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Review Article

Radiohalogen incorporation into organic systems

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Summary

This Review reports the more recent applications of radiohalogen labelling in organic compounds. Modern synthetic methods place more emphasis upon substitution at specific sites. Electrophilic substitution, especially at aromatic carbon atoms, involves displacement of halogen or of metals rather than the earlier popular halogen-deprotiation processes. Nucleophilic displacement, at either aliphatic or aromatic sites, has also become widespread since it may be made more selective by the inclusion of appropriate activating groups or suitable displaced groups. Microwave and thermally induced methods are both reported with a critical assessment of the value of each process. Copyright © 2002 John Wiley & Sons, Ltd.

Key Words: radiohalogen; bromine; fluorine; iodine; substitution; halogenodemetallation

Review

The inclusion of radiohalogens into organic structures may be achieved by many of the conventional processes of organic chemistry. For example, electrophilic halogenation of (activated) aromatic systems by molecular iodine or bromine has been widely applied because the mechanism of the process and the stability of the reaction product to the reaction conditions are well known or readily deduced. The present

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Review reports the more recent methods by which the radiohalogens have been introduced into organic structures, and occasionally reflects changes in the popularity of the various synthetic processes.

The chemistry of these processes is also important. For this reason, the organic substrates which are mentioned in this review are usually named systematically, and their structures given, so that the nature of the halogenation, the function of activating or directing substituents, and the role of the reaction conditions may be appreciated. The nomenclature used in the review identifies the radiohalogen before naming the compound in which it occurs. Where there is only one halogen atom which has been labelled (e.g. [F-18]-4-fluorotoluene; [F-18]-1-chloro-2-fluoronaphthalene) no further information is necessary. Where confusion may occur, a prefix identifying the positions, the radioisotope, and the number of radiolabelled atoms is used (e.g. [2,4-F-18(2)]-pentafluorobenzene; [α-F-18(3)]-octafluorotoluene).

The Review focuses particularly upon work reported since 1990, with some references to material published in 2001. Significant earlier material is included, especially convenient methods of synthesis of the radiohalogens and the ways by which the necessary reagents for halogen incorporation are obtained. Oxidative halogenation – for example, iodination achieved using NaI and chloramine-T, dichloramine-T, iodogen or iodobeads – are reported without giving the detailed chemical identity of these commercially available oxidants. Similarly, when crown ethers or cryptands are used to facilitate the solubilisation and 'ionisation' of metal halides in nucleophilic halogen exchange reactions (e.g. 18-crown-6 or [2.2.2]-1,4-diazabicyclooctane or Kryptand [2.2.2]) these complexing agents are given their more trivial names rather than their more correct chemical names. Lastly, when microwave energy is used to bring about a chemical reaction the irradiating frequency (when available), power and time are given for the same reason as reaction temperature is reported in thermally activated processes: they are reflections of the energies driving the processes, and allow other experimenters to reproduce the reported reaction conditions.

Fluorine: general considerations[1,2]

[F-18]-Fluorine may be obtained by the proton-irradiation of water targets enriched in [O-18]. An example of the experimental conditions is the use of a 16 MeV beam of protons at 15 γA impinging upon a 50% [O-18]-water target over one hour. Alternatively, bombardment of

neon-20 with 15.7 MeV deuterons provides [F-18] through the sequence $^{20}Ne(d,\alpha)^{18}F$. A critical assessment of methods of preparation of [F-18] has been published recently.[3] The radio-fluoride is present as F^- and subsequently [F-18] may be introduced to other reagents by displacement reactions, either of fluorine (as in the labelling of elemental fluorine), or other halogens or displaced groups ($-NO_2$, $-N_2^+$); high specific activities may be achieved. The half-life of [F-18], 109.8 min, allows most but not all of the available methods of organic chemistry to be applied in the synthesis of labelled fluorocarbons. This has meant that some of the older preparative methods have been re-visited.

An example is the displacement of nitrogen from an aromatic diazonium ion by fluoride. Owing to the relatively high basicity of fluoride ion in aqueous media, diazonium ion reactions with it are often carried out in non-aqueous conditions. The Balz–Schiemann reaction, in which the dry diazonium tetrafluoroborate (or, less often, hexafluorophosphate) is pyrolysed, reflects these considerations. It is wasteful of fluorine, since 75% of the halogen is lost as BF_3 (or 83% as PF_5) in the pyrolysis, and satisfactory drying of the diazonium salt takes several hours, or some half-lives if [F-18] is involved. Radio-fluorine could, of course, be recycled by trapping BF_3 or PF_5 with F^-, but the process is time-consuming during which radioactive decay occurs inevitably. High specific activities of fluorine in an aromatic system are not achieved readily in such situations. However, a study of the efficacy of a number of salts of the 4-methylphenyldiazonium ion in their reaction with n.c.a. labelled F^- concluded that the 2,4,6-triisopropylbenzenesulfonate was the most useful, affording [F-18]-4-fluorotoluene in 39% yield.[4]

The more recent wide availability of anhydrous hydrogen fluoride has improved the operation of the Balz–Schiemann reaction by removing, almost completely, the opportunity for water to interfere in the synthesis; aromatic primary amines may be diazotised in anhydrous HF which is then allowed to boil away, during which the diazonium ion decomposes to provide the aryl fluoride. Obviously this method has no place in the synthesis of [F-18]-labelled materials.

In 1886 Wallach observed that diazonium ions may be converted into triazenes ($ArN=N-NR_2$), and that the triazenes could then be decomposed in 40% aqueous HF. This method gave modest yields of fluoroarenes, but was popular until it was superceded by the Balz–Schiemann technique. It became popular again in the latter half of the last century as a means of incorporating radio-fluorine, and other radiohalogens, into aromatic systems; although the resulting organic

fluorides may not always be chemically pure the Wallach process gave the opportunity to incorporate moderate levels of [F-18] into organic structures. The next section of this review deals with present-day means of attaching [F-18] to organic molecules.

Electrophilic fluorination

Fluorine[F-18] may be introduced into aromatic systems by electrophilic processes, similar to those seen with the heavier halogens, and by nucleophilic processes in which fluoride ion displaces another group (often activated by electron withdrawal).[5] Electrophilic molecular fluorination of an aromatic system is usually not very sensitive to substituent effects; an example is the formation of fluorobenzene together with isomeric difluorobenzenes in the low-temperature reaction of benzene with fluorine. This is consistent with the greater chemical reactivity of fluorine compared with the greater selectivity of bromine or iodine, and has the consequence that a number of isomeric fluoroarenes result, with a corresponding difficulty in obtaining a single pure fluorinated product. This effect is seen in the 'direct' fluorination of 3-*O*-methyl-DOPA by acetyl hypofluorite (≡fluorine acetate) to give 3-*O*-methyl-2- and 6-[F-18]-fluoroDOPA,[6,7] though acetyl hypofluorite[8] is apparently selective in the synthesis of [F-18]-L-4-fluoro-*o*-tyrosine.[9] Regioselective substitution of arenes is also reported to take place with [F-18]-*N*-fluoro-*N*-alkyl-sulfonamides.[10] Greater selectivity may be achieved through fluoro-demetallation. For example, trialkylstannyl groups are removed by acetyl hypofluorite or by elemental fluorine,[11] as in the synthesis of [F-18]-3-*O*-methyl-6-fluoro-DOPA.[12] The fluorinolysis of aryl-silicon bonds in aryltrialkylsilanes also affords a selective means of inserting radio-fluorine regiospecifically into aryl systems.[13,14] The displacement is more selective than the corresponding displacement of hydrogen, though it is still somewhat wasteful of the halogen isotope, as the equations reflect:

$$ArSnR_3 + F_2 = ArF + R_3SnF;\ ArSiR_3 + F_2 = ArF + R_3SiF$$

$$\text{cf. } ArH + F_2 = ArF + HF$$

Nucleophilic fluorination[15]

Nucleophilic attack[16] involves the displacement of another fragment by fluoride ion. This process is rather more selective, since it usually

requires activation by an electron-withdrawing substituent (e.g. $-NO_2$, CF_3, halogen, $-N_2^+$) whose effect is greatest when the activator is *ortho-* or *para-* to the site of attack. For example, $\rho^- = 6$ for KF attacking polychlorinated benzenes in sulfolan.[17] Fluoride ion is quite a strong nucleophile in non-aqueous media, where side-reactions involving the conjugate base of a comparatively acidic solvent (HO^- from water; RO^- from ROH) do not interfere. Nucleophilic displacement also requires a labile group. Fluorine and the nitro-group are the most readily expelled of the electrically neutral groups, though the trialkylammonium substituent is also very easily lost. This observation[18] led to an attempt to link success in nucleophilic radio-fluorination with [C-13]-NMR chemical shifts in the displacement of fluorine, nitro, and trialkylammonium groups from aryl aldehydes, ketones, and nitriles. Good agreement was found in the displacement of fluorine and the $-NO_2$ group, but not of $-NR_3^+$, presumably because of ionic interactions.[19]

The usual objection to linking spectroscopic and kinetic properties of a substrate applies. The spectroscopic observations refer to the ground state of a molecule, and an energy difference between this and some excited state of some part of the molecule which may be as small as an atomic nucleus. The kinetic observations deal with energy differences between the ground state of the substrate and that of some transition state perhaps involving both interactions by a second reagent species (molecule, radical or ion) and, in solution, changes in solvent molecule interactions which themselves are often sufficient to drive an otherwise thermodynamically improbable process. Although *empirically* the two energy functions may be found to change proportionately, especially within a closely similar set of substrates or reagents (cf. Hammett equation), there is little *theoretical* reason why the relationship should occur.

The other halogens are rather less easily removed by nucleophiles. Bond-forming rather than bond-breaking is significant in the slow step of the displacement, and the polarisation of the attacked bond is more important than the strength of the bond being broken in the subsequent and faster process in which the Meisenheimer intermediate reverts to aromatic stability.

In these cases, the selective attack at one site occurs through a combination of (a) the extent of activation of the reaction site by electron-withdrawing groups and (b) the ease of removal of the displaced group. Consideration of both these properties of the substrate molecule is essential.

Diaryliodonium cations ($[Ar–I–Ar']^+$) are easy to obtain – for example, by the acid-catalysed electrophilic attack by iodosobenzene (Ar–I=O) upon aromatic systems, and by electrochemical oxidation of aryl iodides in mixtures of acetic acid (70%), acetic anhydride (25%) and sulfuric acid (5%) which also contain an arene which is suitably susceptible to electrophilic attack.[20] In the presence of halide ions, these iodonium ions fragment to give an iodoarene and a halogenoarene. Either C–I bond in an unsymmetrical iodonium cation may break and, in the absence of directing groups, both options occur:

$$[Ar-I-Ar']^+ + X^- = ArI + ArX + Ar'I + Ar'X$$

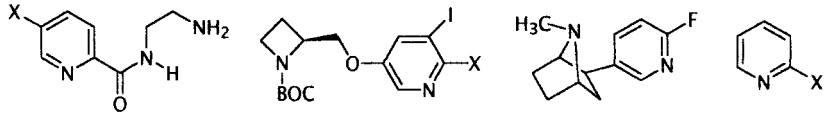
The reaction involves a formal nucleophilic attack upon the cation, similar to the halogen exchange reactions discussed previously. This interpretation is supported by the effects of aryl substituents such as *p*-NO_2 and *p*-OMe upon the direction of cleavage although even early kinetic studies of the process implied a free-radical component to the reaction. This was shown by the effects of copper catalysts and of radical inhibitors, and implied similarities with more mechanistically complicated processes such as the Sandmeyer reaction.[21]

Regardless of the mechanistic complexity, halide-ion cleavage of iodonium ions has recently been used to insert [F-18] into aromatic rings.[22] In principle, other radiohalogens may also be inserted. The reaction has the expected limitations that the structure must be resistant to the reaction conditions, which in some cases may be both strongly acidic and oxidising. On the other hand, many pharmacologically active compounds contain electron-rich aromatic rings as a result of –OH, –OR, or amino substituents, and these are expected to undergo ready electrophilic attack by PhIO to form diaryliodonium ions. The orientation of cleavage, however, may then place the iodine atom in the desired molecule and the entrant halogen upon the phenyl group, and so offer little advantage over a direct electrophilic halogenation. Diaryliodonium ion cleavage has been claimed as more selective than direct electrophilic fluorination, and to give products with much higher specific activities.

