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INCORPORATION OF RADIOHALOGENS VIA VERSATILE ORGANOMETALLIC REACTIONS: APPLICATIONS IN RADIOPHARMACEUTICAL CHEMISTRY

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INCORPORATION OF RADIOHALOGENS VIA VERSATILE ORGANOMETALLIC REACTIONS: APPLICATIONS IN RADIOPHARMACEUTICAL CHEMISTRY

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ABSTRACT

Factors that must be considered for the design of radiohalogenated radiopharmaceuticals include the stability and availability of the substrate, the physical half-life of the radiohalogen and the in vivo stability of the radiolabel. Vinyl and phenyl radiohalogen bonds show more in vivo stability than the alkyl radiohalogen bonds. Consequently, a variety of methods suitable for the synthesis of tissue specific radiopharmaceuticals bearing a vinyl or phenyl radiohalogen have been developed involving the synthesis and halogenation of metallovinyl and phenyl intermediates. The halogens and metallation reactions include iodine and bromine and alanation, boronation, mercuration, stannylation, and thallation, respectively.

INTRODUCTION

There are a number of halogen radioisotopes which exhibit a broad spectrum of radionuclidic properties (Table 1) useful for scanning, tracer techniques and therapeutic applications. The usefulness of these radioisotopes is further enhanced if isotopes can be conveniently incorporated into the organic molecules (or radiopharmaceuticals) appropriate for use as a vehicle for such applications. The ease of incorporation of the radiohalogen in the molecule, stability and availability of the substrate, physical half-life of the radiohalogen and in vivo stability of the carbon halogen bond are important factors to be considered in designing the synthesis of a radiopharmaceutical.

Properties and principle mode of decay of halogen radioisotopes

Isotope	Half-life	Mode of decay	Principle radiation energy (keV)
^{18}F	1.83 h	$^{+}\beta$	511
^{75}Br	1.62 h	$^{+}\beta$,EC	511
^{76}Br	16.2 h	$^{+}\beta$,EC	511
^{77}Br	2.38 d	EC	239
^{82}Br	35.3 h	$^{-}\beta$	554
^{123}I	13.2 h	EC	159
^{125}I	60.14 d	EC	Te-X-rays
^{131}I	8.02 d	$^{-}\beta$	364

Table 1

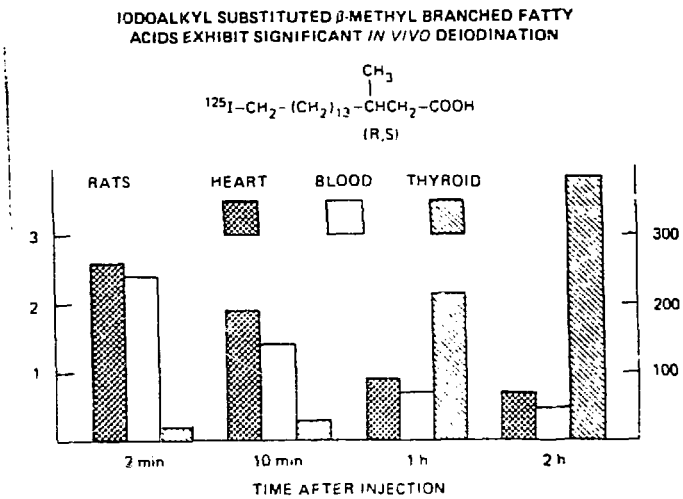


Figure 1

In general, halogens can be attached to a radiopharmaceutical as alkyl, aklenyl and aryl (phenyl) halides. The reactivity of alkyl halides follows the order RI>RBr>RCl>RF. This order is reversed for the stability of these alkyl halides, consequently, RF and RI would be expected to be the most and least in vivo stable of the alkyl halides, respectively. This trend of reactivity and/or stability is obvious from various examples cited in the literature, e.g., the stability of 2-deoxy-2-fluoro-D-glucose as compared to that of 2-deoxy-2-iodo-D-glucose which has eluded synthetic attempts by several investigators (ref.1 and 2). The clinical potential of such radioiodinated agents is often marred due to their in vivo instability or deiodination. For example, 17-[^{123}I]iodoheptadecanoic acid, a useful probe of regional fatty acid metabolism, undergoes in vivo deiodination and special correction methods have to be applied to account for the activity in the blood pool (ref.3 and 4). Similarly, 17-[^{125}I]iodo-3-(R,S)-methylheptadecanoic acid shows high heart uptake in rats but washes out rapidly from the heart with significant accumulation of the activity in the thyroid (Fig. 1) indicating in vivo carbon-iodide bond cleavage of the radioiodinated fatty acid (ref.5).

