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Research Article

Synthesis of carbon-14 labeled dibutyltin dichloride

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Abstract: This report describes the preparation of carbon-14 labeled dibutyltin dichloride from carbon-14 labeled barium carbonate in 30% overall radiochemical yield. The key steps were (a) the preparation of carbon-14 labeled butyl bromide from carbon-14 labeled barium carbonate via carbon-14 labeled butyl mesylate, and (b) the direct preparation of tetrabutyltin by the lithium-mediated reaction of dibutyltin dichloride with carbon-14 labeled butyl bromide. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: carbon-14; DBTC; butyl bromide; butyl mesylate; dibutyltin

Introduction

The widespread use of organotin compounds in numerous industrial applications has led to extensive release of these potentially toxic chemicals into the environment.[1] Of particular concern is the bioaccumulation of organotins in marine animals and the subsequent intake of these materials by humans. The predominant organotin found in human liver is dibutyltin (DBT).[2] In addition to being a known product of the breakdown and metabolism of tributyltin (TBT), which for many years was a major antifouling agent in marine paints, dibutyltin is a stabilizer in polyvinyl chloride pipes and thus has the potential for leaching into drinking water.[3] DBT binds tenaciously to some tissues and other matrices thereby increasing its probability for persistence both in living organisms and in the environment. The toxic effects of organotins have been known[4] for many years and have been the subject of considerable research.[5] DBT has been shown to be immunotoxic,[6] resulting in thymus atrophy[7,8] in rats. DBT is also a neurotoxicant[9] and has been shown to produce greater hepatotoxicity than either TBT or monobutyltin.[10] Since the underlying mechanisms associated with organotin toxicity are still incompletely understood, the synthesis of carbon-14 labeled DBT dichloride (DBTC) was undertaken to enable a study of the disposition of low doses of DBTC in rodent models.

Since the preparation of DBTC is an industrial process the protocol provided by Atofina chemists for the preparation of DBTC was evaluated for its suitability to the synthesis of the carbon-14 labeled analog. The Atofina protocol (Scheme 1) consists of reaction of four equivalents of butylmagnesium chloride with one equivalent of tin tetrachloride to furnish tetrabutyltin, followed by fusion with equimolar tin tetrachloride in the presence of aluminum trichloride to provide the target compound. According to Atofina chemists this procedure afforded DBTC in high yield and purity.

For the radiosynthesis our strategy was to modify the stoichiometries used in the industrial process (Scheme 2). Thus, our approach was to treat two moles of the radiolabeled Grignard reagent (**[^{14}C]-1**) with one mole of tin tetrachloride, and to complete the consumption of tin tetrachloride by treatment of the reaction mixture with excess unlabeled Grignard reagent (**1**). Since exact stoichiometry in the following step is crucial to obtaining the final product **[^{14}C]-2** free from mono-, tri-, and tetrabutylated tin products, complete conversion to tetrabutyl tin (**3**) was essential.

As source of the radiolabel it was planned to use the least expensive starting material available, carbon-14 labeled barium carbonate (Scheme 3). This series of transformations presented its own challenge since the process as described would involve very small amounts of relatively volatile materials.

Results and discussion

Exploration of the proposed synthetic route commenced with determination of the conditions appro-

