentrated acidic media and the high temperatures required for the heterocyclization proved to be an explosive, uncontrollable combination. In

a recent collaboration with the research group of de la Hoz, the heterocyclization has been successfully accomplished by microwave heating when the solvents were excluded. These observations, together with others,<sup>6,24</sup> indicate the considerable benefits that exist in performing reactions in solvent-free or solid support systems.

Potentially all reactions which require polar media and prolonged heating at elevated temperatures may be accelerated through the use of microwave dielectric heating. From the examples given above, it follows that the more recent methods for labeling in metabolically stable positions (*e.g.* Wittig syntheses of carbon–carbon double bonds, Pd-catalysed coupling reactions currently using simpler [ $^{11}\text{C}$ ]alkyl halides to generate carbon–carbon single bonds and [ $^{11}\text{C}$ ]nitroalkane-based syntheses of benzenoids and heterocycles) could all benefit from these techniques.

### 3.4 Fluorine-18

The introduction of fluorine to manipulate the physicochemical and biological properties of lead compounds in industrial and medicinal chemistry is widely practised. Organofluorine chemistry has, however, always been complicated by the need to harness the highly reactive electrophilic reagents or to stringently exclude hydrating agents from fluoride so that its nucleophilic properties can be utilised. Similar struggles have been fought in PET radiochemistry. Although there are relatively few general routes for labeling tracer molecules with fluorine-18 (Table 6), it is frequently used mainly because the

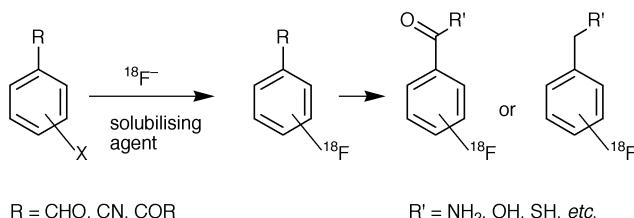
**Table 6** Methods for incorporating fluorine-18 into specific positions in organic compounds

Method	Comments
(a) Electrophilic additions to alkenes and regiospecific aromatic substitutions <i>via</i> fluorodemettallation reactions using reagents such as $^{18}\text{F}_2$ and $\text{CH}_3\text{COO}^{18}\text{F}$	Instantaneous reactions at low temperatures, but give medium to low specific activity products, with the exception of one method in which the electrophilic agents are made from $^{18}\text{F}^-$ .
(b) Nucleophilic aromatic substitutions using activated substrates and $^{18}\text{F}^-$ solubilised with aminopolyethers or tetraalkylammonium salts	Needs good leaving groups and activating substituents. Usually requires making relatively simple aryl fluorides first, followed by lengthy multi-step conversions to the target molecule.
(c) Nucleophilic aliphatic substitutions of halides or sulfonates using $^{18}\text{F}^-$ solubilized with aminopolyethers or tetraalkylammonium salts	Depending on the substrate, moderate to vigorous conditions are usually required. This method is preferred, when possible to use, since the target molecule is often obtained in one or a few steps.
(d) $N$ -, $O$ -, $S$ -alkylations using $^{18}\text{F}$ -( $\text{CH}_2$ ) $_n$ X ( $n = 2$ or 3, X = halides, sulfonate esters)	Similar to the [ $^{11}\text{C}$ ]alkyl iodide and triflate based methods for labeling side chains. The fluorinated agents are, however, more difficult to make.

half-life of nearly 2 h permits not only longer synthetic strategies but also the use of the final product over longer periods. The examples from fluorine-18 radiochemistry which are presented here have been chosen either because they illustrate some special advantages of microwave dielectric heating or because the presence of the radionuclide has been instrumental in tracing some of the reactions and side-reactions occurring.

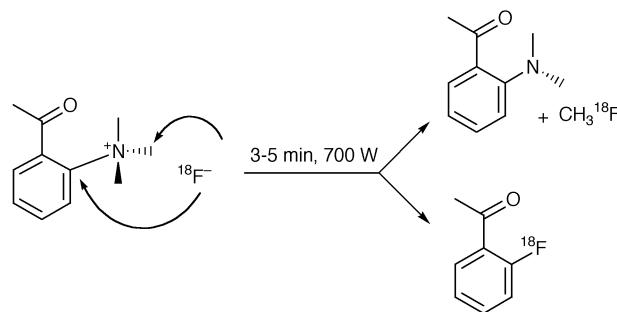
Probably the most common route for introducing fluorine is through nucleophilic aromatic substitutions using  $^{18}\text{F}^-$ , amino-

