

CONF.
T10521--2

MASTER

AN EFFICIENT MICROSCALE PREPARATION OF TIN-117m-TIN
TETRACHLORIDE-A PIVOTAL INTERMEDIATE FOR
THE SYNTHESIS OF TIN-117m-LABELED RADIOPHARMACEUTICALS

David V. Woo, Furn F. Knapp, Jr., Thomas A.
Butler, and Alvin P. Callahan

Nuclear Medicine Technology Group
Health and Safety Research Division
Oak Ridge National Laboratory
Oak Ridge, Tennessee 37830

NOTICE
...
...

ABSTRACT

A microscale technique has been developed for the preparation of $^{117m}\text{SnCl}_4$. The radiolabeled tin tetrachloride is an important intermediate for the synthesis of ^{117m}Sn -labeled organic radiopharmaceuticals. The "flow-through" system involves high temperature chlorination of metallic ^{117m}Sn with subsequent cryogenic collection of the $^{117m}\text{SnCl}_4$ in a special reaction vessel. This vessel can then be used for the conversion of the tin tetrachloride to various useful intermediates. The reactions that have been studied include the formation of tetraalkyl and tetraaryl tin compounds by reaction of SnCl_4 with Grignard or alkyl and aryl lithium reagents ($\text{SnCl}_4 \rightarrow \text{R}_4\text{Sn}$ or Ar_4Sn). In addition, by stoichiometric control, the comproportionation of SnCl_4 with tetramethyltin can yield any one of the mixed methylchlorotin intermediates, MeSnCl_3 , Me_2SnCl_2 or Me_3SnCl . These products are important intermediates for the preparation of ^{117m}Sn -labeled steroids, fatty acids, amino acids, barbiturates and a variety of other potentially useful agents.

By acceptance of this article, the publisher or recipient acknowledges the U.S. Government's right to retain a nonexclusive, royalty-free license in and to any copyright covering the article.

EAB

INTRODUCTION

The Sn-117m radionuclide decays by isomeric transition with the emission of a primary single γ -photon in 87% abundance with an energy of 158 keV. The efficient detection of the 158 keV photon with sodium iodide crystals and the moderate 14 day physical half-life suggests that Sn-117m-labeled agents would be an attractive new class of radiopharmaceuticals. In addition, these agents would have a reasonable shelf-life and the absorbed tissue dose would be lower than the dose experienced with agents labeled with longer-lived radionuclides such as Te-123m and Se-75. Organotin chemistry is very versatile and such compounds are often quite stable (1) and one could thus envision the preparation of a wide variety of tissue-specific Sn-117m-labeled radiopharmaceuticals. This combination of favorable radionuclidic properties, well-defined chemistry and synthetic versatility has prompted us to explore the preparation of organotin compounds of biological interest.

The synthesis of ^{117m}Sn -labeled organotin compounds requires the initial conversion of metallic ^{117m}Sn to a suitable intermediate. In our estimation, tin tetrachloride (SnCl_4) fills the requirements of a versatile and useful intermediate for the synthesis of a wide variety of organotin compounds. We now report a high-yield microscale method for the conversion of metallic ^{117m}Sn to the pivotal SnCl_4 intermediate. This flow-through method involves chlorination of the metallic tin with the subsequent distillation and trapping of the SnCl_4 in a specially designed reaction vessel. This reaction vessel can be subsequently used to prepare a variety of useful ^{117m}Sn -labeled intermediates.

APPARATUS FOR PREPARATION OF TIN TETRACHLORIDE

The apparatus shown in Figure 1 was specially designed for the in-line microscale preparation of SnCl_4 . The receiver-reaction vessel can be used for the synthesis of various organotin intermediates. The Vycor reduction tube (48 cm x 2.5 cm) is connected to Pyrex tubing at either end with graded seals. A glass manifold fitted with Teflon gas-inlet stopcock valves is connected via a 35/20 ball joint to the inlet side of the reduction tube. The flow-rates of gases introduced through the manifold are monitored by precision flow meters. The reduction tube is heated with a split-tube furnace (20 cm x 3 cm; Hevi Duty Electric Co., Milwaukee, WI) with a maximum rating of 1000°C. A pyrex receiver-vessel is attached to the reduction tube to trap the SnCl_4 . This vessel can subsequently be used to convert the SnCl_4 to various useful organotin intermediates by the introduction of reagents through a rubber or silicon septum. The conical shape of the reaction vessel enables the use of a conical magnetic stirring bar to agitate small volumes. Finally, the exit gases are passed through a tube filled with activated charcoal and then a NaOH scrubber.