A detailed animal tissue distribution study in our laboratory with a variety of functionallized radioiodinated agents indicate the following order of carbon-iodine (C-I) bond stability in vivo: iodoaryl>iodovinyl>iodoalkyl. This order of in vivo stability would indeed be expected for the following reasons. In aryl and vinyl halides the iodine bearing carbon is sp^2 hybridized and the C-I bond is resonance stabilized by electron delocalization giving C-I bond a double bond character as compared to pure single bond in alkyl iodides in which carbon bearing iodine is sp^3 hydribized.

Methods were subsequently investigated for easy, straight forward and facile incorporation of radiohalogens into the tissue specific radiopharmaceuticals functionallized as vinyl and aryl halides. A comprehensive report on the radiohalogenation subject is beyond the scope of these proceedings and only the incorporation of radiohalogens via organometallic reactions is briefly described here.

Synthesis of radiohalogenated radiopharmaceuticals via organometallic reactions

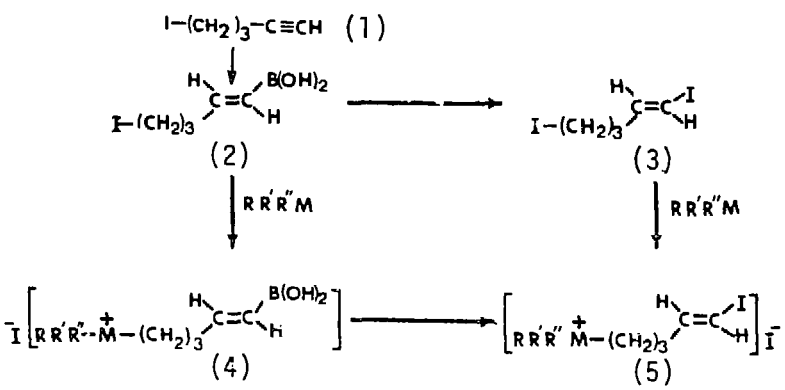
The synthetic procedure normally involves the preparation of an appropriately metallated organic intermediate which can be readily radiohalogenated. The metallated intermediates should preferably be stable at room temperature under normal conditions to allow shipment for an offsite radiohalogenation. Metallation methods which appeared to provide appropriate radiohalogenation substrates in our laboratory include boronation, thallation, mercuration and stannylation. Hydroalumination of alkynes gives, in situ, the alkylvinyl alanes which can also be readily iodinated or brominated (ref.6). This method, however, appeared less useful for radiohalogenations due to the highly reactive nature of the hydroaluminating reagent and the alane intermediate formed in situ.

Halogenation via boronic acid intermediates

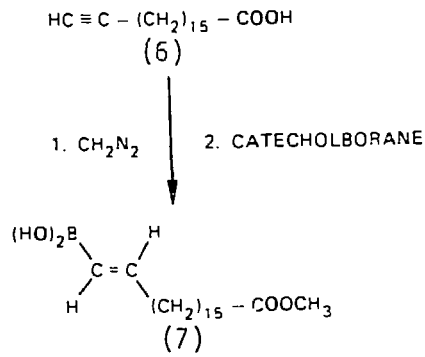
Hydroboronation of various alkynes (1) gives the corresponding alkylvinyl boronic acids (2) as stable and crystalline intermediates suitable for radioiodination using sodium iodide and chloramine-T. This radioiodination method developed by Dr. G. W. Kabalka (ref.7) who will discuss this subject in the later part of these proceedings. Our experience with this reaction pertaining to radiopharmaceutical development is described here.

Several radioiodinated iodopentenyl-trisubstituted phosphonium, arsonium and ammonium iodides (5) have been prepared and evaluated in rats to determine the effects of structural variations of the cations on myocardial uptake and

retention. The synthesis of (5) involved condensation of (E)-1,5-diiodopentene (3) with trisubstituted phosphine arsine and amine precursors respectively. Alternatively the crystalline vinylboronic acid intermediates (4) were first synthesized and radioiodinated using $Na^{125}I$-sodium iodide and chloramine-T (Scheme 1). The radioiodinated cations showed good heart uptake and retention in rats (ref.8).