Similar displacements might be anticipated using pyrylium ions or, particularly, pyridinium ions such as those shown by Katrizsky to afford a route to fluoro-alkanes or arenes.

Fluorine: specific systems

Aromatic nucleophilic substitution. The pyridine aromatic system activates nucleophilic aromatic attack substantially, especially at the 2- and 4-positions, so that no furthur electron-withdrawal is usually required. *N*-(2-Aminoethyl)-5-chloropyridine-2-carboxamide (Ro 19-6327; **1**, X = Cl) powerfully inhibits monoamine oxidase B. This reversible inhibition is site-specific. The 5-fluoro (**1**, X = F) and 5-iodo (**1**, X = I) analogues have been prepared, since [F-18] and various of the iodine isotopes are readily available, and allow PET (Positron Emission Tomography) and SPET (Single Photon Emission Tomography) applications.[23] Displacement usually occurs at sites *ortho*- or *para*- to the endocyclic nitrogen atom, so that the [F-18]-6-fluoro-derivative of **2** (X = ^{18}F) is the only product of fluorodeiodination of the 5,6-diiodo-compound **2** (X = I).[24] Similarly, the preparation of [F-18]-'norchlorofluoroepibatidine' (NFEP) shows an unusually high yield (70%) in the fluorodeamination of 7-tert-butyloxycarbonyl-exo-2-(2′-N,N,N-trimethylammonium-5′-pyridinyl)-7-aza-[2.2.1]-heptane iodide. Deprotection with trifluoroacetic acid and reductive methylation (CH_2O-$NaCNBH_3$) provided exo-2-(2′-fluoro-5′-pyridinyl)-7-methyl-tropane (**3**).[25,26]

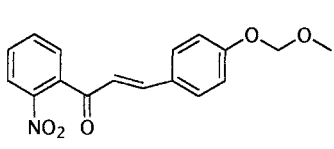


1 **2** **3** **4**

Incorporation of [F-18] may be complete and high specific activities are achievable by nucleophilic displacement, provided that the back-reaction does not contribute greatly.[27] This was the assessment of Ametamey and his co-workers who evaluated various routes to the 5-fluoropyridyl derivative **1** (X = ^{18}F) and concluded that nucleophilic fluorination gave better yields of more highly isotopically enriched material.[23] An even more exhaustive study of the synthesis of [F-18]-2-fluoropyridine (**4**, X = ^{18}F) by nucleophilic displacement of a number of groups concluded that microwave irradiation (100 w, 1 min) was at least as effective as conventional thermal conditions (180°, 5 min) in encouraging such reactions. The order of displacement was X = NMe_3^+ (96%; 88%) > NO_2 (88%, 77%) > Br (-, 71%) > Cl (-, 22%), in which the first figure in parentheses represents the yield of 2-fluoropyridine under microwave conditions, and the second shows the yield under thermal reaction conditions, both with DMSO as solvent.[28]

Carbonyl and allied systems

The best yields of [F-18]-4-fluoroacetophenone are obtained (21%; DMSO, Kryptand [2.2.2], 160°, 20 min) when the (4-acetylphenyl) trimethylammonium cation reacts with labelled KF.[29] In the three-stage synthesis of SR46349B,[30] *trans*-1-(2-nitrophenyl)-3-(4-methoxymethoxy-phenyl)-2-propenone (**5**) was treated with n.c.a. [F-18]-fluoride anion in the presence of Kryptofix and K_2CO_3 to give the labelled fluoro-ketone which then, by condensation, gave the desired product (5% radio-chemical yield, 1140 Ci mmol^{-1} EOB, 96% radio-chemical purity).



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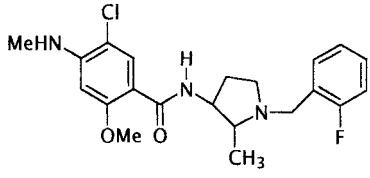

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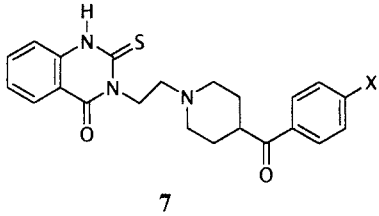
Fluorodenitration has been used in the synthesis of *o*- and *p*-[F-18]-fluorobenzaldehydes (and the derived benzyl alcohols and halides which were used, for example, in the synthesis of [F-18]-labelled *cis*-*N*-[(2RS,3RS)-1-(2′-fluorobenzyl)-2-methyl-3-pyrrolidinyl]-5-chloro-2-methoxy-4-methylaminobenzamide, **6**).[31] The -CHO group is an effective activator of the nucleophilic displacement of nitrite. Yields of 55–70% of [F-18]-2-fluorobenzaldehyde are reported from Kryptofix-encouraged nucleophilic attack of 2-nitrobenzaldehyde by [F-18]-KF in a synthesis of 2-fluoro-2′-aminobenzhydrols leading to various benzo-diazepinones.[32] The $-NMe_3^+$ group is displaced very readily when (4-formylphenyl)trimethylammonium triflate is treated with $^{18}F^-$. The resulting 4-fluorobenzaldehyde may be reduced ($NaBH_4$) to the alcohol, which is further converted into 4-fluorobenzyl bromide (Ph_3PBr_2); both steps proceed nearly quantitatively.[33] Activation by a ketone function is seen in the synthesis of [18-F]-fluoroaltanserin (**7**, X = F) from the nitro-analogue (**7**; X = NO_2).[34]

In the synthesis of Ro41-0960 (**8**) fluoride ion selectively substituted the 2-nitro group in 3,4-dimethoxy-2′,5-dinitrobenzophenone, a tribute to the activating properties of the *ortho*-acyl substituent. The 4-methoxy group, however, was made electron-poor by the combined effects of the adjacent nitro-group and the acyl fragment. This was demonstrated by the formation of much [F-18]-fluoromethane during the nucleophilic displacement step.[35]

Comparable activation by the ester function is seen in one synthesis of [18-F]-4-fluorobenzoic acid from **9**[36] and in the preparation of a labelled 4-fluorobenzoate (Kryptand [2.2.2], DMSO, 90°, 0.5 h).[37] Even the carboxyl group of an amide will suffice, as in the synthesis of [18-F]-4-fluoro-*N*-{2-[4-(6-trifluoromethyl-2-pyridinyl)-1-piperazinyl] ethyl}benzamide **10** (s.a. > 18.5 TBq mmol^{-1} 500 Ci mmol^{-1}. Microwave energies, 700 W, 5 min).[38] The sulfonamido fragment causes similar activation.[39]



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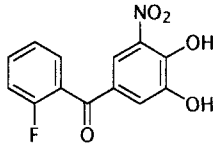

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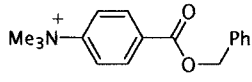


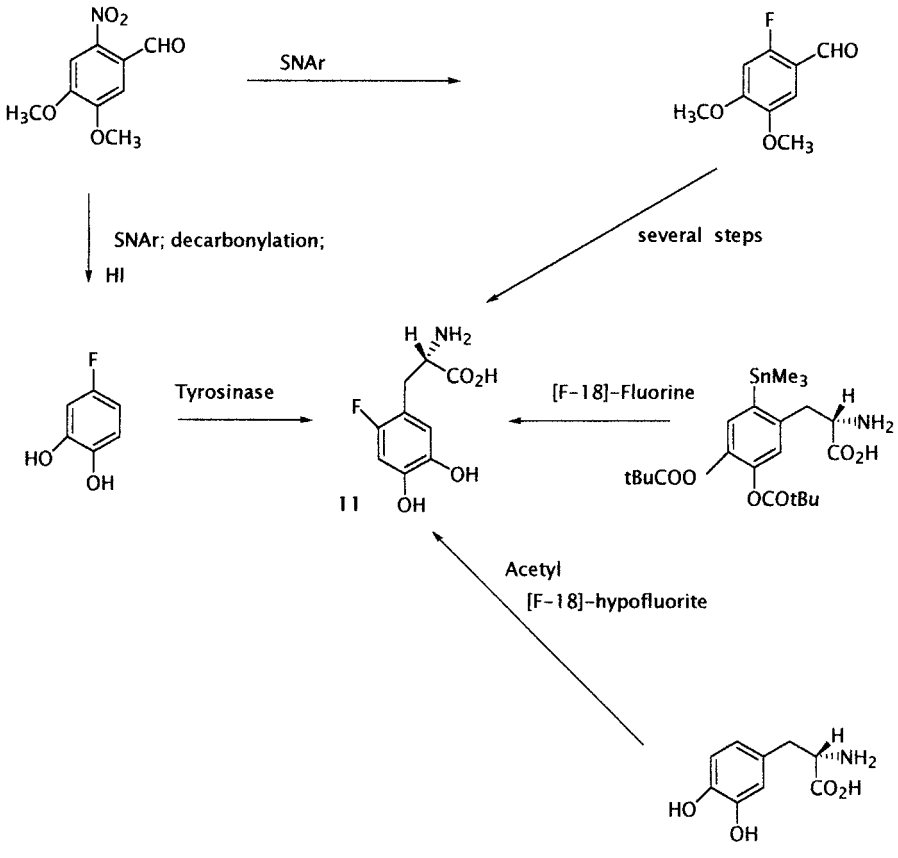
9

The first step in a synthesis of 6-[F-18]-fluorodopamine involves n.c.a. [F-18]-fluoride nucleophilic attack upon 6-nitropiperonal (3–10%, decay-corrected, EOB).[40] In another report, the resulting [F-18]-6-fluoropiperonal (KF, Kryptand [2.2.2], DMSO, 145°, 20 min) is decarbonylated and demethylated to provide [18-F]-4-fluorocatechol from which labelled 6-fluoro-L-DOPA (**11**; Scheme 1) is obtained by an enzymatic reaction using β-tyrosinase.[41] Other methods involving electrophilic fluorination are discussed later.

The cyano substituent is also a potent activator towards nucleophilic displacement.[37] Labelled 4-fluorobenzonitrile is similarly prepared from 4-(cyanophenyl)trimethyl-ammonium triflate and [18-F]-KF in DMSO.[42] This process was also used in the preparation of [F-18]-*N*-hydroxysuccinimidyl 4-fluorobenzoate via 4-fluorobenzonitrile.[43]

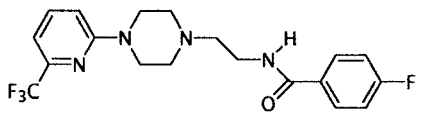
The cyano-group encourages fluorodenitration (67% radio-chemical yield) and fluorodechlorination (35% yield) in the preparation of 4-fluorobenzonitrile, the starting point in the synthesis of [F-18]-labelled haloperidol. Halogen exchange with haloperidol itself (**12**; X = F; 5% yield; s.a. 1 Ci mmol^{-1}) or with the chloro-analogue (X = Cl; 2–3% radio-chemical yield; s.a. 5000 Ci mmol^{-1}) may also be achieved with [F-18]-Bu_4NF in DMSO for 15 min at 150–155°. The low specific activity when haloperidol itself is used is probably a reflection of the isotopic dilution which inevitably results.[44]

As an aside, there are in fact two aryl chlorine systems in the chloro-analogue of haloperidol. Both have *p*-substituents, but only the one with an electron-withdrawing acyl substituent undergoes halogen exchange.