PREPARATION OF TIN TETRACHLORIDE

The preparation of $^{117m}\text{SnCl}_4$ requires several steps rather than the direct chlorination of reactor produced metallic ^{117m}Sn as a result of the necessity

to accurately determine the production yield of ^{117m}Sn . The ^{117m}Sn was formed by neutron irradiation (n, γ) of 94.74% enriched ^{116}Sn in the Oak Ridge High Flux Isotope Reactor (HFIR) at a thermal neutron flux of $2.5 \times 10^{15} \text{ n/cm}^2 \cdot \text{sec}$. The reactor target was dissolved in conc. HCl to give a solution of hydrated tin dichloride ($^{117m}\text{SnCl}_2 \cdot \text{H}_2\text{O}$) (Figure 2). Aliquots of this solution were assayed to accurately determine the radionuclidic purity, specific activity and production yield of the ^{117m}Sn . A preliminary assessment of the factors influencing the reactor production of ^{117m}Sn by the HFIR irradiation of enriched ^{116}Sn targets can be made on the basis of five irradiation experiments. All irradiations were conducted in the same physical location in the HFIR hydraulic tube facility. The ^{116}Sn targets varied in weight from 10 to 73 mg and the irradiation periods varied from 2 to 14 days. The ^{117m}Sn production yields are consistent with an effective cross section (σ) of 13.1 millibarns and follow the radioisotope production equation $A = N\phi\sigma(1 - e^{-\lambda t})$. After a seven day irradiation a ^{117m}Sn product with a specific activity of 1.3 mCi/mg was obtained and this increased to 2.2 mCi/mg after a fourteen day irradiation. The maximum specific activity of ^{117m}Sn which we can achieve is calculated to be ~ 4.4 mCi/mg and an excess of 140 days irradiation would be required to reach this value. We can conclude that ^{117m}Sn does not have a significant neutron capture cross section and that target self-shielding is not a significant factor.

Tin(II) dichloride can be conveniently converted to tin(II) oxide by treatment with sodium carbonate (reaction 2). The hydrated $^{117m}\text{SnCl}_2$ solution is reduced to a minimal volume (~ 5 ml) and a saturated Na_2CO_3 solution added until the phenolphthalein end-point is reached. The hydrated ^{117m}SnO is formed as a fine colloidal solid and is heated for 2-3 hours resulting in the quantitative conversion to a crystalline allotropic form having a blue-black metallic luster. This product is washed several times with distilled water, centrifuged and dried in an oven at $\sim 140^\circ\text{C}$. Carrier $\text{SnCl}_2 \cdot \text{H}_2\text{O}$ can be added to the $^{117m}\text{SnCl}_2 \cdot \text{H}_2\text{O}$ acid solution if a product with a lower specific activity is required.

The high temperature hydrogen reduction of tin(II) oxide gives metallic tin (reaction 3). The ^{117m}SnO is transferred to a 76 mm x 16 mm x 10 mm silica boat (Amersil, Inc.; Hillside, NJ) which is placed in the center of the reduction tube. The apparatus is purged with argon and the reduction tube gradually heated to $\sim 200^\circ\text{C}$ to remove all traces of moisture. Hydrogen gas is introduced through the system while the temperature of the reduction tube is slowly raised to 580°C over a one hour period. The water of hydration volatilizes at about 450°C and is swept out of the reaction system in the hydrogen stream. The ^{117m}SnO reduction is allowed to proceed for two hours and the system is then cooled to ambient temperature and flushed with argon. A minimal argon flow is maintained to prevent introduction of atmospheric oxygen and possible re-oxidation of tin.

Tin tetrachloride can be obtained in high yield by high temperature chlorination of tin metal (reaction 4). After cooling, the reaction system is

flushed with dry chlorine gas at a flow rate of ~ 20 - 30 ml/min. The furnace temperature is raised to $\sim 150^\circ\text{C}$ and the $^{117\text{m}}\text{SnCl}_4$ forms as clear liquid droplets on the glass surface of the reduction tube. The receiver-reaction vessel is cooled to -30°C in a dry ice-trichloroethylene bath. The $^{117\text{m}}\text{SnCl}_4$ is then distilled cryogenically from the reduction tube into the receiver-reaction vessel by gentle heating of the reduction tube with a forced-air heat gun. A minimal flow of chlorine gas is required during this stage to sweep the $^{117\text{m}}\text{SnCl}_4$ vapor into the receiver-reaction vessel. The chlorination is terminated when there is no further evidence of tin metal in the silica boat. The furnace is removed and the system then flushed with a minimal flow of argon. The cooling bath is removed from the receiver-reaction vessel and the $^{117\text{m}}\text{SnCl}_4$ is allowed to warm to about 10°C . The reaction vessel is maintained at this temperature to minimize any potential evaporation and loss of the $^{117\text{m}}\text{SnCl}_4$ product. At this stage the $^{117\text{m}}\text{SnCl}_4$ appears a light yellow color due to trace amounts of dissolved chlorine. The color gradually fades as the dissolved chlorine is volatilized and swept away in the argon stream. The resulting colorless $^{117\text{m}}\text{SnCl}_4$ solution is ready at this stage for subsequent transformations.