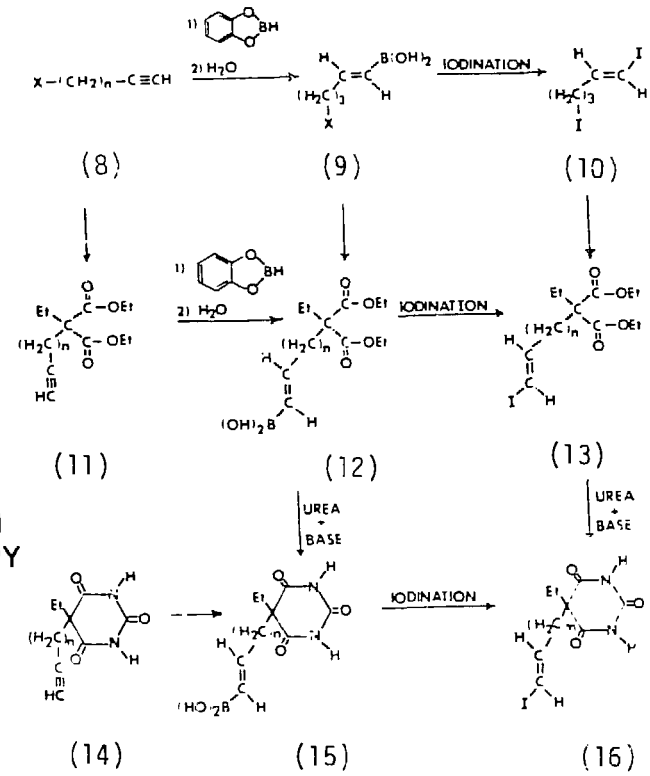


Scheme 1



Scheme II

Various radioiodinated fatty acids in which radioiodine is stabilized as a terminal vinyl iodide have been conveniently prepared by this method (ref.9). It is also pertinent to discuss here certain limitations this reaction may have. The hydroboration of alkynes with reducible or carbon-hetero atom multiple bond groups is difficult and often impossible. For example, the hydroboronation of 17-octadecynoic acid (6) with catecholborane (Scheme II) required special conditions (ref.10), where as similar boronation of 5-ethyl-5-(1-pentyn-5-yl)barbituric acid (14) failed to give the corresponding borono intermediate 15, prepared alternatively by a long route (Scheme III), as iodination substrate (ref.11).



Scheme III

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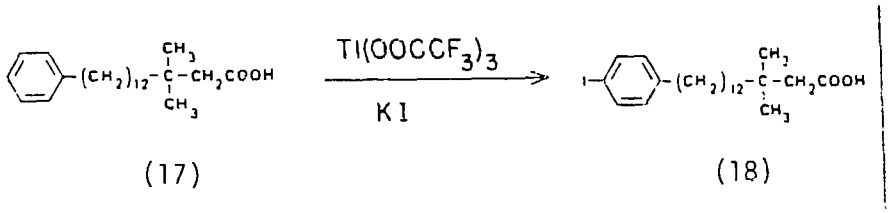
Halogenation via thallation of vinyl and aryl compounds

Aryl iodination via thallation developed by Taylor et al. (ref.12) has been found satisfactory for the corresponding radioiodination reactions and has been used extensively in our laboratory for aryl radioiodination of phenyl (ref.13) and thienyl (ref.14) fatty acids. Recently a new β,β-dimethyl-branched fatty acid, 15-p-[^{125}I]iodophenyl-3,3-dimethylpentadecanoic acid (18) has been prepared by thallation-iodination treatment of the corresponding phenyl fatty acid 17 (Scheme IV). Compound 18 shows excellent myocardial uptake and retention properties (ref.15).



Scheme IV

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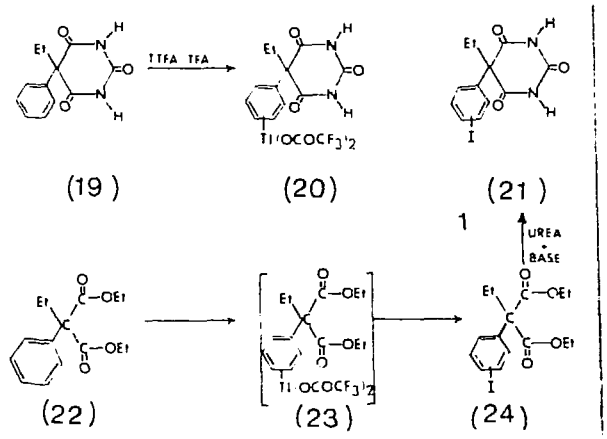
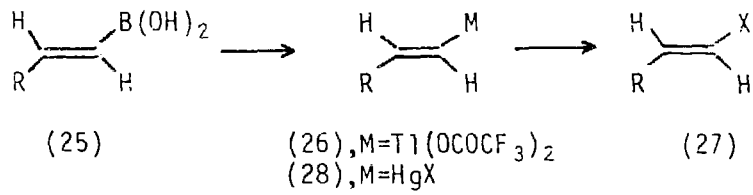


Scheme V

Direct thallium(III)trifluoroacetate/trifluoroacetic acid (TTFA/TFA) thallation of molecules with NH and OH tautomeric groups (such as in 5-ethyl-5-phenylbarbituric acid, 19) has been found to be difficult. Under these conditions, however, an alternate approach, thallation-iodination of a TTFA-insensitive substrate (22) followed by the product (21) formation was found more convenient (Scheme V, ref.16).