Scheme 1. Routes to [F-18]-6-fluoro-DOPA and derivatives

The other has an alkyl system in the 4-position, which is effectually electronically neutral and confers no reactivity towards nucleophiles.



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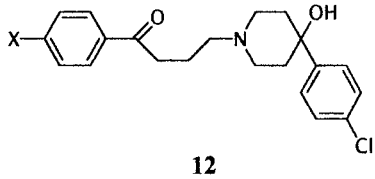
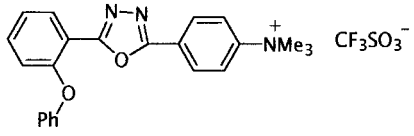


12

A recent example of the speed with which $-NMe_3^+$ is displaced in aromatic systems is found in the reaction of *N,N,N*-trimethyl-4-[(2-phenoxy)phenyl-1,3,4-oxadiazole-5-yl]-anilinium triflate (**13**) with [F-18]-KF and Kryptofix, which took place at 90° in DMSO to give the labelled fluoro-analogue (15 min, 70–75% radio-chemical yield, 3000 Ci mmol^{-1}).[45]



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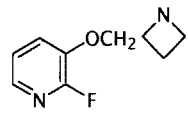
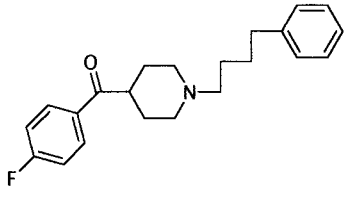


14

The synthesis of 2-[F-18]fluoro-3-[(2S)-2-azetidinylmethoxy]pyridine (**14**) is reported to involve fluorodenitration in DMSO. Both conventional conditions (150°, 20 min) and microwave conditions (100 w, 1 min) are reported for the reaction. After 105–110 min, 110–140 mCi of material with a specific activity of 1500–2500 Ci mmol^{-1} could be obtained.[46] Kryptofix-[2.2.2] also facilitated the formation of n.c.a. 2-[F-18]fluoro-3-((2S)-azetidinylmethoxy)pyridine from the *N*-BOC-protected 2-iodo-analogue.[47] Fluorodenitration, activated by an acyl substituent, also is used in the synthesis of *N*-(4-phenylbutyl)-4-(4-fluorobenzoyl)piperidine (4-PBFBP, **15**), again using Kryptofix [2.2.2] in DMSO with [F-18]-F$^-$.[48]



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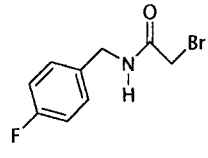

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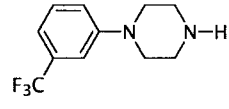


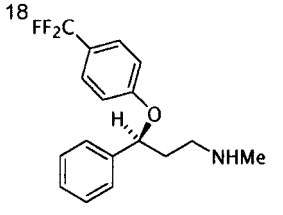
17

Oligodeoxynucleotides may be labelled by incorporating small molecules containing a radio-label. *N*-(4-Fluorobenzyl)-2-bromoethanamide (**16**) may be prepared with [F-18] labelling, and subsequently introduced into appropriate nucleotides (those with a phosphorothiolate group at the 3′-end) at substantial levels so that activities of 750 Ci mmol^{-1} (EOS, after two half-lives) or about 30 mCi are reported. The analogous incorporation of [Br-76] or [I-123] in the *para*-position of the benzyl group is an expected extension of the work.[49]

Aliphatic halogen exchange

Bromine and chlorine displacement. The displacement of bromine from ethyl bromodifluoroacetate by [F-18]-KF (5 min, 80°, DMSO, 45–60%) is the first step in a published synthesis[50] of [2-F-18(1)]-2,2,2-trifluoroethyl triflate. However, there seems to be evidence of substantial scrambling of halogen, for although no carrier was added

to the [F-18]-KF the resulting ethyl trifluoroacetate contained much unlabelled material. The product was isolated by removal in a gas stream, when the separation of less fully fluorinated material of similar b.p. is unlikely and no evidence for the chemical identity of the product was given. The synthesis of 1-[3-([ααα-[F-18]-trifluoromethyl)phenyl]-piperazine (**17**)[51] relies upon similar chemistry. The synthesis of [α-F-18]-4-chlorobenzotrifluoride by nucleophilic displacement is an essential step in the preparation of [F-18]-(S)-*N*-methyl-3-[4-(trifluoromethyl)-phenoxy]-3-phenylpropylamine (**18**; s.a. 100–150 Ci mmol^{-1}; 9–10% radio-chemical yield (decay-corrected); total synthesis time, 150 min).[52]



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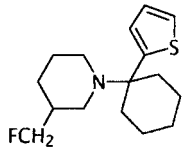

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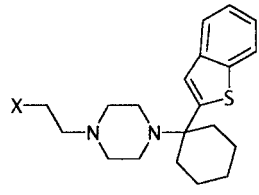

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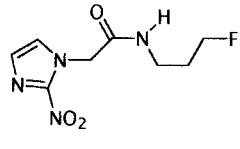
Fluorodebromination is the essential step in preparing labelled [F-18]-SR144385 (s.a. 1850 Ci mmol^{-1}),[53] and 3-[F-18]-fluoromethyl-1-[1-(2-thienyl)cyclohexyl]piperidine (**19**),[54] though [F-18]-1-[1-(2-benzo-(b)thiophenyl)-cyclohexyl]-4-(2-fluoroethyl)-piperazine (**20**, X = F) was obtained from the corresponding chloroethyl compound (**20**, X = Cl).[55] 2-(2-Nitroimidazol-1[H]-yl)-*N*-(3-fluoropropyl)acetamide (**21**) was obtained in 2% yield from the 3-bromopropyl-analogue.[56] [F-18]-Fluoromethyl halides (F.CH_2.X; X = Br or I) have been made from the appropriate dihalogenomethane, CH_2X_2.[57]



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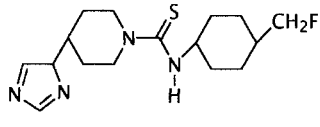

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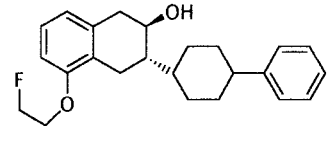

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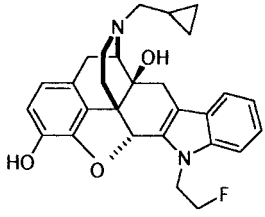
Such displacements brought about the syntheses of *N*-(*cis*-4-[F-18]-fluoromethylcyclohexyl)-4-(1(H)-imidazol-4-yl)piperidine-1-thiocarbonamide (VUF 5000, **22**; 23% radio-chemical yield, s.a. 2600 Ci mmol^{-1}, 4 h after EOB),[58] of [F-18]fluoroethoxybenzovesamicol (**23**; (−)-(2R,3R)-*trans*-2-hydroxy-3-(4-phenylpiperidino)-5-(2-[F-18]fluoroethoxy)-1,2,3,4-tetralin[59] and of [F-18]-*N1′*-(2-fluoroethyl)-naltrindole (**24**; 10% radio-chemical yield, uncorrected, s.a. 846 Ci mmol^{-1}, 77 min

EOB).[60] When 2-*O*-methanesulfonyl-β-D-mannopyranose was treated with Kryptofix and [F-18]KF in the presence of K_2CO_3 at 60° in CH_3CN-THF the formation of a mixture of 1-α- and 1-β-glucopyranosyl [F-18]-fluorides surprised the researchers, who were unable to find conditions to prevent this rearrangement.[61] The synthesis of [1,2-F-18(2)]-2-deoxy-2-fluoro-β-mannosyl fluoride[62] and of [F-18]-2-fluoro-2-deoxy-D-glucose[63–65] have also been reported. A column containing cationic groups (-PBu_3^+ or dimethylaminopyridinium) was used to extract and retain [F-18]-fluoride ion,[66] providing an exceptionally effective environment for the synthesis of 2-deoxy-2-fluoro-D-glucose in >70% radiochemical yield (EOB).[67] 3,4-Di-*O*-acetyl-6-*O*-trifluoromethanesulfonyl-2-deoxy-2-fluoro-D-glucopyranosyl fluoride similarly gave the corresponding [F-18]-6-fluoride.[68]



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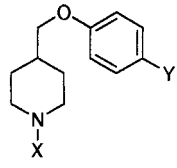

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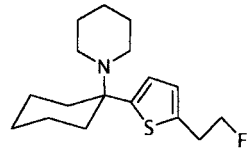

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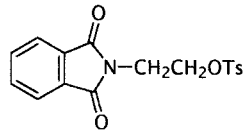
Mesylate and tosylate displacement

Displacement of mesyloxy (methanesulfonyloxy-) or tosyloxy (4-methylbenzenesulfonyloxy-) fragments nucleophilically is the basis of a synthesis of n.c.a. potassium [F-18]-fluoroacetate in which ethyl *O*-mesyl or *O*-tosylglycollate reacts with fluoride.[69] [F-18]-2-Fluoroethyl systems have been obtained by the displacement of mesylate,[70] tosylate,[71,72] and triflate[73] functions; the [F-18]-3-fluoropropyl system has been obtained analogously, as from 3-bromopropyl triflate (KF, MeCN, 120°, 2 min, 65–78%).[74] The synthesis of [F-18]-2-fluoroethylamine has also been reported recently.[75] Nucleophilic displacement of mesylate led to [F-18]-1-(3-fluoropropyl)-4-([4-cyanophenoxy]methyl)-piperidine (**25**, X = $-(CH_2)_3F$, Y = CN. 56–70% yield EOB, s.a. 74 TBq $mmol^{-1}$, >95% radio-chemical purity, 80 min reaction time),[76] and to (1S*,2R*)-2-(methoxymethoxymethyl)- and (1S*,2R*)-2-(hydroxymethyl)-1-(*N*-piperidyl)-1-[2-(2′-[F-18]fluoroethyl)thienyl]cyclohexane (**26**, R = MeO.CH_2O– or HO–) in 4–4.5% radio-chemical yield and s.a. of >31 GBq mol^{-1}.[77] Similarly, fluorodetosylation introduced [F-18] at the first stage of a synthesis of [F18]-*N*-(2-fluoroethyl)-*N*′-methylthiour-

ea ([F-18]FEMTU), in which *N*-[2-(*p*-toluenesulfonyloxy)ethyl]phthalimide (**27**) was treated with [F-18]-KF. Although the hydrolysis stage of the Gabriel synthesis is notoriously difficult in some systems, the authors were able to use the Ing modification to provide labelled 2-fluoroethylamine, and made this amine react with methyl iso-cyanate to give the desired labelled material (s.a., 3.3 ± 0.5 TBq mmol^{-1}).[78]



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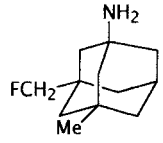

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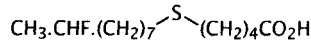