polyethers [in particular Kryptofix™ 2.2.2 (K2.2.2 or APE 2.2.2)] or tetraalkylammonium salts and polar, aprotic solvents. Good leaving groups are required ( $-\text{NO}_2$  or  $-\text{NMe}_3^+$ , but usually not halogens). The aromatic substitutions are favored by the presence of *ortho*- or *para*- electron-withdrawing groups (e.g.  $-\text{CN}$ ,  $-\text{CHO}$  or  $-\text{COR}$ ), which after incorporation of the radioactive fluorine, often function as 'linkers' through which the tracer molecule can subsequently be assembled. The presence of electron-donating groups slows down the fluorinations. Depending on the degree of activation of the substrate, these reactions require 10–30 min at temperatures up to 160 °C.



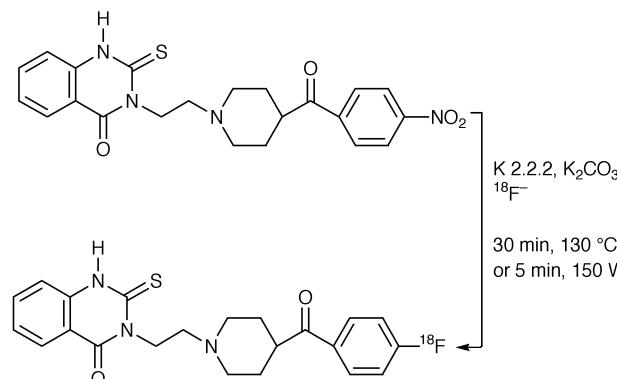
The first applications of multimodal<sup>15</sup> and monomodal<sup>12</sup> techniques in liquid phase labeling with positron-emitting radionuclides focused on this type of reaction. Microwave dielectric heating considerably reduces reaction times for many nucleophilic aromatic fluorinations to 15 s up to 5 min, depending on the equipment and substrate used. In general, the microwave yields also follow the trends observed for procedures using conventional heating and they reflect the reactivity of the substrate for nucleophilic substitution. The reductions in times for this single step represent 25–50% of the total time required for the tracer production and isolation, which explains why this application for dielectric heating has been so frequently used in the PET area.

However, there have been observations that different results may sometimes be obtained with microwave and conventional heating. For example, the trimethylammonium leaving group is readily displaced by fluoride with good yield after only 10 min at 100 °C. These substrates are particularly affected by microwave heating since the ionic groups attempt to follow the direction of the rapidly reversing electromagnetic fields. At high field strengths and/or long heating times, activated starting materials may decompose with probable elimination of trimethylamine. The evolution of gas during the process may cause a rapid build-up of pressure in closed vessels. It has been reported that silica-Teflon septa in screw caps on the reaction vessels have blown during prolonged microwave heating of these substrates. The yields of the desired fluoroaromatic will be, of course, very low. Although the decomposition may be minimised by using intense fields for very short treatment times,<sup>33</sup> caution should be exercised when attempting this reaction for the first time. It has also been observed that, for certain substrates, the fluoride may instead attack a methyl group on the trimethylammonium group, a side reaction which was detected when radioactive methyl fluoride was evolved. Using the radionuclide to follow the competition between aliphatic and aromatic attack (Scheme 10) with acetophenones, it was found that fluorination of the methyl group was favoured for the *ortho*- but not the *para*-substituent.<sup>34</sup> The authors postulated that the differences for the *ortho* compound could be caused by a possible anchimeric assistance by the ketone oxygen favouring the aliphatic substitution and/or by a steric hindrance for the ketone-aromatic resonance overlap or for the aromatic substitution by the bulky crown ether-complexed fluoride. Yields of both the aliphatic and aromatic fluorinations were much lower with conventional heating. The microwave-assisted reaction of fluoride with the *ortho*-substrate was in fact so large that this route could be optimised for the preparative synthesis of  $\text{CH}_3^{18}\text{F}$  for use as a blood flow tracer.



**Scheme 10** Competing nucleophilic aromatic and aliphatic fluorinations in acetophenone with an *ortho*-trimethylammonium leaving group.