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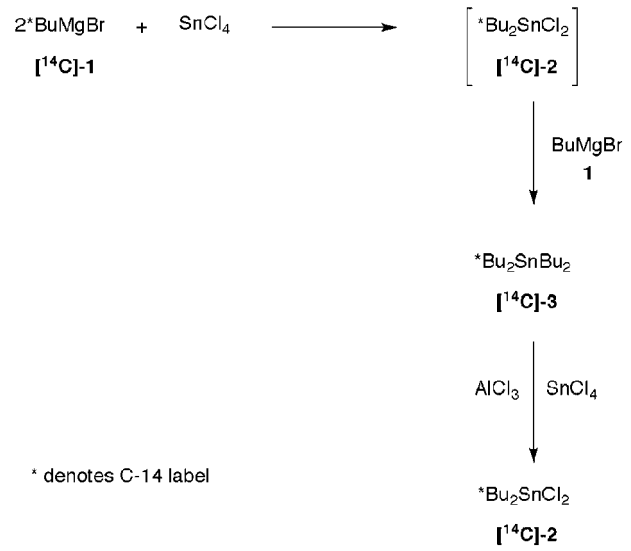
priate to the conversion of unlabeled butanol (**8**) (obtained as shown in Scheme 3) to the Grignard reagent **1**. Attempts to use thionyl chloride, thionyl bromide, or triphenylphosphine-imidazole-iodine for the conversion of butanol (**8**) to butyl halide (**9**) revealed that these conditions were unsuitable since the presence of trace amounts of acids and/or moisture completely blocked Grignard formation. Eventually a protocol using triphenylphosphine-N-bromosuccinimide in anhydrous THF was used to convert butanol (**8**) to butyl bromide (**9**) in acceptable yield and with purity suitable for the Grignard reaction. Conversion of the synthetic product to butylmagnesium bromide (**1**) proceeded in nearly quantitative yield.

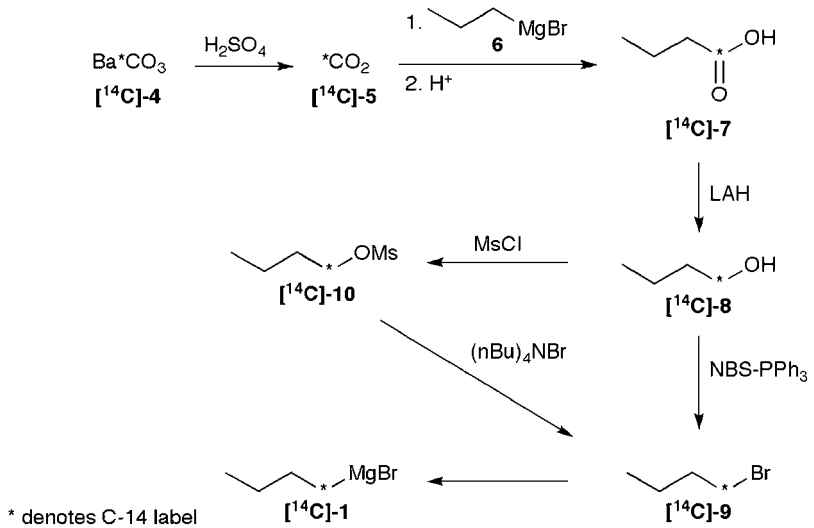
Before proceeding further with the synthesis the development of an efficient reliable method for monitoring and analyzing the butylation of tin and butyltin analogs was undertaken. In addition to TLC analysis it was found that ^{1}H-NMR chemical shift and integration data provided exquisitely sensitive tools for detecting and analyzing all four butyltin analogs and their mixtures to a ratio of 1:25. Thus, each of the four butylated tin compounds possessed unique, well-separated, identifying resonances. Specifically, tetrabutyltin (**3**) was the only one with resonances at 0.8 ppm, tributyl tin chloride (**11**) had a unique cluster of resonances at 1.65 ppm, DBTC (**2**) had signals at 1.8 ppm, and butyltin trichloride had signals at 2.4 ppm (Figure 1). The key intermediates DBTC and tetrabutyltin could be readily identified down to 1–2% presence in a butyltin mixture.

When the freshly prepared Grignard reagent **1** was reacted with 60% of the calculated quantity of tin tetrachloride (see Scheme 2) a butylated tin analog **2** precipitated. For simulation of reaction conditions to be used in the radiosynthesis, this product was reacted with 50% excess of commercial **1** without isolation. Workup of the reaction mixture afforded 60% of tetrabutyltin (**3**) in satisfactory purity. Subsequent treatment of **3** with equimolar tin tetrachloride in the presence of a catalytic amount of aluminum trichloride furnished DBTC (**2**) in 37% overall yield. Purity and recovery of **2** were considered adequate and, therefore, the same reaction conditions were utilized in a tracer radiosynthesis. Thus, carbon-14 labeled butanol **[^{14}C]-8** was treated with triphenylphosphine-N-bromosucci-