Alkylvinylthallium trifluoroacetate intermediates (26) can be easily generated in situ from the corresponding vinylboronic acids (25) and TTFA to undergo facile radioiodination with sodium radioiodide to yield vinyl iodides (27). This reaction (Scheme VI, ref.17), recently developed in our laboratory may find applications for radioiodination of substrates sensitive to an acidic medium such as TFA and an oxidizing agent such as chloramine-T.



Scheme VI

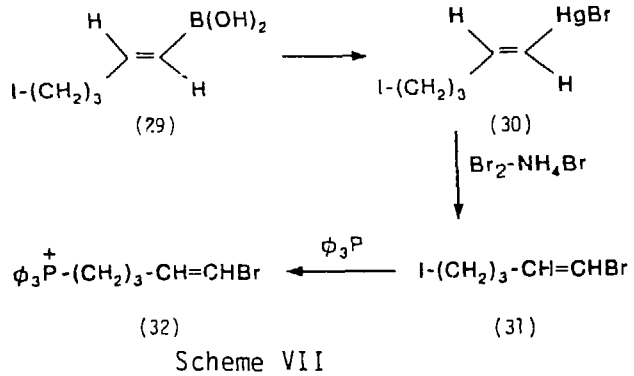
Halogenation via mercuration

Treatment of vinylboronic acids (25 or 29) with mercuric acetate in tetrahydrofuran gives the corresponding vinyl mercuric acetates in situ which after treatment with a halide such as sodium iodide or sodium bromide give the corresponding vinylmercuric halides (28 or 30) in the crystalline form. The mercury halide intermediates (28) undergo radioiodination similar to boronic acids when treated with sodium radioiodide and chloramine-T to furnish vinyl radioiodides (27). Iododemercuration of p-aminophenylmercuric acetate with I_2-$^{125}I^-$ has proven to be a very convenient and facile method for the synthesis of p-[^{125}I]iodoaniline (ref.17). The mehtod could be used for the synthesis of similar aryl iodides.

Treatment of 30 with bromine-radiobromide gives, almost instantaniously, the corresponding vinylradiobromide (31) as a mixture of cis and trans isomers. The cis/trans-1-[^{82}Br]bromo-5-iodo-1-pentene (31) thus prepared has been used for the synthesis of a potential myocardial perfusion agent, triphenyl-(cis/trans-1-[^{82}Br]bromo-1-penten-5-yl)phosphonium iodide (32) (Scheme VII).

Iodination via stannylation

Hydrostannylation of alkynes with tri-n-butyltin hydride (n-Bu_3)SnH is a versatile reaction which gives the corresponding trans-vinyl-tri-n-butyltin compounds as stable substrates for radioiodination. The method has successfully been used for the radioiodination of steriods and fatty acids, functionallized as trans-vinyl-(tri-n-butyl)tin substrates, with $^{125}I^-$-hydrogen peroxide (ref.18) and $^{125}I^-$-N-chlorosuccinimide (ref.5), respectively.



Scheme VII

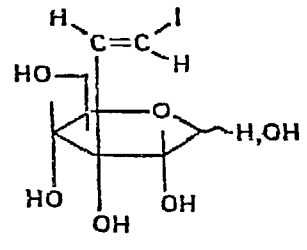


Figure 2

Further application of this reaction has been demonstrated in our laboratory by the synthesis of (E)-C-3[^{125}I]iodovinyl-D-allose (Fig. 2) from the corresponding iodovinyltin precursor to study the in vivo stability of sugars functionallized as vinyl iodides (ref.19).

The investigation of various radiohalogenation procedures in our laboratory has enabled us to synthesize a variety of radiohalogenated radiopharmaceuticals to study the relative in vivo stability of radioiodide attached to alkyl, vinyl and aryl groups and the tissue uptake in laboratory animals and human models. With recent advances in imaging techniques, increasing interest in radioiodinated agents and availability of pure iodine-123, undoubtedly, these methods will find useful applications in radiopharmaceutical development.

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