One-step nucleophilic substitutions of  $-\text{NO}_2$  by  $^{18}\text{F}^-$  in complex aromatic substrates have benefited from the use of microwave techniques. Not only are reaction times reduced, but also there is often less decomposition and yields are improved. The fact that the aromatic substrate to be fluorinated is typically in large excess compared to the fluorinating reagent is used to drive these reactions towards completion. However, subsequent isolation of the product from the structurally similar starting materials and side-products which may arise during prolonged heating can be as difficult a task as accomplishing the fluorination. When the amounts of the nitroaltanserin precursor were varied in the synthesis of  $[^{18}\text{F}]$ altanserin (Scheme 11),



**Scheme 11** Nucleophilic aromatic fluorination in the synthesis of  $[^{18}\text{F}]$ altanserin.

consistently higher yields were obtained by using microwave treatment than by using conventional heating<sup>35</sup> (Table 7). The possibility of being able to vary the amount of substrate over a

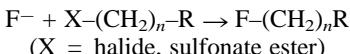
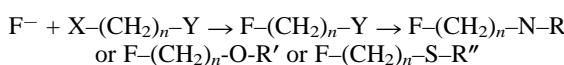
**Table 7** Yields (%) of  $[^{18}\text{F}]$ altanserin with varying amounts of substrate ( $\text{NO}_2$ -altanserin) with conventional and microwave heating

	15 mg	9 mg	5 mg	3 mg	1 mg
135 °C, 30 min	20	5–10	<5	<2	<1
150 W, 5 min	50	40	25	20	2

wider range without appreciable decreases in yields is of considerable importance in synthetic procedures where the starting materials are expensive. The same is true where the product distribution is complex and isolation difficult.

Aliphatic fluorinations, as in aromatic substitutions, may be used in one-step radiolabeling procedures as well as being one of many steps in complicated synthetic strategies. Most often fluorine is introduced into side-chains of the target molecules after first synthesising the labeling precursors, fluoroethyl and fluoropropyl halides or sulfonates, and then using them to alkylate amines, alcohols or thiols. However, these alkylations are often difficult and one-step fluorinations may instead be attempted with appropriate substrates containing a sulfonate

ester or halide leaving group. In both the one- and two-step approaches, competing eliminations or other degradations due to the basicity of the media, or the high temperatures and long reaction times may limit the yields obtained.

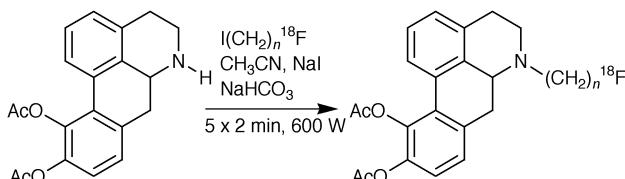


Advantages of microwave techniques for performing this type of reaction have been convincingly demonstrated in the *N*-alkylations of apomorphine and tetralin derivatives with [<sup>18</sup>F]ethyl iodide and [<sup>18</sup>F]propyl iodide.<sup>31</sup> The dielectric heating was enhanced by the addition of non-reacting sodium salts. As discussed above for the cyano-dechlorination reaction, adding ionic species to a sample in a microwave field enhances the heating effects. When sodium salts were added to acetonitrile in digestion vessels with pressure monitoring, the pressure generated during microwave treatment could be related to their solubility and amounts added. A pressure of 10 atm was reached in 0.3, 2.3 and 10 min after adding 10 mg NaI, 50 mg NaBr and 145 mg NaCl, respectively. If harnessed, these pressures could be used to drive the reactions to completion in a much shorter time. *N*-Alkylation yields with F(CH<sub>2</sub>)<sub>n</sub>I (*n* = 2 and 3) were improved by adding more NaI to the sample and performing the microwave treatment in vessels capable of withstanding the

**Table 8** Yields of fluoroalkylations of 2-[*N*-(4-fluorophenyl)ethyl]amino]-5-methoxytetralin (I) and acylated norapomorphines (II) as a function of the amount of NaI added to the reaction mixture during microwave heating

Product	$\text{I}(\text{CH}_2)_n\text{F}$	Reaction conditions	Alkylation yields with different NaI additions (%)			
			0 mg	2 mg	3 mg	4 mg
Ib	<i>n</i> = 3	5 × 1.5 min, 600 W	0.5	—	8.4	11.1
IIa	<i>n</i> = 2	6 × 1.5 min, 600 W	1.2	2.4	4.5	—
IIb	<i>n</i> = 3	5 × 1.5 min, 600 W	2.3	10.5	—	28.8

pressures generated (Table 8). The syntheses of these fluoroalkyl compounds in useful quantities and within reasonable reaction times by conventional heating were seriously hampered by their slow reaction kinetics. Tetralin yields of only 2.5–5% were obtained after heating at 120 °C for 30–60 min. In the case of the norapomorphines (Scheme 12), *O*-deacylation