In a parallel experiment, non-radioactive tin metal was converted to SnCl_4 using the apparatus shown in Figure 1. Since SnCl_4 is a highly reactive and corrosive substance the identity of the tin tetrachloride was experimentally supported by freezing point and boiling point measurements. The experimentally determined freezing point (-35°C) and boiling point (114°C) values were identical to similar values determined with commercially available tin tetrachloride. Furthermore, the tin tetrachloride prepared with the apparatus shown in Figure 1 was converted to tetraphenyltin, a stable, crystalline substance having a well-defined melting point and which was readily characterized by a variety of physical methods (*vide infra*).

CONVERSION OF TIN TETRACHLORIDE TO ORGANOTIN INTERMEDIATES

The $^{117\text{m}}\text{SnCl}_4$ can be converted to a variety of $^{117\text{m}}\text{Sn}$ -labeled organotin intermediates by the direct introduction of reagents into the receiver-reaction vessel. The center neck of the vessel (Figure 1) is fitted with a septum through which the reagents are conveniently introduced with a hypodermic syringe. Reaction mixtures can be heated or cooled by immersing the conical tip of the reaction vessel in a water bath, and the reaction mixtures are stirred using a magnetic stirrer. The most important aspect of this system is of course that the highly reactive tin tetrachloride is distilled directly into the reaction vessel in an argon atmosphere eliminating exposure to atmospheric moisture.

Table I illustrates the variety of organotin intermediates that have been prepared using this system. The synthesis of tetraphenyl tin ($\phi_4\text{Sn}$) will be used to illustrate the conversion of SnCl_4 to an organotin intermediate using this apparatus since $\phi_4\text{Sn}$ is a crystalline, well characterized substance.

Tin metal (115 mg, 1 mmol) was chlorinated as described earlier and the SnCl_4 distilled into the special reaction vessel. Three milliliters of a 1.75 M phenyl lithium solution in benzene-ether, 70:30 (Aldrich Chemical Co.) were added dropwise over a 30 minute period to the SnCl_4 solution cooled to 0-4°C. The solution was gently stirred under argon and as the reaction proceeded a milky white precipitate of lithium salts appeared. After addition of the ϕLi solution the temperature was raised to 40°C and the reaction allowed to proceed for 30 minutes. After cooling to 0-4°C, 3-4 ml of water was added cautiously and the mixture was then agitated and heated to 70-80°C. The hydrolyzed mixture was then allowed to stand until the aqueous and organic layers separated. The benzene layer was decanted and the aqueous phase then extracted with warm chloroform. This procedure was repeated twice and the combined benzene and chloroform extracts washed well with water and evaporated to dryness under argon. The resulting white solid was re-crystallized from chloroform with cooling. The crystalline solid had an uncorrected melting point of 227°C (commercially available $\phi_4\text{Sn}$ melted at 227°C). In addition, the synthetic sample exhibited thin-layer chromatographic, ultraviolet, mass spectral and ^1H and ^{13}C nuclear magnetic resonance properties identical to similar values determined using an authentic sample of tetraphenyl tin (Aldrich Chemical Co.)

DISCUSSION

The apparatus shown in Figure 1 was specially designed for the preparation of a variety of useful intermediates from tin tetrachloride. As an example, reaction of SnCl_4 with excess Grignard reagents or alkyl lithium or aryl lithium reagents gives the tetraalkyl or tetraaryl tin products in good yields (Table 1). Another interesting reaction is the non-statistical ratio of products (comproportionation) formed by treatment of SnCl_4 with Me_4Sn (1). As an example, reaction of SnCl_4 and Me_4Sn in a 1/3 molar ratio gives $\text{Me}_3\text{Sn}-\text{Cl}$ as the sole end product. Similar reaction of these reactants in an equal molar ratio gives Me_2SnCl_2 and a 3/1 molar ratio yields MeSnCl_3 . These products are formed in each case by reaction of the neat reactants without the use of a solvent. This is an obvious advantage since subsequent transformations on the products are therefore simplified. One of the most useful intermediates for the synthesis of trimethyltin substituted compounds is formed by simple reaction of $\text{Me}_3\text{Sn}-\text{Cl}$ with lithium metal in tetrahydrofuran (2). A unique class of trimethyltin substituted steroids have been prepared from $\text{Me}_3\text{Sn}-\text{Li}$ (3). Trimethylchloromethyltin ($\text{Me}_3\text{SnCH}_2\text{Cl}$) is another interesting and useful intermediate which can be prepared by the following route: $\text{SnCl}_4 + \text{Me}_4\text{Sn} \longrightarrow \text{Me}_3\text{Sn}-\text{Cl} + \text{CH}_2\text{N}_2 \longrightarrow \text{Me}_2(\text{CH}_2\text{Cl})-\text{Sn}-\text{Cl} + \text{CH}_3\text{MgBr} \longrightarrow \text{Me}_3\text{SnCH}_2\text{Cl}$ (4). In this case the methylene group can serve as a "spacer" for introduction of the $\text{Me}_3\text{Sn}-$ moiety into regions of molecules that are subject to steric hindrance. These are just a few examples of how the wealth of known organotin chemistry can be applied for the potential synthesis of $^{117\text{m}}\text{Sn}$ -labeled compounds of biological interest.

