Preparation and Use of $LiEt_3BT$ and $LiAlT_4$ at Maximum Specific Activity

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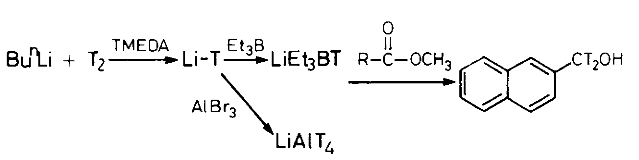
Carrier-free $LiEt_3BT$ and $LiAlT_4$ have been generated and used to reduce methyl 2-naphthoate to 2-(hydroxymethyl)naphthalene containing two tritium atoms per molecule.

We report a simple and facile synthesis of $LiEt_3BT$ ($LiEt_3B^3H$) and $LiAlT_4$ ($LiAl^3H_4$) at maximum specific radioactivity. The availability of these reagents, and of other complex hydrides at the carrier-free level, will allow the production of many highly tritiated materials from new reactions, including the reduction of acids, esters, aldehydes, ketones, and epoxides to the corresponding alcohols, and reduction of alkyl halides, amides, nitriles, and toluene-*p*-sulphonates. $LiEt_3BT$ and $LiAlT_4$ were used in exemplary reductions of methyl 2-naphthoate to 2-(hydroxymethyl)naphthalene, which was shown to have >95% of the maximum theoretical specific activity, and all of the tritium at the reduced position. Hence, we have demonstrated that the products of these reactions are both specifically and maximally labelled at the reduced positions.

Since the first report of the use of $LiEt_3BH$ (superhydride)[1] it has been applied in many chemical reactions,[2] proving to be



Scheme 1. R = β-naphthyl.

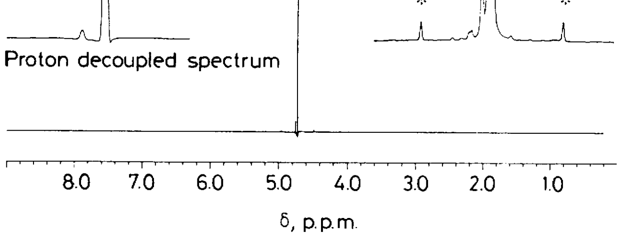


Figure 1. 320 MHz ^1H decoupled ^3H NMR spectrum of 2-(hydroxymethyl)naphthalene produced by reduction of methyl 2-naphthoate with supertritiide made from carrier-free tritium. Inset (a) shows an expansion (4.85—4.60 ppm) with the smaller singlet due to molecules containing only one tritium atom. Inset (b) shows an expansion from 5.1—4.4 ppm, with larger vertical scale.

a highly nucleophilic and powerful reagent.[3] The versatility and potential of partially tritiated superhydride has been amply demonstrated,[4,5] but until the present report the possibility of using these tritiated materials with more than 10% tritium content was remote. Recent advances in the synthesis of Na, K, and Li hydrides[6,7] have enabled carrier-free LiT to be prepared, and the highly dispersed form and reactive nature of this LiT also allows facile conversion to a series of useful tritiated reducing agents.

We illustrate this advance in labelling technology with two examples, and Scheme 1 outlines the procedure for formation of $LiEt_3BT$ and $LiAlT_4$ and their reaction to form 2-(hydroxymethyl)naphthalene. For the supertritiide reaction, a solution of n-butyl-lithium in hexane (0.1 mmol) was rapidly stirred in the presence of an atmosphere of carrier-free tritium gas. Tetramethylethylenediamine (TMEDA; 0.125 mmol) was added, and the LiT started to precipitate immediately. After one hour a stoicheiometric amount of triethylborane (0.1 mmol) in tetrahydrofuran (THF) was added to the mixture to form the supertritiide. After 5—10 min the substrate (0.05 mmol) was injected as a THF solution. The reaction was stopped after one hour by the addition of methanol to destroy any excess of reagent. A similar procedure was used for the production of $LiAlT_4$. The tritiide was formed, the hexane and TMEDA were then evacuated, and addition of $AlBr_3$ (0.025 mmol) generated the reagent.

The products were isolated, and then analysed by radio-HPLC followed by both ^{1}H and ^{3}H NMR spectroscopy.[8] The HPLC analyses showed that only 5—10% of the starting material remained, and that essentially all the radioactivity was in the desired product. Estimates of yields and specific radioactivities were also made from the HPLC data, and showed moderate radiochemical yields ($LiEt_3BT$ reaction, 27%; $LiAlT_4$, 38%) with very high specific activities (S.A.). The $LiEt_3BT$ reaction gave products at 54.2 Ci/mmol, and the $LiAlT_4$ experiment 60.5 Ci/mmol. Since the maximum theoretical S.A. with two tritium atoms per molecule is 57.52 Ci/mmol, and NMR analyses revealed no other labelled positions, we believe the high value (60.5 Ci/mmol) is due to the combined uncertainties (*ca.* 8%) in the calculations from HPLC data. ^{3}H NMR analyses showed almost identical traces for the two experiments, and the spectrum for the product of the supertritiide reaction is shown in Figure 1. The large peak at δ 4.71 (100%) is due to the RCT_2OH species, and that at δ 4.74 (3.5%) is from $RCTHOH$. The calculated specific activity from these peak integrals gives a value of 55.6 Ci/mmol, in excellent agreement with the radio-HPLC result (54.2 Ci/mmol). Note the ^{13}C satellite peaks [Figure 1, inset (b), marked with asterisks] with J_{CT} = 149.89 Hz, which help to give scale to the abundance of the singly labelled species.

As foreshadowed in earlier work with low specific activity supertritiide,[4,5] the availability of carrier-free LiT, and the ability to generate a large range of reducing agents such as $LiEt_3BT$ and $LiAlT_4$ opens the door to an entire new phase of labelling chemistry. Examples of regio- and chemo-selectivity, the generation of other reagents such as L-Selectride ($LiBu^s_3BT$) and borane, along with a more complete experimental description of this work are in preparation,[9] and will be published in a specialist journal. We should also note that three different groups have made use of the technology and reagents developed in our laboratories to give high yields of essentially carrier-free products.[10] While our primary goal was to elaborate a simple route to high-level *tritiide* reagents, it is obvious that *deuterides* may also be made (*e.g.*, $LiBu^s_3BD$) which are not commercially available.

This research was partly supported by the Biotechnology Resources Program, Division of Research Resources, U.S. National Institutes of Health under Grant P41 RR01247, and by the U.S. Department of Energy under Contract DE-AC03-76SF00098.

Received, 5th January 1990; Com. 0/00096E

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