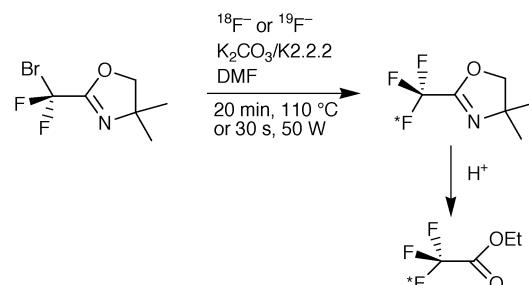


**Scheme 12** Alkylation of the secondary amine of norapomorphine with fluoroethyl or propyl iodide.

was much faster than the *N*-fluoroalkylation. Therefore, under prolonged heating, the starting material and any product that might have been formed were degraded. Almost no deacylation was observed, however, during the microwave treatment, demonstrating that the rapid microwave-assisted procedures may significantly improve the competition between desired and undesired reactions.

Another substitution reaction which benefited from the rapid heating achieved with microwaves dealt with a fluoro-debromination performed on a polyfluorinated oxazoline.<sup>36</sup> Nucleophilic substitutions on polyfluorinated compounds are often

complicated by the fact that the substrates may decompose in polar media and release <sup>19</sup>F<sup>−</sup>. Attempts to radiofluorinate such compounds will indirectly reveal the extent of decomposition since the trace amounts of <sup>18</sup>F<sup>−</sup> will not be able to compete with increasing amounts of non-radioactive fluorine in the medium. Thus, the radiochemical yields as well as the specific radioactivity of the final products will be low when the fluorine release is large. Methods which reduce the amount of fluorine-containing substrate required and/or the time they need to be heated will directly influence the quantity and quality of the final product. In the radiofluorination of the masked ester, 2-(bromodifluoromethyl)-4,4-dimethyl-2-oxazoline (Scheme 13), use of a



**Scheme 13** Fluoro-debromination of 2-(bromodifluoromethyl)-4,4-dimethyl-2-oxazoline.

microwave cavity accelerated the fluoro-debromination. Reaction times were reduced from 20–30 min to 30 s and yields were 4–6 times higher than with conventional heating. Acceptable radiochemical yields were obtained even after a 10-fold decrease in the amount of substrate. As predicted, the specific activity of the product (indicating the degree of competition with <sup>19</sup>F<sup>−</sup> in the medium) also increased as the amount of substrate was decreased (Table 9). These results demonstrate

**Table 9** Radiochemical yields (%) and specific activity of [2-<sup>18</sup>F]-2-(bromodifluoromethyl)-4,4-dimethyl-2-oxazoline achieved with microwave heating

BrCF <sub>2</sub> -oxazoline/ $\mu\text{L}$	Solvent	Conditions	Radiochemical yield (%)	Specific activity/Ci mmol <sup>−1</sup> <sup>a</sup>
25	DMF	50 W, 30 s	55	
10	DMF	50 W, 30 s	57	
5	DMF	50 W, 30 s	50	8.1
5	DMF	50 W, 15 s	59	8.6
1	DMF	50 W, 15 s	41	22.7
0.5	DMF	50 W, 20 s	37	29.2

<sup>a</sup> End of synthesis and based on starting <sup>18</sup>F<sup>−</sup> = 50 mCi.

once again that a more favorable balance between a desired reaction and decompositions or side-reactions may sometimes be achieved with focused electromagnetic fields.

Finally, one of the most often expressed doubts about using microwave techniques is related to concerns about reproducibility. This is most probably due to the fact that the results obtained are very much apparatus-dependent and therefore require that users are well acquainted with the strengths and limitations of the particular microwave device they are using. Syntheses of PET radiopharmaceuticals for immediate use in humans require not only a high degree of control and predictability, but also validation that procedures can meet the requirements of good manufacturing practice. Microwave techniques have been applied in the synthesis of the most widely used PET radiodiagnostic, 2-[<sup>18</sup>F]fluoro-2-deoxyglucose.<sup>37</sup> The use of a mono-modal device not only reduced reaction times but also increased the yields. The uncertainties in the yields as well as in the synthesis time were also decreased, illustrating that the

reproducibility of optimized microwave-based chemistry can even be superior to that of more conventional techniques.

#### 4 Acknowledgements

NE and SSE thank the Swedish Technical Research Council and the National Board for Technical Development as well as the Karolinska Institute for research grants. The work of JRJ and co-workers has been generously supported by EPSRC (previously SERC), the EU, NATO and the chemical industry over many years. We are grateful to Professor C. Strauss and Dr T. Cablewski for providing Fig. 1. This work was undertaken as part of the EU sponsored D10 COST Programme (Innovative Methods and Techniques for Chemical Transformations).

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