

Use of organoboranes in modern medical imaging

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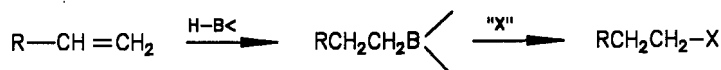
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Abstract - Isotopically labeled materials have proven to be invaluable in chemical, medical, and biological research. Organoboranes are beginning to play a significant role in the synthesis of medically important materials which contain both stable and short-lived isotopes. The organic compounds of boron possess characteristics which make them ideal intermediates in radiopharmaceutical pathways; these include the facts that boron reactions tolerate a wide variety of physiologically active functionality and that the reactions proceed rapidly and in high yields. Boranes have found important applications in modern medical imaging techniques such as positron emission tomography (PET) and magnetic resonance imaging (MRI).

INTRODUCTION

Isotopically labeled compounds have traditionally played an important role in chemistry, biology, and medicine. In recent years the development of new routes to labeled compounds has become more important due to the availability of relatively inexpensive cyclotrons which are capable of producing a selection of useful isotopes (ref. 1). Organoboranes were the first of the modern organometallic reagents to be utilized for synthesizing labeled compounds of interest in medical imaging (ref. 2). During the decade which followed the early organoborane research, a variety of reactions were developed which utilize boron, tin, mercury, and other metal-based reagents (ref. 3).

An important aspect of organoborane chemistry is that boron can be incorporated into a large number of physiologically active compounds in a stereochemically defined manner. Even more significantly, we have demonstrated that the boron atom can be rapidly replaced by a large number of medically useful isotopes. It is also noteworthy that non-radioactive



(where R can contain: $-\text{NO}_2$, $-\text{CN}$, $-\text{CO}_2\text{R}$, etc. and X represents a variety of isotopes such as ^{123}I , ^{11}C , ^{13}C , ^{15}N , ^{13}N , ^{15}O , etc.)

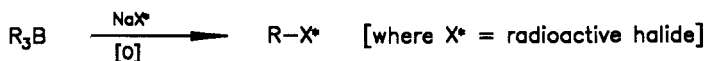
isotopes are beginning to play a more significant role in biomedical research because of recent developments in high resolution mass spectrometry and multinuclear magnetic resonance imaging (MRI); carbon-13, nitrogen-15, oxygen-17, and fluorine-19 labeled compounds now widely used.

In recent years, the focus of our research has been on the development of organoborane reactions with biomedical applications (ref. 4). These reactions complement the extensive repertoire of organoborane transformations of use in organic syntheses (ref. 5). Highlights of current research are presented in the following discussions.

HALOGEN ISOTOPES

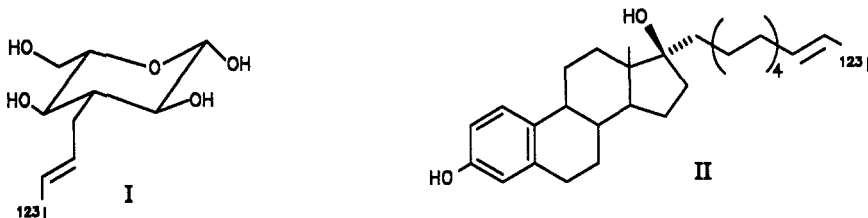
The reactions of organoboranes with molecular iodine and bromine were effectively developed by H. C. Brown and his coworkers (ref. 6). The method was not suited to the production of radiohalogenated reagents due to the dangers and cost associated with radiohalogens in the

molecular state. We developed a new halogenation methodology which utilizes the halogen in the readily availability halide form and involves an experimentally simple in situ oxidation (ref. 7).



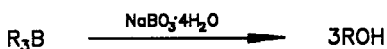
The method is equally suited for isotopes of iodine and bromine (ref. 8). Significantly, the reaction can be used to prepare a wide variety of aryl, vinyl, and alkyl halides including amphetamines (ref. 9), fatty acids (ref. 10), and steroidal derivatives (ref. 11).

Currently, our research is focused on the syntheses of a series of iodovinylglucose, derivatives, I, which are being screened for metabolic activity in the myocardium and brain and modified 17 α -iodovinylsteroids, II, for tumor imaging.

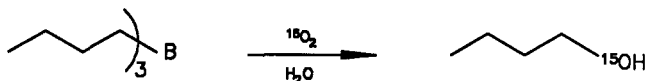


OXYGEN

Organoboranes are readily oxidized by a wide variety of agents. One of the most convenient methods involves the use of sodium perborate, a safe and inexpensive reagent which tolerates a wide variety of functional groups (ref. 12).