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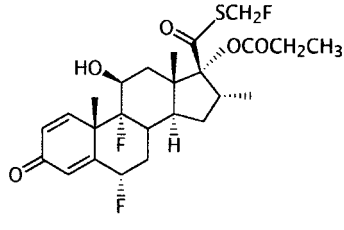
Kryptofix-[2.2.2] was used to assist the attack by [F-18]-KF in DMSO upon the 3-(tosyloxymethyl) function in the synthesis of 1-amino-3-[F-18]fluoromethyl-5-methyladamantane (F-18-MEM, **28**),[79] and for the same displacement in the synthesis of (R,S)-[F-18]-14-fluoro-6-thiaheptadecanoic acid (**29**, FTHA; 35–65% yield of >98% pure material after 50 min).[80] Displacement of a tosyloxy function by [F-18]F^- was also central to the synthesis of fluticasone propionate ((S)-[[F-18]-fluoromethyl]-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carbothioate, **30**); interestingly, the chosen synthetic method involved preparing the necessary tosylate from the chloromethyl derivative, which implies that direct halogen exchange was not an effective synthetic route here.[81] [F-18]-4-Fluoro-*N*-(1-(2-thienyl)cyclohexyl)piperidine (**31**), in contrast, was prepared by mesylate displacement.[82] Either mesylate or tosylate may be successfully used when *bis*-1,4-benzenedimethanol (**32**) is converted into the diester, reaction of which with [F-18]-fluoride ($Bu_4N^+OH^-$, THF, 90°, 5 min) gave the corresponding ester of 4-(fluoromethyl) benzyl alcohol.[83]



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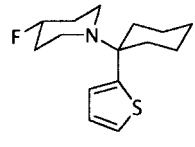

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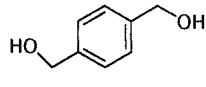

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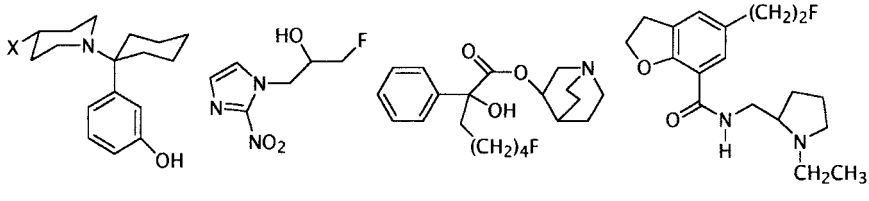
Nucleophilic displacement was central to syntheses of 4-fluoro- and 4-iodo-1-[1-(3-hydroxyphenyl)cyclohexyl]piperidines (**33**), and the

[I-123]-labelled derivative (**33**, X = ^{123}I) could be readily obtained through displacement of the mesylate group from the appropriate precursor (40% radio-chemical yield). The unlabelled iodo-compound was made in 54% yield, using 3 molecular equivalents of Bu_4NI, with no evidence of competition by elimination reactions. In contrast, Bu_4NF (3 equivalents) in MeCN caused extensive elimination (97%) with only very little fluorodemesylation (3%). The situation was no better (0–4% radio-labelling) when [F-18]-KF was used, with or without added Kryptofix. In this instance, perhaps the added cryptand would not be expected to encourage substitution, since its function would be to free the fluoride ion from the countercation rather than affecting the relative nucleophilicity and basicity of the generated halide ion.[84]

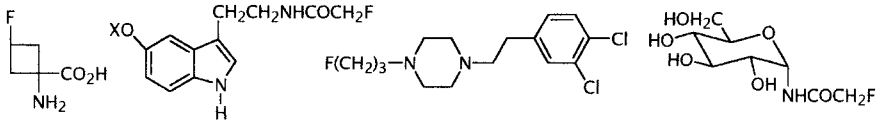
[F-18]Fluoromisonidazole (1H-1-(3-[F-18]fluoro-2-hydroxypropyl)-2-nitroimidazole, **34**) has been prepared from [F-18]-KF and (R)-(−)-glycidyl tosylate. The process took ca. 80 min, giving a radio-chemical yield of 20%, and radio-chemical purity > 98%).[85]



33 **34** **35** **36**

l-Azabicyclo [2.2.2]oct-3-yl α-(1-fluoropent-5-yl)-α-hydroxy-α-phenylacetate (**35**; FQNPe) has been separated into its four stereoisomers, of which the (RR)- and (RS)-forms have been obtained labelled with [F-18] in a two-step process giving 12–21% radio-chemical yield.[86] The 2-fluoroethyl fragment in *N*-[(1-ethyl-2-pyrrolidinyl)-methyl]-5-(2-[F-18]fluoroethyl)-2,3-dihydrobenzofuran-7-carboxamide (**36**; s.a., > 15-Ci mmol^{-1}; 7% yield) was similarly prepared.[87] An early synthesis of [F-18]-fluoromethane from labelled fluorine first treated the halogen with Ag_2O-$Et_4N^+OH^-$ to provide labelled F^-. In the presence of silver ion, iodomethane reacted rapidly to give the required fluoro-alkane in an elegant process in which no labelled fluorine need be lost as F^-.[88]

Triflate displacement by fluoride ion was used to insert [F-18] in the synthesis of 1-amino-3-fluorocyclobutane-1-carboxylic acid (**37**; FACBC),[89] while the similar displacement of tosyloxy or bromo substituents provided [F-18]-derivatives of some diacylglycerols.[90]

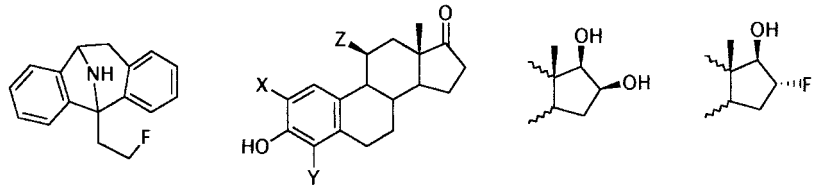


37 **38** **39** **40**

The first stage of a rapid (90-min) synthesis of *Nω*-[F-18]-fluoroacetylserotonin (*Nω*-[F-18]fluoroacetyl-5-hydroxytryptamine, **38**, X = H)[91] and of *Nω*-[F-18]-fluoro-acetylmelatonin (*Nω*-[F-18]fluoroacetyl-5-methoxytryptamine, **38**, X = CH_3)[92] introduces the label by the reaction of [F-18]-KF with ethyl *p*-tosyloxyacetate; the synthesis of [F-18]-20-fluoroarachidonic acid, and the preparation of the labelled dihalogenopropane intermediate in the synthesis of 1-(3-[F-18] fluoropropyl)-4-(2-[3,4-dichlorophenyl]ethyl)piperazine (**39**),[93] involve similar displacements. The preparation of 2-deoxy-2-[F-18]fluoroacetamido-D-glucopyranose (*N*-[F-18]fluoro-acetyl-D-glucosamine, **40**)[94] and [F-18]-5-(2-fluoroethyl)-10,11-dihydro-5H-dibenzo-cycloheptene-5,10-imine (**41**)[95] also uses the same chemistry.

Ring-opening by fluoride ion

In contrast, [F-18]-1-(2-nitro-1-imidazoyl)-3-fluoro-2-propanol (**34**) may be obtained by ring-opening of the epoxide system in 2-nitro-*N*-(glycidyl)imidazole.[96] Ring-opening of epoxides has been used to incorporate radiohalogens in a few instances, especially those involving sugar chemistry. They are mentioned in the appropriate sections of this review. While direct substitution of estrone (**42**, X = Y = Z = H) and 11*β*-methoxyestrone (**42**, X = Y = H; Z = OCH_3) by *N*-fluoropyridinium cation gave a mixture of the 2- (X = F, Y = H, Z = H or OCH_3) and 4-fluoro (X = H, Y = F, Z = H or OCH_3) analogues, the corresponding 16*β*,17*β*-diols (partial structure, **43**) gave a cyclic sulphate ester which, with [F-18]-fluoride ion, gave exclusively the [F-18]-16*α*-fluoro-17*β*-hydroxy systems, **44**.[97]

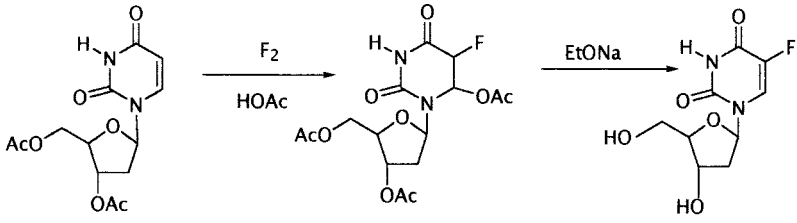


41 **42** **43** **44**

Addition processes

Addition across a double bond by a fluorine derivative XF, and subsequent elimination of the elements of HX, affords a means of radiofluorinating structures if they are resistant to the combination of reagents to which they are then exposed. An example, based upon a previous description of [F-18]-2-deoxy-2-fluoro-D-glucose,[98] is the preparation of [F-18]-5-fluoro-2′-deoxyuridine. A solution of labelled fluorine in acetic acid is used to add what is formally 'fluorine acetate' across the 5,6-double bond. Elimination of acetic acid by treatment with NaOEt provides (**45**).[99] The synthesis of [F-18]-5-deoxy-5-fluorouridine was achieved exactly analogously.[100]

Labelled acetyl hypofluorite reacts with 3,4,6-*O*-triacetyl-2-fluoro-D-glucal to give, after deprotection, 2-deoxy-2,2-[F-18]-difluoro-glucose.[101] [F-18]-2′-Fluorodeoxy-lactose (*β*-*O*-D-galactopyranosyl-(1,4′)-2′-[F-18]-fluoro-2′-deoxy-D-glucopyranose) results enzymatically from [F-18]-2-fluoro-2-deoxyglucose.[102]



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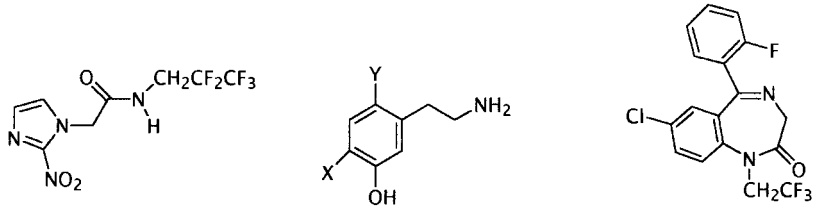
Simple addition of [F-18]-fluorine across $>C=C<$ is seen in the preparation of [F-18]-2-(2-nitro-1[H]-imidazol-1-yl)-*N*-(2,2,3,3,3-pentafluoropropyl)acetamide **46** from the *N*-2,3,3-trifluoroallyl analogue through treatment with [F-18]-molecular fluorine in acetic acid.[103]



46 **47** **48**

Fluorodemetallation and other electrophilic substitutions

Fluorodestannylation affords a route to [F-18]-6-fluoro-L-DOPA where BOC groups are used to protect both the amino functionality and the two aromatic hydroxy functions in the 6-(trimethylstannyl)-L-phenylalanine ester (see Scheme 1) which reacts with [F-18]-fluorine.[104] This method was reported as the most suitable for an automated process for preparing labelled 6-fluoro-L-DOPA.[105] Radiofluorodestannylation has similarly been applied to the preparation of [F-18]-6-fluorodopamine, and 4- and 6-[F-18]-fluoro-*m*-tyramine (**47**; X = F, Y = H or X = H, Y = F), though the radiochemical yields are not good.[106] Displacement of the trimethylstannyl group by labelled fluorine or acetyl hypofluorite gives a route to 7-chloro-1-(2,2,2-trifluoroethyl)-1,3-dihydro-5-(2-[F-18]-fluorophenyl)-2H-1,4-benzodiazepine-2-one (2-Oxoquazepam, **48**). The authors comment upon the particular success of this method in the fluorination of acid- and base-sensitive molecules.[107] Like fluorodestannylation, fluorodemercuriation may be used to insert fluorine into the DOPA system. Metallation again goes in the 6-position, and has been carried out using an appropriately substituted polymer; on treatment with gaseous [F-18]-acetyl hypofluorite followed by HI hydrolysis 2–23% overall chemical yield of labelled 6-fluoro-L-DOPA resulted.[108]