Scheme 1



Scheme 2



Scheme 3

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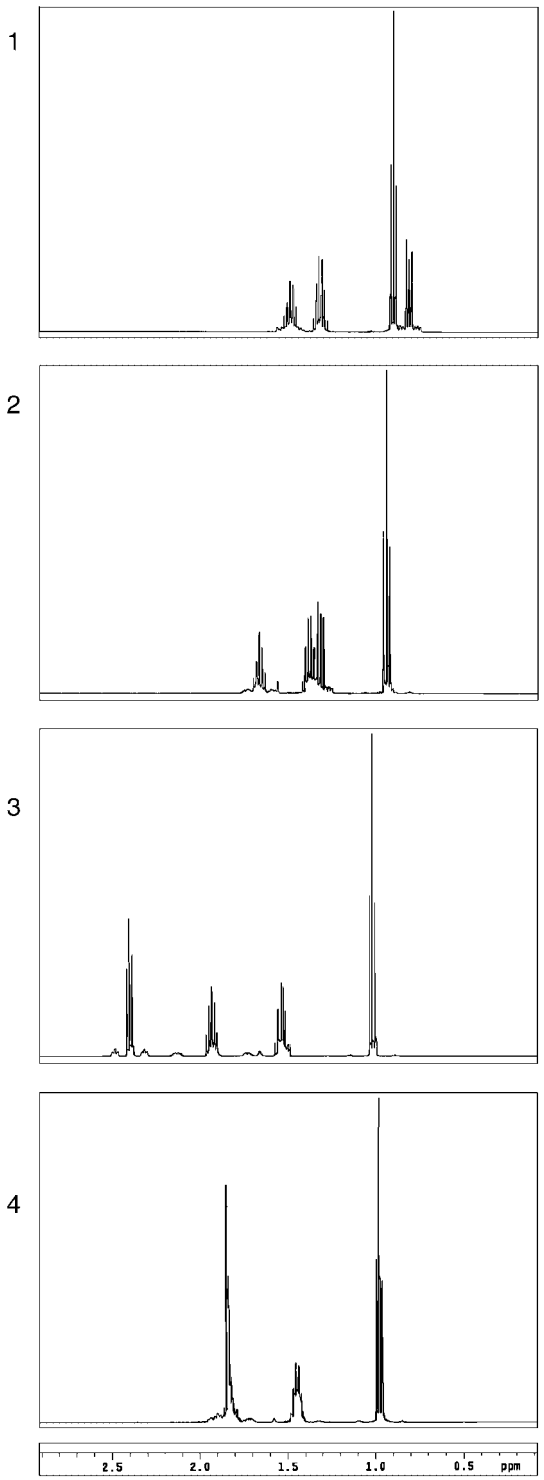

Figure 1 ^{1}H NMR spectra of (1) tetrabutyltin (2); (b) tributyltin chloride (**11**); DBTC (**2**); (d) butyltin trichloride in $CDCl_3$ at 300 mHz.

nimide (Scheme 3) and the product was used to prepare the Grignard **[^{14}C]-1**.

Unfortunately all attempts to recover **[^{14}C]-1** from this mixture failed. Attempts to facilitate the Grignard formation using Mg anthracene complex were also unsuccessful. Analysis of the crude reaction mixture by GC indicated the presence of butanol (**[^{14}C]-8**), but not of butyl bromide (**[^{14}C]-9**), suggesting that traces of water interfered with conversion of **[^{14}C]-8** to **[^{14}C]-9** (Scheme 3).