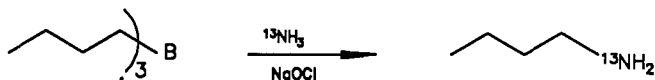
Molecular oxygen is readily available labeled with essentially all known oxygen isotopes. Consequently the most straightforward routes to oxygen-labeled agents involves the direct reaction of borane reagents with oxygen gas. The method has been used to incorporate oxygen-18, oxygen-17 and oxygen-15 (ref. 13). The synthesis of oxygen-15 labeled butanol



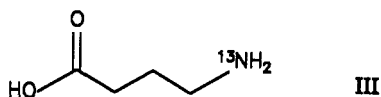
has been utilized as a blood flow agent in clinical brain imaging studies (Ref. 14). Our current emphasis has been on the production of polymeric organoboranes which can be utilized in microprocessor-controlled automatic synthesis units for use in the medical arena (ref. 15).

NITROGEN

A number of effective amination reactions have been developed over the years (ref. 16). All involve amine reagents which contain stable anionic leaving groups. An in situ method for generating chloramine was developed for synthesizing isotopes of nitrogen (ref. 17). The method is suitable for preparing nitrogen-13 labeled amines (ref. 18).



Current research in our laboratories is focused on the synthesis of nitrogen-13 labeled γ -aminobutyric acid, III, for use in neurological studies.



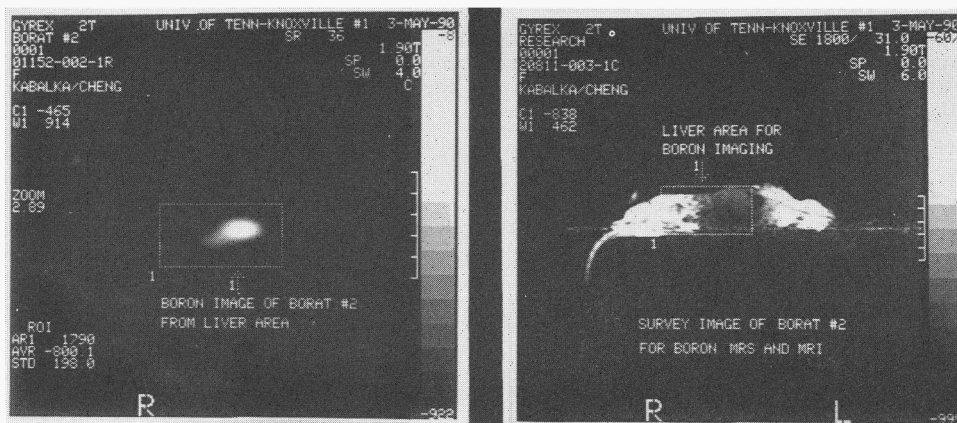
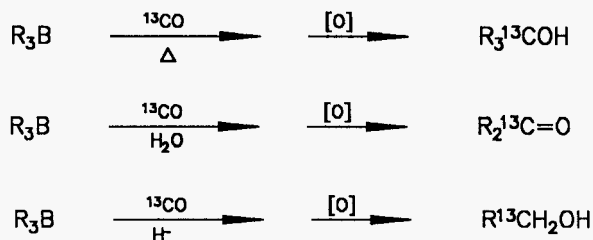


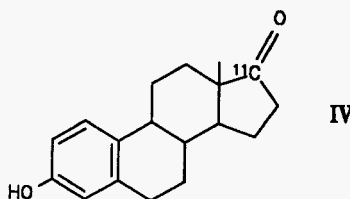
Fig. 1. Hydrogen MR image (right) and boron-11 MR image (left) of rat infused with BNCT agent

CARBON

Isotopes of carbon have played an important role in medical and chemical research. Organoboranes readily react with isotopically labeled carbon monoxide and cyanide ion to produce a variety of labeled ketones and alcohols (ref. 19).



Our research efforts are now focused on preparing carbon-11 labeled steroidal derivatives, IV, (ref. 20).



BORANES AS IMAGING AGENTS

Interestingly, boron itself can be used in medical imaging. This has become important due to the resurgence of a therapeutic technique known as boron-neutron-capture therapy (BNCT). The therapy is based on the fact that boron-10 has a high neutron capture cross-section and a great deal of energy is released when a neutron is captured (>2.4 MeV!). This energy can be utilized to kill tumors if the boron can be localized at the tumor site (ref. 21). There is a significant amount of research being focused on the design of new, organ-specific, boron-rich agents for use in BNCT. Unfortunately, it has not been possible to verify whether or not the agents successfully accumulated in the desired location until after postmortem. Realizing that both boron-10 and boron-11 were magnetically active, we developed the first magnetic resonance imaging (MRI) protocol for imaging boron in an intact animal (ref. 22). Development in the area has continued (ref. 23) and includes our recently created method for imaging boron and other nuclei with very short T_2 relaxation rates (ref. 24). The image presented in Fig. 1 on this page is that of a live rat injected with a sulphydryldodecaborane BNCT agent; the highlighted area reveals that the boron agent accumulated in the liver.

Acknowledgements

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