1-(β-D-glucopyranosyl)-5-fluorouracil, 1-(β-D-galactopyranosyl)-5-fluorouracil and 1-(2-deoxy-β-D-glucopyranosyl)-5-fluorouracil were obtained by fluorination of appropriate precursors, using [F-18]-F_2 in acetic acid solution, and acid-catalysed deacetylation.[109]

Bromine[110]

[Br-75] and [Br-76]. [Br-75] ($t_{1/2}$, 100 min) has been made by the bombardment of an arsenic isotope with helium-3, according to the sequence $^{75}As(^{3}He, 3n)^{75}Br$. Because 30–50 MeV ^{3}He ions are not readily obtainable, and lower-energy protons are, the bombardment of ^{78}Kr by protons of 12–15 MeV energies to provide ^{75}Br by the process $^{78}Kr(p, \alpha)^{75}Br$ is more easily available to many research institutes with cyclotron facilities. Although [Br-76] is also formed in the process, it represents little of the product and is easily allowed for.[111] [Br-76] is usually obtained[112] by the sequence $^{76}Se[p,n]^{76}Br$.

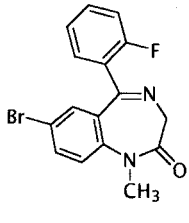
The triazene method has been used to insert either [Br-75] or [Br-77] giving labelled 7-bromo-1,3-dihydro-5-(2′-fluorophenyl)-1-methyl-2H-1,4-benzodiazepine-2-one (**49**, BFB). Bromide ion reacted with the

precursor in the presence of CF_3SO_3H in CCl_4; after a reaction time of 55 min material of s.a. $> 20\,000$ Ci mmol^{-1} ([Br-75]) was obtained.[113]

Oxidative bromination has also been applied. Metaraminol, with the amino group protected by the *N*-BOC group, was substituted in the electron-rich aromatic ring by a mixture of [Br-76]-ammonium bromide and peracetic acid to give the 4-(17%) and 6-(38%) bromo-derivatives. The syntheses took 3.5 h, including the preparation of the labelled ammonium salt, and both isomeric products showed activities of 130 Ci mmol^{-1}.[114] [Br-75]- or [Br-76]-7-Bromo-8-hydroxy-2,3,4,5-tetrahydro-3-methyl-1-phenyl-1*H*-3-benzazepine (**50**) were obtained from bromodeprotiation of the dehalogeno-analogue using labelled Br^- and H_2O_2-HOAc.[115]

Bromodemetallation

The same mixture of NH_4Br and peracetic acid brings about bromodestannylation of the tributyltin derivative to give both normal and [Br-76]-labelled (E)-*N*-(3-bromo-prop-2-enyl)-2β-carbomethoxy-3β-(4′-tolyl) nortropane (PE2Br. **51**; X = (E)-BrCH:CH.CH_2-, Y = CH_3). The latter isotopomer was formed in 80% radio-chemical yield, > 98% radio-chemical purity, and s.a. 20 TBq mmol^{-1}.[116] Labelled (R,S)-bromo-3-quinuclidinyl benzilate (radio-chemically and chemically pure; 30% radio-chemical yield) was obtained by electrophilic oxidative displacement of the tributyltin substituent using [Br-76]-NaBr in the presence of peracetic acid.[117] [Br-76]-2β-Carbomethoxy-3β-(4-bromophenyl)-tropane ([Br-76]-β-CBT, 51; X = CH_3, Y = ^{76}Br. 20 TBq mmol^{-1}) may be made from [Br-76]-Br^- by a number of processes: by electrophilic bromination of the tributylstannyl derivative with peracetic acid as oxidant (80%), by nucleophilic substitution of the iodo-analogue (Cu(I)-assisted; 60%) or by electrophilic bromination of the unhalogenated compound (< 5%).[118]



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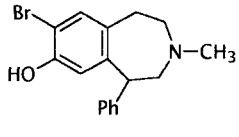

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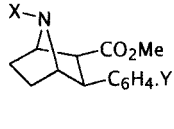

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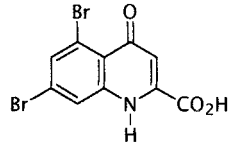

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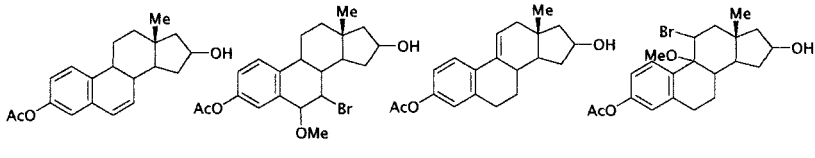
[Br-76]-4-Bromodexetimide and its pharmacologically inert enantiomer, [Br-76]-4-bromolevetimide, were obtained from the appropriate 4-(trimethylsilyl)-derivatives, [Br-76]-NH_4Br, and Chloramine-T. Chemical yields of 80%, radio-chemical purities of 98%, and s.a. of 300 Ci mmol^{-1} were found for both isomers after the 60-min synthesis and formulation.[119] The (trimethylstannyl)-derivatives were also used to make the *N*-succinimidyl esters of [Br-76]-4-bromobenzoic acid and [Br-76]-5-bromopyridine-3-carboxylic acid, using dichloramine-T to oxidise the labelled bromide ion.[120]

[Br-77]. Copper-catalysed halogen-exchange has also been applied to the introduction of [Br-77] into organic molecules. [Br-77]-5,7-Dibromo-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (**52**) was obtained from the 5-iodo-7-bromo-analogue. Under the best conditions, 85% incorporation of the isotope was achieved, though its position within the molecule was not clearly identified.[121]

A tumour-associated monoclonal antibody, 7E8, was labelled with [Br-77] using Chloramine-T and [Br-77]-bromide ion; 34% of the label was incorporated.[122]

In methanolic solution, [Br-77]Br^- and *N*-chlorosuccinimide react with Δ^6- or Δ^9-estradiol-3-acetate (**53** and **54**, respectively) to give respectively the 7-bromo-6-methoxy- (**53a**) or the 11-bromo-9-methoxy-estradiol-3-acetate (**54a**) in a classic illustration of the nucleophilic trapping of a bromonium ionic intermediate.[123]



53 **53a** **54** **54a**

[Br-80m]. [Br-80m]-5-Bromouracil (50% yield; 150–550 Ci/mmol) may be obtained from deoxyuridine, *N*-chlorosuccinimide and the radioactive halide in dilute sulfuric acid; correspondingly, 5-[I-123]-iodouracil (60–70% yield; >2000 Ci mmol^{-1}) can be prepared. Using uracil, and under the same oxidising conditions, [Br-80m]-5-bromouracil results in 89% yield. The analogous bromoantipyrine may be similarly made, though peracetic acid was a more effective oxidising agent (90% yield;

4000 Ci mmol^{-1}) than *N*-chlorosuccinimide (50% yield; 2000 Ci mmol^{-1}) in this instance.[124]

[Br-82]. [Br-82]-2-Deoxy-2-bromo-D-mannose and -D-glucose (**55**) are obtained by the addition of [Br-82]-bromine in chloroform to D-glucal; treatment with 1 M-HCl at 110° provides both products.[125]

55

Iodine

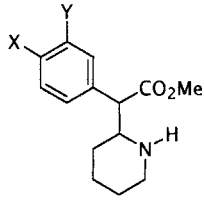
Various isotopomers of 5-iodo-2′-deoxyuridine have been obtained through electrophilic substitution, using nitric acid as the oxidising agent.[126] Although direct electrophilic substitutions of hydrogen have been widely reported in iodine labelling, halogen exchange, and electrophilic iododemetallation (especially tin, but including silicon, mercury and thallium[127]), represent the most popular methods of the present day.

[I-123]. [I-123] may be obtained from the reaction ^{123}Xe(p, 5n)^{123}I; details of a multi-Curie generator have been reported.[128]

Iododeprotiation

[C-11]-Ritalin (methyl phenidate, **56**, X = Y = H) has useful properties in PET applications, and two [I-123]-labelled analogues were prepared as potential SPECT tracers. Methyl [I-123]-*p*-iodophenidate (**56**; X = I, Y = H. 85% radio-chemical yield; s.a. > 10 000 Ci mmol^{-1}) was prepared from the *p*-tributylstannyl derivative, while methyl [I-123]-*m*-iodo-*p*-hydroxy-phenidate (**56**, X = OH, Y = I. 80% radio-chemical yield) was obtained by substitution of aromatic hydrogen by iodine, in both cases generated from Chloramine T and [I-123]-NaI in acidic conditions.[129] In a less detailed report, the preparation of 2-(aminomethyl)-4-tert-butyl-6-iodophenol hydrochloride (**57**, MK-447) labelled by [I-123] by a similar substitution under similar reaction conditions is described; a number of analogues were also prepared,[130] and also [I-123]-4′-iodococaine.[131] The three isomeric [I-123]-labelled 2-deoxy-2-(iodobenzoyl)-D-glucosamines have been reported.[132] Two apparently separate reports note the superiority of peracetic acid over

Chloramine-T, hydrogen peroxide, sodium persulphate or *m*-chloroperoxybenzoic acid as an oxidising agent in achieving iodination of an activated aromatic ring to give [I-123]- or [I-125]-(S)-3-iodo-2-hydroxy-6-methoxy-*N*-[1-ethyl-2-pyrrolidinyl)methyl]benzamide (IBZM, **58**).[133]



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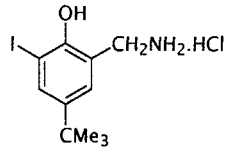

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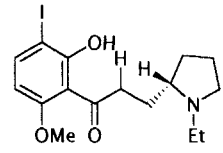

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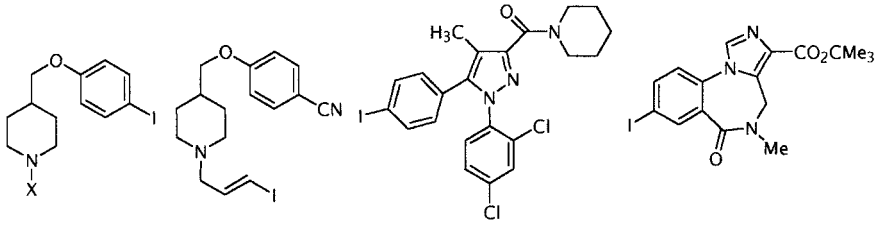
Iododemetallation and halogen exchange

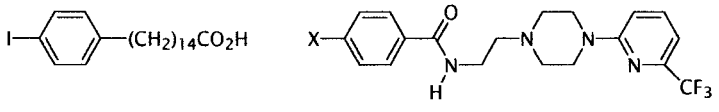
Exchange between [I-123] or [I-124] and the organic substrate has provided labelled MIBG (*m*-iodobenzylguanidine). Ammonium sulphate assists this reaction.[134, cf 198] [I-123]-Derivatives of iodoamphetamine have been made by electrophilic substitution[135] and also by halogen exchange.[136]