A microscale method for $^{117\text{m}}\text{SnCl}_4$ production had to be developed and

optimized before the subsequent preparation of ^{117m}Sn -labeled organic radio-pharmaceuticals could be initiated. Now that this efficient method has been developed for the preparation of the crucial SnCl_4 intermediate, we envision the synthesis of an exciting array of ^{117m}Sn -labeled agents, including various steroids, fatty acids, amino acids, barbituates and other unique compounds that are potentially useful for *in vivo* tissue imaging procedures.

ACKNOWLEDGEMENTS

Research sponsored by the Office of Health and Environmental Research, U. S. Department of Energy under contract W-7405-eng-26 with the Union Carbide Corporation. The authors thank R. A. Grigsby for his assistance in several of the tin tetrachloride conversions and C. A. Floyd for typing the manuscript.

REFERENCES

- (1) NEUMANN WP: *The Organic Chemistry of Tin*, New York, John Wiley & Sons, 1970
- (2) TAMBORSKI C, FORD FE, SOLOSKI EJ: Preparation and Reactions of Trialkyltinlithium. *J Org Chem* 28:237-239, 1963
- (3) Unpublished experiments, 1979
- (4) SEYFERTH D, ROCHOW EG: The Reaction of Organotin Halides with Diazo-methane. *J Amer Chem Soc* 77:1302-1304, 1955

Table 1. The apparatus shown in Figure 1 was used for the conversion of tin oxide to metallic tin by high temperature hydrogen reduction. The metallic tin was subsequently converted to tin tetrachloride by reaction with chlorine gas. The tin tetrachloride was distilled into the special reaction vessel and then reacted with a variety of alkyl metal reagents to form selected tin intermediates.

<u>Experiment</u>	<u>Substrate</u>	<u>Initial Product</u>	<u>Reagent</u>	<u>Final Product</u>	<u>Overall Yield</u>
I	$\text{SnO} \rightarrow \text{Sn}$	SnCl_4	ϕLi	$\phi_4\text{Sn}$	54%
II	$\text{SnO} \rightarrow \text{Sn}$	SnCl_4	CH_3MgBr	Me_4Sn	59%
III	$\text{SnO} \rightarrow \text{Sn}$	SnCl_4	Me_4Sn	Me_3SnCl	86%
IV	$*\text{SnO} \rightarrow *\text{Sn}$	$*\text{SnCl}_4$	72%
V	$*\text{SnO} \rightarrow *\text{Sn}$	$*\text{SnCl}_4$	Me_4*Sn	Me_3*SnCl	55%

(*Sn denotes the tin-117m radionuclide)

FIGURE 1

Diagram of the apparatus that was developed for the microscale preparation of tin tetrachloride. The apparatus consists of essentially two important components. The split-tube furnace heats the reaction tube in which the $\text{SnO} \longrightarrow \text{Sn}$ and $\text{Sn} \longrightarrow \text{SnCl}_4$ conversions are conducted. The receiver-reaction vessel is used to cryogenically trap the SnCl_4 as it is distilled from the reaction tube. It can also be used for subsequent conversions, and the products listed in Table 1 were prepared in this receiver-reaction tube.

FIGURE 2

The sequence of reactions developed for the conversion of reactor produced $^{117\text{m}}\text{Sn}$ to $^{117\text{m}}\text{SnCl}_4$. The target is initially dissolved in HCl (reaction 1) so that aliquots can be counted to accurately determine the production yield and radionuclidic purity of $^{117\text{m}}\text{Sn}$. Reaction 2 converts the tin chloride to the insoluble Tin(II) oxide in high yield. Reactions 3 and 4 are performed in the specially designed apparatus shown in Figure 1