To address this problem, it was decided to utilize a butyl sulfonate as an intermediate in the preparation of the bromide **[^{14}C]-9** (Scheme 3). This approach had the advantage of being less sensitive to moisture because an excess of the sulfonyl chloride could be used and any hydrolysis product would be easily separable from the sulfonate product. In fact, the preparation of carbon-14 labeled butyl tosylate as an intermediate in the conversion of carbon-14 labeled butanol to carbon-14 labeled butyl chloride has been reported.[11] In a comparative study using unlabeled butanol (**8**) we observed that reaction with mesyl chloride took place at significantly lower temperature and provided higher product recovery than reaction with tosyl chloride. An added advantage was that due to its higher volatility a large excess of mesyl chloride could be used and readily removed under vacuum. In preliminary tests treatment of unlabeled **8** with mesyl chloride gave **10**, which was readily converted to the required butyl bromide (**9**) by reaction with tetrabutylammonium bromide. This product appeared to undergo quantitative conversion to the Grignard reagent **1**, based on the observation that the stoichiometric quantity of magnesium was consumed. However, subsequent butylation of tin tetrachloride with the obtained **1** furnished at best 60% of the stannane **3**, presumably due to side reactions of the Grignard reagent. This led us to investigate whether alkylation of tin tetrachloride could be performed directly in a heterogenous reaction by treating tin tetrachloride with butyl bromide (**9**) in the presence of magnesium or other metals.

Analysis of the product mixtures from the one-pot sonication of tin tetrachloride with butyl bromide (**9**) in the presence of magnesium or lithium showed the mixtures to consist of multiple butylated stannanes, with tetrabutylstannane (**3**) as a major component. Since this mixture was unsuitable for conversion to DBTC (**2**), the use of these conditions to form tributyltin chloride by reaction of equimolar DBTC (**2**) with butyl bromide (**9**) was examined. In the presence of metallic lithium a mixture containing mainly tributyltin chloride/bromide was obtained. Treatment of this mixture with butylmagnesium bromide (**1**) gave tetrabutylstannane (**3**). Further experimentation demonstrated that the conversion of tributyltin halide to **3** could be achieved by reaction with butyl bromide (**9**) and that this product was of significantly higher purity than that obtained from reaction of tributyltin halide with **1**.

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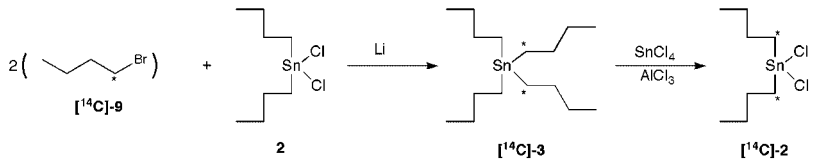

Scheme 4

These observations led to the development of a protocol (Scheme 4) in which DBTC (**2**) was reacted with two equivalents of butyl bromide (**9**) and excess lithium, without sonication, to furnish tetrabutyltin (**3**) in high yield and satisfactory purity.

With this information in hand the radiosynthesis was undertaken. The preparation of [^{14}C]-butanol (**[^{14}C]-8**) was carried out as shown in Scheme 3 (77%). Conversion to butyl bromide (**[^{14}C]-9**) (Scheme 3), followed by treatment with DBTC (**2**) (Scheme 4) furnished **[^{14}C]-3** in 55% yield. Fusion of **[^{14}C]-3** with equimolar tin tetrachloride in the presence of aluminum trichloride as catalyst gave [^{14}C]DBTC (**[^{14}C]-2**) in >98% radiochemical purity and 30% overall yield from $Ba^{14}CO_3$.

Experimental

Proton magnetic resonance spectra were obtained on a Bruker Avance 300 spectrometer. Decolorizing carbon Norit N (Fisher Scientific Co) was activated by heating *in vacuo* at 250°C for 10 min. Radioactive samples were counted using a Packard Tri-carb 2100 TR liquid scintillation spectrometer in Packard Utlima Gold cocktail using the external standard channels ratio as a method of quench correction.

[^{14}C]butyl mesylate [^{14}C]-10

[^{14}C]Butanol **[^{14}C]-8**[11] (115 mCi, 2.03 mmol) was cooled to 0°C, and triethylamine (650 mg, 6.43 mmol) followed by mesyl chloride (550 mg, 2.03 mmol) were added with stirring at 0°C. After a few minutes a white precipitate began to separate. The mixture was allowed to come to ambient temperature and stirring was continued 1 h. The product was concentrated to $\frac{1}{2}$ the volume and the solution was cooled to −2°C overnight. The supernatant was carefully siphoned from a white solid, then water was added to the residue and the product was extracted with isooctane (2 × 2 ml). The combined organic extract was evaporated to a colorless oil (288 mg, 96 mCi, 83% yield) which based on ^{1}H NMR analysis was of adequate purity for further synthesis. ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.96 (t, 3H, CH_3); 1.40 (m, 2H, CH_3-**CH_2**); 1.74 (m, 2H, CH_2-**CH_2**-CH_2O); 3.01, (s, 3H, SCH_3); 4.22 (t, 2H, **CH_2**O).