The preparation of [I-123]iodoimidazenil and [I-123]-*N*-ethyliodoimidazenil has been achieved both by iododebromination (ethanoic acid, 150°) and by iododestannylation of the (trimethyltin)-derivatives, using Chloramine-T or peracetic acid to oxidise labelled NaI. The yields in the latter process (25%) were much inferior to those in the halogen-exchange synthesis (80%), as much of the radioiodine is lost as [I-123]-iodomethane. The product obtained by iododebromination was 98% pure by radio-chemical and chemical analysis, with a specific activity $>2500\,\mathrm{Ci\,mmol^{-1}}$.[137] Material of similar specific activity has also been made, however, by electrophilic iodo-destannylation ([I-123]-NaI/Chloramine T; 80%) to give [I-123]- (*S*)- or (*R*)-bretazenil, each showing >98% enantiomeric purity, and 97% radio-chemical and chemical purity in a 50-min process.[138] The same reagents gave [I-123]-1-(2-hydroxyethyl)-4-(4-iodophenoxymethyl)piperidine (**59**; s.a., $10\,000\,\mathrm{Ci\,mmol^{-1}}$; 63–77% radio-chemical yield EOS; >99% radio-chemical purity) from the appropriate tin-substituted precursor,[139] and electrophilic iododestannylation was similarly applied successfully (60–80% radiochemical yield EOS; 99% radio-chemical purity, $>2500\,\mathrm{Ci\,mmol^{-1}}$) to the synthesis of [I-123]-1-(*trans*-iodopropen-2-yl)-4-(4-cyanophenoxy-methyl)piperidine (**60**),[140] of [I-123]-*N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide (**61**, AM251; 62% yield, radio-chemical purity

$>95\%$, $2500\,Ci\,mmol^{-1}$) and tert-butyl [I-123]-8-iodo-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate[141] (**62**), of [I-123]-15-(4′-iodophenyl)pentadecanoic acid (**63**),[142] and of [I-123]-4-iodo- *N*-{2-[4-(6-trifluoromethyl-2-pyridinyl)-1-piperazinyl] ethyl}benzamide (**64**, X = I) from the 4-stannylated benzamide derivative (**64**, $X = SnR_3$).[143]

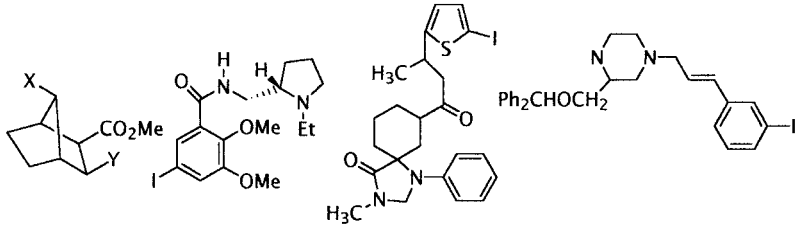


59 **60** **61** **62**



63 **64**

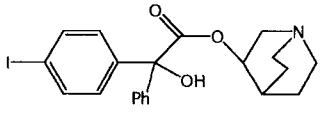
The synthesis of (E)-*N*-(3-iodoprop-2-enyl)-2β-carbomethoxy-3β-(3′,4′-dichloro-phenyl)nortropane (**65**, X = ICH:CH.CH_2-, Y = 3,4-$C_6H_3Cl_2$; β-CDIT), labelled either with [I-123] or [I-125], was also achieved using iododestannylation processes in which the 3-tributylstannyl system was lost.[144] By the same chemistry, 2β-carbomethoxy-3β-(4′-trimethylstannylphenyl)tropane was converted into [I-123]-βCIT (**65**, X = Me, Y = 4-C_6H_4I).[145] The same processes gave [I-123]-(S)-(−)-*N*-[(l-ethyl-2-pyrrolidinyl)ethyl]-5-iodo-2,3-dimethoxybenzamide ([I-123]-epidepride, **66**) and its [I-125]-isotopomer.[146] They were also recommended for the synthesis of [I-123]-8-[4-[2-(5-iodothienyl)]-4-oxobutyl]-3-methyl-1-phenyl-1,3,8-triazaspiro[4.5]-decan-4-one (**67**),[147] and provided [I-123]-[2-(diphenylmethoxy)ethyl]-4-[3-(3-iodo-phenyl)-2-propenyl]piperazine (**68**) in 90% radio-chemical yield.[148]



65 **66** **67** **68**

Iododemercuration was used in the preparation of [I-123]-*N,N*-dimethyl-[2-(3,4-diacetoxy-6-iodophenyl)]ethylamine, with NaI and Chloramine-T.[149]

[I-123]-Iodinated 3-quinucidinyl benzilate ((R)-(−)-azabicyclo[2.2.2]-oct-3-yl (R)-(+)-α-hydroxy-α-(4-iodophenyl)-α-phenylacetate; **69**, IQNB) has also been made (56% yield) by a Cu(I)-catalysed iododebromination. The product showed high specific activity (80 TBq mmol^{-1}).[150] Another preparation of IQNB, labelled with either [I-123] or [I-127], was described earlier.[151] Analogously, iodine-labelled epibatidine, **70**, was prepared from the bromopyridyl compound through iodode-bromination, using [I-123]- or [I-125]-NaI at high temperatures (200–220°) and a Cu(I) catalyst. Both isotopomers were obtained in satisfactory radio-chemical yield (>96%) and high specific activities ([I-123], 20% chemical yield, >1750 Ci mmol^{-1}, 65 TBq mmol^{-1}; [I-125], 31–50% chemical yield, >1540 Ci mmol^{-1}, 57 TBq mmol^{-1}).[152] [I-123]-5-Iodonicotinamide is also reported to have been prepared by nucleophilic halogen exchange with the bromo-analogue.[153] [I-123]-7-Chloro-5-iodo-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (chloroiodokynuretic acid, **71**) was simlarly made by iodo-debromination (Cu(I), EtOH-HOAc).[154] [I-123]-7-Iodotacrine (9-amino-7-iodo-1,2,3,4-tetrahydroacridine, **72**) was also made in a four-step process with high s.a..[155] A chromatographic method of producing high s.a., n.c.a. 3-iodobenzylguanidine, labelled by [I-123] or [I-131] has been reported.[156]



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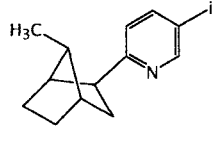

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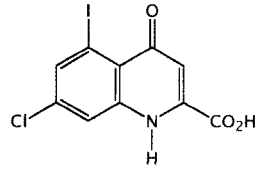

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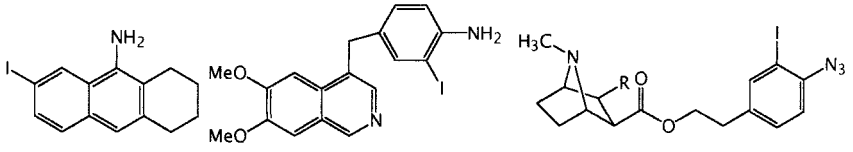
[I-124]

[Te-124] is the usual source of [I-124] through the sequence ^{124}Te (p,n)^{124}I. In one described process, a proton beam of 9.8–12.3 MeV energies (10 μA) impinged upon a TeO_2 target which was 98% enriched with [Te-124].[157] Direct substitution gave [I-124]insulin by attack upon tyrosine residues.[154]



72 **73** **74**

The [I-124]-3- and -4-iodobenzoates of *N*-hydroxysuccinimide were prepared from the unlabelled compounds through trimethylstannylation (Sn_2Me_6, $(PPh_3)_2Pd(II)Cl_2$, dioxan, N_2, 60°, 90 min) followed by oxidative iododemetallation after esterification.[158]

[I-125]

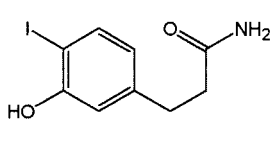
Electrophilic iododeprotiation. Direct electrophilic substitution by iodine in the anilino-fragment inserts [I-125], as in the synthesis of [I-125]-6,7-dimethoxy-4-(4′-amino-3′-iodobenzyl)isoquinoline (**73**).[159] The azido group which was required in the preparation of some photoaffinity reagents could then be introduced through diazotisation and treatment with azide ion to give a range of iodoazidoisoquinolines (40–64% yield; 350–1500 Ci mmol^{-1}).[160] The *m*-([I-125]-iodo)-*p*-azidophenethyl ester of 3*β*-(*p*-chlorophenyl)tropan-2*β*-carboxylic acid (**74**, R = *p*-Cl.C_6H_4-; RTI-82; 1490–1880 Ci mmol^{-1}) was made similarly.[161]

In discussing various oxidative methods of iodination, the literature advocates a range of oxidisers which appear to show remarkably specific effects, both adverse and promoting. Peracetic acid was found to be better than chloramine-T, hydrogen peroxide, sodium persulfate or *m*-chloroperoxybenzoic acid in the synthesis of n.c.a. radio-iodinated BZM (**58**; (S)-(−)-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2-hydroxy-3-iodo-6-methoxy-benzamide). It is claimed to give higher radio-chemical yields in a shorter reaction time, and to provide material of high radio-chemical purity, whether [I-123] or [I-125] was the radio-label.[162]

Hyaluronic acid may be derivatised by reducing ($NaBCNH_3$) the Schiff's base made by condensing the terminal aldehyde function with tyramine. [I-125]-Iodine attacks the activated aromatic ring so produced, giving labelled material (40% yield; 15 Ci mmol^{-1}).[163] The iodine 'analogue' of racopride has been made by iododeprotonation of 5-dechloro-racopride. Far the best of three alternative processes used *N*-iodo-succinimide, or a mixture of NaI and *N*-chlorosuccinimide, to introduce [I-125] into the 5-position. Chloramine-T, or iodo-beads, were

markedly inferior in achieving this substitution.[164] The octapeptide Glu–Gly–Val–Tyr–Val–His–Pro–Val was also labelled either through [I-125]-NaI and Chloramine-T iodination of the Tyr aryl ring, or through coupling the [I-125]-labelled Bolton–Hunter reagent to the terminal group.[165] This reagent was also involved in the synthesis, from desmethylzopiclone, of [I-125]-*N*-(3-(4-hydroxy-3-iodophenyl)-propionamide (**75**).[166] Direct iodination (Chloramine-T or iodobeads and NaI) gave [I-125]iodobuprenorphine.[167] Two coumarins, 4-bromomethyl-7-methoxy-2-oxo-2H-benzopyran and the 6,7-dimethoxy analogue (**76**, X = H or Me; Y = H), were iodinated using [I-125]- or [I-127]-trifluoroacetyl hypoiodite. Both took up the label at the 3-position (**76**, X = H or Me, Y = I. 30% yield), though the mono-methoxy compound also showed isomeric attack at C-6 (10% of the product); no attack at C-8 was seen, probably through steric factors.[168] [I-125]-2-Butyl-3-[3,5-diiodo-4-(*N,N*-diethylamino)-2-ethoxybenzoyl)]-benzofuran (**77**) hydrochloride,[169] some derivatives of 12-[(4-azidosalicyl) amino]-dodecanoic acid (**78**),[170] and [(3R)-amino-(2S)-sulfhydryl)-5-sulfonato]pentanoyl-(S)-3-iodotyrosyl-(S)-aspartic acid (**79**)[171] were also made by direct substitution.

A synthesis of [I-125]- or [I-127]-*N*-succinimidyl 4-iodobenzoate relies upon the decomposition of a triazene derivative by labelled NaI



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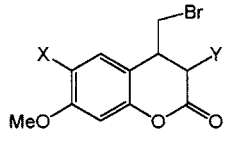

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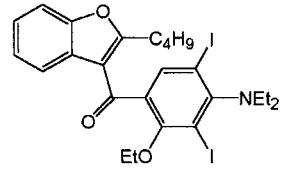

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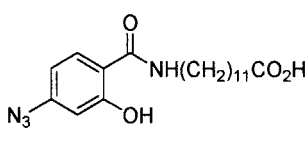
in the presence of trimethylsilyl chloride. This proceeds in 90% yield (75°; 45 min) or in 81% yield using microwave energy (2400 MHz; 8 min).[172]



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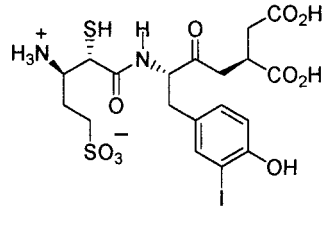

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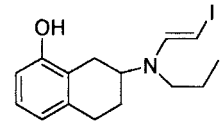

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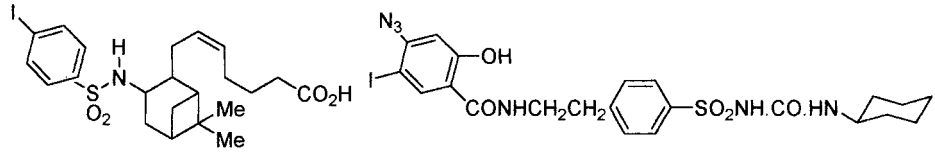
Iododemetallation and halogen exchange

Iododestannylation of the resolved enantiomers of the 3-(tributylstannyl) analogue gave (R)-(+) or (S)-(−) [I-125]-5-hydroxy-2-[*N*-(3-iodo-2-propenyl)-*N*-propyl]-amino-tetralin (**80**; trans-5-hydroxy-PIPAT)[173] for which inhibition constants were derived for the D2H, D3 and D4H receptors of dopamine. Similarly, a vinylstannane derivative was used to obtain [I-125]-7-(α-O-iodoallyl)diprenorphine.[174] Iododestannylation, using [I-125]-NaI/Chloramine-T to displace the $-SnMe_3$ group, gave good yields of high quality material in the synthesis of 7-[(2R,2S,3S,5R)-6,6-dimethyl-3-(4-[I-125]-iodobenzene-sulfonyl-amino) bicyclo[3.1.1]hept-2-yl]-5(Z)-heptenoic acid (**81**, [I-125]-ISAP).[175] A process which is effectively an iodine-exchange process is the formation of [I-125]-RP 62203. The first step in the three-stage synthesis is the iodination at C-4 by ICl of 1,8-naphthasultam. The iodine substituent is carried through the synthetic sequence, at the end of which Pd-catalysed coupling with hexamethylditin gives the 4-(trimethylstannyl)-analogue (83%) and this, under oxidative attack by [I-125]-NaI, gives [I-125]-RP 62203 (80–86%, >99.6% radio-chemical purity, 1200–2000 Ci mmol^{-1}).[176] Similarly, [I-125]-*N*-[4-(2-(4-azido-2-hydroxy-5-iodobenzamido)ethyl)benzenesulfonyl]-*N*′-cyclo-hexylurea (**82**; 56% radio-chemical yield; s.a. 2130 Ci mmol^{-1}).[177] An [I-125]-labelled derivative of MK-571 was obtained by iododestannylation of the coupling product of (±)-3-[[[3-[2-(7-chloro-2-quinolinyl)-(E)-ethenyl]phenyl] [[3-[(3-aminopropyl)amino]-3-oxopropyl]-thio] methyl]thio]propionic acid (**83**) with *N*-hydroxysuccinimidyl 4-(trimethyl-stannyl)phenylacetate,[178] and [I-125]-iodocaramiphen (50% radio-chemical yield; s.a. >1000 Ci mmol^{-1}) was analogously prepared.[179] Iododestannylation was used effectively in the synthesis of 17α-(2-(E)-[I-125]-iodovinyl)-19-nortestosterone; [I-125]-NaI was the source of the radioisotope, but the oxidation was brought about by the use of Fe(III) sulfate, an unusual oxidant which presents a low standing concentration of free iodine.[180] The synthesis of [I-125]-(E)-4-[4,4-dimethyl-2,5-dioxo-3-{1′-iodo-1′-propen-3′-yl}-1-imidazolidi-nyl]-2-trifluoromethylbenzonitrile used iododestannylation in the synthesis of the intermediate [I-125]-(E)-1-chloro-3-iodoprop-2-ene (**84**).[181] The synthesis of [I-125]-3-{4-[2-(2-aminopyridin-6-yl)ethyl]ben-zoylamino}-(2S)-4-iodobenzenesulfonylamidopropionic acid (**85**) rests upon the synthesis of [I-125]-4-iodobenzenesulfonic acid, in the same way.[182]



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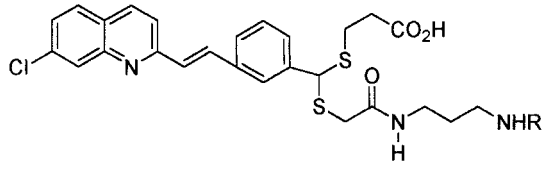

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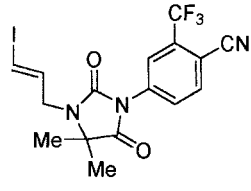

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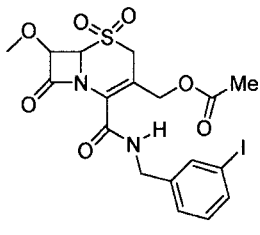

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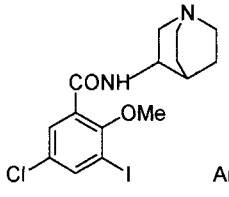

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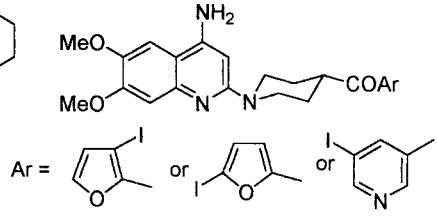


87

Idoxifene (pyrrolidino tamoxifen) may be iodinated through electrophilic iododetrialkylstannylation. This provides n.c.a. material of good radiochemical purity (95%) which may be further purified by HPLC with 70% recovery.[183]

Iododestannylation was the essential step in the synthesis of [I-125]iodoproxyfan, the arylstannane being obtained through the Pd-catalysed coupling of hexabutylditin and the aryl bromide. Radio-iodine was generated from [I-125]-NaI and Chloramine-T. The authors concluded that this process was preferential to the Cu(I)-catalysed halogen exchange as a means of labelling this pharmaceutical.[184] In a similar way, [I-125]-3-iodobenzyl-(6R,7S)-7-methoxy-3-acetoxymethyl-3-cephem-4-carboxamide-1,1-dioxide (partial structure, **85**),[185] [I-125]-(S)-5-chloro-3-iodo-2-methoxy-*N*-(1-azabicyclo-[2.2.2]oct-3-yl)benzamide (**86**; [I-125]DAIZAC),[186] [I-125]-4-amino-6,7-dimethoxy-2-[4-(3- or 5-iodofuroyl)piperazinyl]quinoline (and the 5-iodonicotinyl analogue: **87**),[187] and [I-125]-4-(5′,6′,7′,8′-tetrahydro-4′-iodo-5′,5′,8′,8′-tetramethyl-2′-anthracenyl)benzoic acid (**88**)[188] were attempted by the displacement of the tributyltin group using

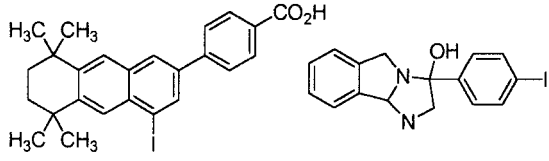
[I-125]-NaI and Chloramine-T. This was ineffective in the synthesis of **85**, in which the coupling of 3-(tributylstannyl)benzylamine to the appropriate carboxylic acid precursor gave the desired organometallic from which iododestannylation produced the required isotopically labelled material.

In this case, displacement of the (tributylstannyl) substituent by [I-125]-NaI with Chloramine-T was superior either to nucleophilic halogen exchange or to use of the Wallach triazene process for the preparation of high s.a., n.c.a. material.[189]

Iododestannylation was also used in the synthesis of [I-125]-labelled 2β-carbomethoxy-3β-(3′-iodo-4′-isopropylphenyl) nortropane (**65**, X = H, Y = $C_6H_3I(CHMe_2)$; LBT-44), which was obtained in 75% radio-chemical yield and 95% radio-chemical purity.[190] Displacement of the same group gave [I-125]-3β-(4-iodophenyl)tropane-2β-pyrrolidinecarboxamide (RTI-229; s.a. 2125 Ci mmol^{-1}; 89% radio-chemical yield and 98% radio-chemical purity).[191] Significantly, the trimethylstannyl groups were displaced by Chloramine-T or peracetic acid with [I-125]-NaI without the substantial losses, through formation of iodomethane, reported in other systems.[35,137,192] An earlier paper reports the synthesis of 2α- and 2β-carbomethyl-3β-phenyltropanes labelled with [I-125] by oxidative iodination using various acids.[193] *O*-6-(4-[I-125]-Iodobenzyl)-2′-deoxyguanosine, *O*-6-(4-[I-125]-iodobenzyl)-*N*-acetylguanosine and *O*-6-(4-[I-125]-iodobenzyl)-guanosine were each also prepared by de(tributyl)stannylation of appropriate derivatives with [I-125]-NaI.[194]

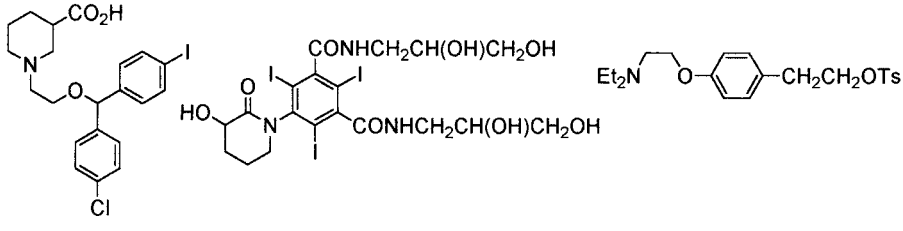
Another route to [I-125]-labelled aryl iodides is shown in the preparation of two iodinated analogues of xylamine, *N,N*-diethyl-2-iodobenzylamine and *N*-(2-chloroethyl)-*N*-ethyl-2-iodobenzylamine. The radiohalogen substituents were introduced through halogen exchange, using brominated precursors, though *N,N*-diethyl-2-iodobenzylamine was obtained directly from the bromo-analogue.[195] In the same way iododebromination provided a [I-125]-labelled analogue of mazindol, 5-(4-iodophenyl)-2,3-dihydro-5-hydroxy-5H-imidazo[2,1-a]isoindole (**89**). The influence of a number of parameters upon the yield and rate of the Cu(I)-catalysed process was reported.[196] The synthesis of [I-125]-2′,4′,6′-trihydroxy-3-(3-iodo-4-hydroxyphenyl)-propiophenone (**90**) is another example of Cu(I)-catalysed iododebromination; in this case, the phloroglucinol fragment diverted electrophilic iodine in attempts to prepare the compound through iododeprotonation.[197]