[^{14}C]butyl bromide [^{14}C]-9

A mixture of **[^{14}C]-10** (96 mCi, 1.69 mmol) and tetrabutylammonium bromide (700 mg, 2.17 mmol) in isooctane (5 ml) was heated under reflux in a N_2 atmosphere for 2 h. The mixture was cooled to 0°C and the isooctane carefully removed. The remaining suspension was diluted with isooctane (3 ml) and the mixture was refluxed for an additional 2 h. The suspension was cooled to 0°C, the isooctane phase carefully siphoned from the precipitated salts and the organic solution combined with the first extract. This solution contained 87 mCi (90% yield) of **[^{14}C]-9**. Because of its highly volatile nature the product was used directly in the next synthesis step.

[^{14}C]tetrabutyltin [^{14}C]-3

To a solution of **[^{14}C]-9** (87 mCi, 1.52 mmol) in THF (95 ml) at 0°C was added $SnCl_4$ (215 mg, 0.827 mmol) and hexane-washed lithium (30 mg, 4.29 mmol). The suspension was stirred at 0°C for 15 min, then at 25°C for 30 min. The mixture was cooled to 0°C and small chips of ice were added followed by 1 N HCl to pH1. The organic phase was isolated, the aqueous layer re-extracted with isooctane, (2 ml) and the combined organic phase was concentrated to ∼1 ml. The residue was cooled to −20°C overnight and a small amount of precipitate that formed was removed by filtration. The filtrate contained 63 mCi (72% yield) of **[^{14}C]-3**; ^{1}H NMR analysis of an aliquot indicated the product was of adequate purity. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.80 (t, 8H, CH_2Sn); 0.89 (t, 12H, CH_3); 1.28 (m, 8H, **CH_2**CH_2Sn); 1.47 (m, 8H, **CH_2**CH_3). The isooctane extract was evaporated to a colorless oil that was used for the preparation of the target compound.

[^{14}C]dibutyltin dichloride [^{14}C]-2

In a Teflon sealed vial a mixture of [^{14}C]tetrabutyltin **[^{14}C]-3** (178 mg, 0.5 mmol), $SnCl_4$ (176 mg, 0.677 mmol) and $AlCl_3$ (20 mg, 0.150 mmol) was heated at 115–125°C for 3–4 h under an atmosphere of argon. The cooled oil

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was sonicated with 1 N HCl (2 ml) resulting in a light beige crystalline material. The aqueous phase was carefully removed and the solid was dissolved in hexane and carefully passed though a column of Norit N which had been activated by heating to 250°C for a few min. The substrate was eluted with hexane (2 ml) followed by CH_2Cl_2 (2 ml). Evaporation of the eluate furnished white crystalline **[^{14}C]-2** (212 mg, 44 mCi) of 96% chemical purity on the basis of ^{1}H-NMR data in comparison with a commercial sample. ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.96 (t, 6H, 2 CH_3); 1.44 (m, 4H, 2 **CH_2**CH_3); 1.78 (m, 8H, $(CH_2CH_2)_2Sn$). Radiochemical purity was determined as 98% by TLC-radioscan (SiO_2; EtOAc-MeOH-HOAc 80:20:2, Rf 0.37). The specific activity was 63.7 mCi/mmol (gravimetrically determined).

Conclusions

A novel procedure for the alkylation of tin has been developed. The process has been used for the preparation of carbon-14 labeled DBTC and is readily adaptable to the radiosynthesis of other stannane derivatives. In light of the recent interest in the biological activity of alkyl tin analogs the described synthesis might be a helpful tool.

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