In contrast, CIPCA ([2-(4-chlorophenyl)(4-iodophenyl)methoxyethyl]-1-piperidine-3-carboxylic acid, **91**) was radiolabelled through exchange with sodium iodide-[I-125], using ammonium sulfate as a solid-state heterogeneous catalyst. This surprising reaction gave [I-125]-CIPCA with 34% incorporation of the original label.[198]



88 **89** **90**

Aurichloric acid ($HAuCl_4$) was successful in catalysing exchange between [I-125]-iodide and aryl iodo-substituents in the preparation of [I-125]-*N,N′-bis*(2,3-dihydroxypropyl)-5-(3-hydroxy-2-oxo-1-piperidinyl)-2,4,6-triiodo-1,3-benzene-dicarboxamide, (**92**, [I-125]-3H2-iopiperidol-A. 98.7% uptake, s.a. 6.6 Ci mmol^{-1}).[199] Exchange labelling of the three isomeric 2-deoxy-2-*O*-(*o*-, *m*- or *p*-iodobenzyl)-glucoses with [I-123]-NaI has been described.[200]



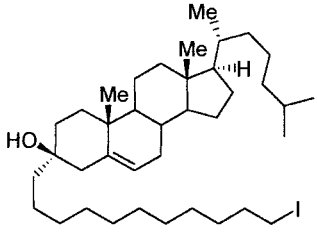
91 **92** **93**

When 2-(4-[2-(diethylamino)ethoxy]phenyl)ethyl tosylate (**93**) alkylated a large excess of 1,4,8,11-tetraazacyclotetradecane (Cyclam) in DMF, the mono-*N*-substituted cyclam resulted. This cyclam formed stable complexes with [Tc-99 m], and the activated phenyl ring system in the attacking agent allowed substitutive labelling with [I-125].[201] For similar reasons, the Park nucleoside may be labelled with [I-125] by electrophilic iododestannylation, the high electron density of the phenyoxyacyl fragment allowing the formation of the necessary precursor, the trialkylstannyl function, and of *p*-iodo-phenoxyacyl-Ala-(D)-iso–Glu–Lys-(D)-Ala-(D)-Ala–OH.[202]

Neurotensins have been labelled using 2-bromophenylacetyl derivatives and [I-125] for SPET purposes.[203] The synthesis by standard methods of *N*-succinimidyl [I-125]-3-iodobenzoate has been reported.[204]

Aliphatic iodination

Aliphatic nucleophilic displacement by radio-iodide ion is used in the synthesis of [I-125]-11-iodoundecyl cholesteryl ether (**94**).[205]



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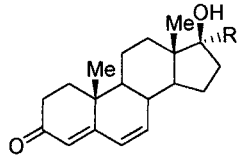

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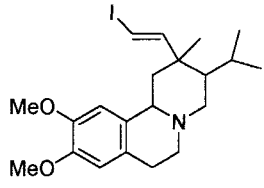

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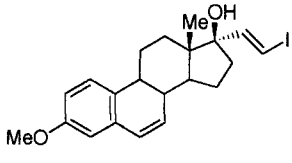
Side-chain iodination is unusual, but the chemistry of the terminal alkyne system allows the synthesis of [I-125]-17α-(iodoethynyl)-4,6-androstadien-17β-ol-3-one (**95**, R = IC≡C–). The transient formation of the silver salt led to subsequent iododemetallation by using [I-125]-*N*-iodosuccinimide, itself made by reaction of silver succinimide with a dioxan solution of [I-125]-iodine (from NaI and $NaNO_2$ in dilute acid), and the alkyne in the presence of silver nitrate.[206] A synthesis of 17α-[(E)-2-[I-125]-iodoethenyl]androsta-4,6-dien-17β-ol-3-one (**95**, R = ICH = CH–) relied upon the reaction of 17α-[(E)-2-(tributyltin)ethenyl] androsta-4,6-dien-17β-ol-3-one with [I-125]-NaI and hydrogen peroxide in acetic acid.[207] The iodovinyl derivative of tetrabenazine (**96**; 2-(2′-iodoethenyl)-3-(2′-methylpropyl)-9,10-dimethoxy-1,3,4,6,7,-11b-hexahydro-2H-benzo[a]quinolizin-2-ol) was achieved by similar chemistry, using H_2O_2 as oxidant.[208] When 3-methoxyestra-1,3,5(10),6-tetraen-17-one was treated with lithium acetylide the corresponding 17α-ethynyl-17β-ol was formed. Tri-butyltin hydride added across the triple bond to provide the *E*-isomer (PhMe, AIBN, Bu_3SnH, 90°, 3 h: 60%) or *Z*-isomer (HMPA, 70°, 45 h: 25%) of the 2′-(tributylstannyl) derivatives. These, in turn, reacted with labelled iodine in chloroform to give [I-125]-*E*- or -*Z*-17α-(2′-iodoethenyl)-3-methoxyestra-1,3,5(10),6-tetraen-17β-ol (**97**).[209]



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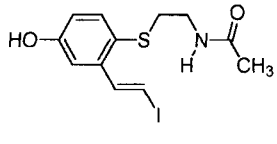

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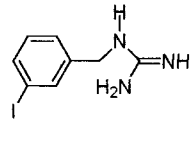

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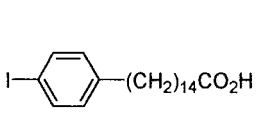
The synthesis of [I-125]-3-(E)-(2-iodovinyl)-N-acetyl-4-cysteaminyl-phenol (**98**) in high s.a. and 85% radio-chemical yield involved two unusual aspects. Firstly, the iodine atom was substituted by displacing a trialkylsilyl group: and secondly, the displacement was brought about by heating a mixture of this precursor and [I-125]-NaI in a microwave oven for 5 min, using energy of frequency 2450 MHz.[210]

[I-131]. [I-131]-2-Iodo-*N,N*-dimethyltryptamine, [I-131]-2-iodo-*N*-methyltryptamine, [I-131]-2-iodo-5-methoxy-*N,N*-dimethyltryptamine, [I-131]-2-iodobufotenine ([I-131]-2-iodo-5-hydroxy-*N,N*-dimethyltryptamine), [I-131]-2-iodotryptamine and the known [I-131]-2-iodo-*N*-acetyl-5-methoxytryptamine ([I-131]-2-iodomelatonin) were both made by a 'high yield novel process' which proved to involve the aminolysis of the methyl ester of an appropriate carboxylic acid, and the reduction of the resulting amide to the corresponding primary amine. Also, the syntheses of [I-131]-2-iodo-4,5-dimethoxyphenethylamine, [I-131]-2-iodo-4,5-dimethoxy-*N,N*-dimethylphenethyl-amine, [I-131]-2-iodophenethylamine, [I-131]-2-iodo-*N,N*-dimethylphenethylamine and [I-131]-2-iodo-3,4,5-trimethoxyphenethylamine (iodomescaline), and of [I-131]-6- and -8-iodo-1-methyl-7-methoxy-β-carboline ([I-131]-iodoharmine), [I-131]-6- and 8-iodo-1-methyl-β-carbolin-7-ol (or [I-131]-iodoharmol), [I-131]-8-iodo-1-methyl-7-methoxy-3,4-dihydro-β-carboline ([I-131]-8-iodoharmaline), [I-131]-8-iodo-3,4-dihydro-1-methyl-β-carbolin-7-ol ([I-131]-8-iodoharmalol), and [I-131]-6-iodo-1-methyl-β-carboline ([I-131]-6-iodoharmane) are described.[211] Chloramine-T was also suitable in the oxidative substitution required to prepare [I-131]-4-iodoantipyrine.[212]

MIBG (*m*-Iodobenzylguanidine, **99**) has been labelled with [I-131] by Cu(I)-catalysed exchange (HOAc, 160°, 30 min), giving material which is 98% pure and in a 90% radio-chemical yield.[213,214] The incorporation of [I-131] through an exchange process with L-*p*-iodophenylalanine (p-IPA), catalysed by $CuCl_2$, has been studied in some detail. The best yields (87%) were achieved after 60 min at 150°; the effects of selected inorganic salts and organic solvents were also studied. The interesting observation that solvents supported the reaction in the order dioxan > DMSO > DMF and the low activation energy (13 Kcal mol^{-1}) encourage further studies. The same school reported the exchange between [I-131] and 15-(*p*-iodophenyl) pentadecanoic acid (**100**),



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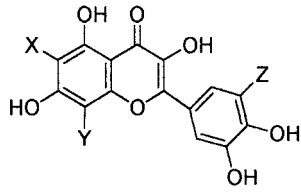

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using ethanol containing benzoic acid as solvent. Similar yields (> 80%; 50 min, 170°), but a much higher activation energy for the process (34 Kcal mol^{-1}), are reported.[215] Iodine-exchange which was Cu(II)-catalysed has also been reported for 3-iodotyrosine and for (4-iodophenyl)alanine, together with activation energies for the exchange.[216]Farah and Farouk have also investigated the optimisation of yield of [I-131]-3-iodotyrosine and two of its derivatives, using NaI and either Chloramine-T or iodogen as the oxidising agent. Good yields were found with both the parent system and its α-methyl derivative (ca. 90%), but poorer were found with the methyl ester of the parent molecule (53 and 78%).[217]

Techniques similar to those used for incorporating other iodine isotopes are expectedly applicable here. [I-131]-2′-Iodoquercetin (**101**; X = Y = H, Z = I) and 2′,6,8-triiodoquercetin (**101**; X = Y = Z = I) were obtained through thalliation, followed by treatment with [I-131]-iodide ion.[218]

[At-211]. The commonly available isotope of astatine is usually obtained by proton bombardment of [Bi-209] through the process $^{209}Bi[\alpha,2n]^{211}At$. A multi-Curie generator employing this process has been described.[219] Much of the limited reported chemistry of astatine is predictable from the analogy with iodine. For example, its application to pharmaceutical chemistry is represented by the labelling of an antigastric cancer monoclonal antibody using [At-211]-4-astatinobenzoic acid,[220] and of pyrimidines by astatinodemercuriation.[221] Astatine, distilled from the bismuth target, could be treated with *N*-succinimidyl 3-(trimethylstannyl)benzoate to obtain the [At-211]-labelled benzoic acid.[222]

Conclusions

The electrophilic inclusion of radiohalogen as a label may still be achieved through displacement of hydrogen from aromatic systems, or

addition across multiple bonds, but the displacement of other groups has become more often used. Trialkyl derivatives of Group IV elements (Sn, Si) may be readily obtained from organic halogeno (Br, I) derivatives; such organometallic groups may be specifically and selectively displaced by radiohalogen. Such a process is available even for fluorine. Nucleophilic inclusion of radiohalogen, especially of [F-18], is widely reported and apparently becoming more popular. The reasons are again that groups such as other halogens, nitro-groups, or trialkylammonium substituents may be more selectively displaced (especially when their displacement is encouraged by appropriate electron withdrawing substituents such as –CN, –CHO and –COR, $–CO_2R$ $–CO.NR_2$, $–NO_2$, $–N_2^+$, and halogens), leading to a single product often with a high specific activity.

Radioisotopes of fluorine and iodine are widely studied, probably because of their ready availability. In contrast, bromine isotopes are less popular even though the chemistry of their inclusion into organic molecules is more well-behaved. The absence of suitable isotopes of chlorine explains its absence from this review. Chlorine-36 decays very slowly ($t_{1/2}$, 300 000 y) and emits comparatively 'soft' radiation, making it generally unsuitable for labelling in pharmacological or physiological applications.

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