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PREPARATION AND USE OF LITHIUM TRITIDE AND LITHIUM TRIMETHOXYBOROTRITIDE

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Abstract: Two new tritide reducing agents, Li^3H and $Li(CH_3O)_3B^3H$, have been prepared at the carrier-free level and used to reduce 2-naphthaldehyde to tritiated β-naphthalene methanol, to produce C^3H_3OR, and to synthesize a methyl-tritiated secondary amine.

As part of our program to develop new reagents for tritium labelling, we have prepared carrier-free Li^3H and $Li(CH_3O)_3B^3H$ (Scheme 1). The availability of these reagents enables the synthesis of tritiated compounds from the reduction of carbonyl systems. Aldehydes, acid chlorides, esters, ketones and carbonates recently have been reduced with the corresponding hydrogen- and deuterium-containing reagents.[1] We now describe the reduction of 2-naphthaldehyde to illustrate the usefulness of these reagents for tritium labelling, and also apply them to two entirely new labelling approaches, one of which yields C^3H_3OR and the other gives a methyl-tritiated secondary amine.

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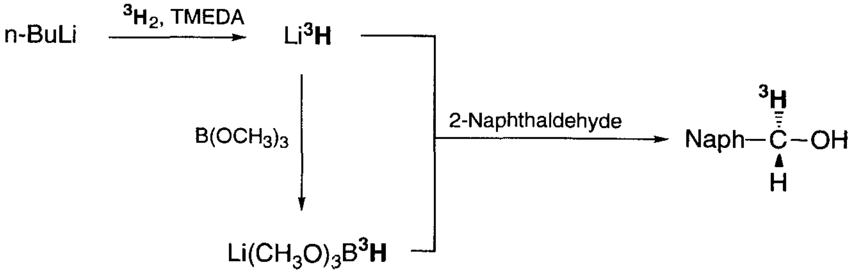


Scheme 1

LiH has seen limited use as a reducing agent,[2] but recent synthetic advances have allowed for the preparation of a finely divided and, thus, very reactive form of the reagent.[3] This has enabled its use as a reducing agent for tritium incorporation, in addition to serving as a precursor to other tritide reducing agents,[4] including $Li(CH_3O)_3B^3H$. It is known that $Li(CH_3O)_3BH$, prepared from commercial LiH and trimethyl borate, readily disproportionates into a somewhat undefined complex hydride.[5] Nevertheless, $Li(CH_3O)_3B^3H$, generated from reactive Li^3H, is an attractive reagent due to its ease of preparation and handling, and because its selectivity and specificity are not well-characterized.

In order to demonstrate the utility of these reagents, finely divided Li^3H was prepared by the reaction of n-butyllithium and tritium gas in the presence of tetramethylethylenediamine (TMEDA). The appearance of a white, creamy precipitate over the next 40 minutes indicated the formation of Li^3H. For the preparation of $Li(CH_3O)_3B^3H$, trimethyl borate was added to the suspension of Li^3H producing a clear solution, from which the hydride slowly precipitated. Reduction of 2-naphthaldehyde was accomplished with each reagent. The organic phase of each reaction was then lyophilized, the products were dissolved in

$CDCl_3$, and aliquots were analyzed by radio-HPLC, and by ^1H and ^3H NMR spectroscopy.

HPLC analysis of the Li^3H reaction product showed that 15% of the aldehyde remained and that essentially all the radioactivity was in the desired product. A chemical yield of 35% was calculated, while the specific activity (S.A.; 14.6 Ci mmol^{-1}) was approximately half of that expected.[6] An NMR study revealed that exchange of tritium with the aldehyde proton took place, leading to dilution of the tritium content of the Li^3H. As a result, the product consisted of a 1:1 mixture of unlabelled and monotritiated alcohols, with a trace of the ditritiated isotopomer. As shown in the proton spectrum in Figure 1A, the RCH_2OH signal is a singlet at 4.87 ppm, while the RCH^3HOH species gave rise to a doublet centered at 4.84 ppm ($J_{H\text{-}T}$ = 13.68 Hz), one signal of which overlays the RCH_2OH singlet. Selective ^3H decoupling experiments confirmed this assignment as the doublet collapsed to a singlet at 4.84 ppm (Figure 1B). In the ^1H decoupled ^3H NMR spectrum in Figure 1C, a signal due to a small amount of alcohol labelled with two tritium atoms occurs at 4.82 ppm. Since the RCH^3HOH species appears in both the ^1H and ^3H NMR spectra, the abundance of RCH_2OH, RCH^3HOH and RC^3H_2OH molecules may be related, and the specific activity calculated.[7] The value obtained (14.5 Ci mmol^{-1}) was in excellent agreement with that determined by HPLC analysis. A feature of academic interest in the NMR spectra is that the primary isotope effect on the ^1H ($\Delta\delta = 8.54 \pm 0.31$ Hz) and ^3H ($\Delta\delta = 9.78 \pm 0.24$ Hz) chemical shifts arising from tritium substitution at the methylene carbon is readily observed, and is consistent with previous measurements.[8]

For the reaction of naphthaldehyde with $Li(CH_3O)_3B^3H$, HPLC analyses showed that 12% of the aldehyde remained and that essentially all the

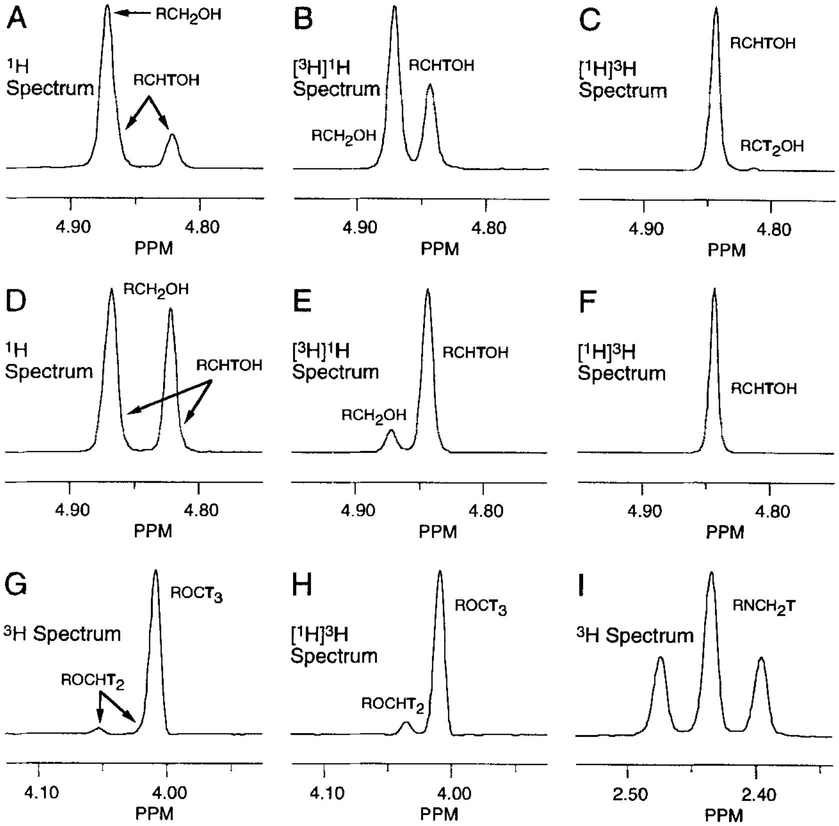


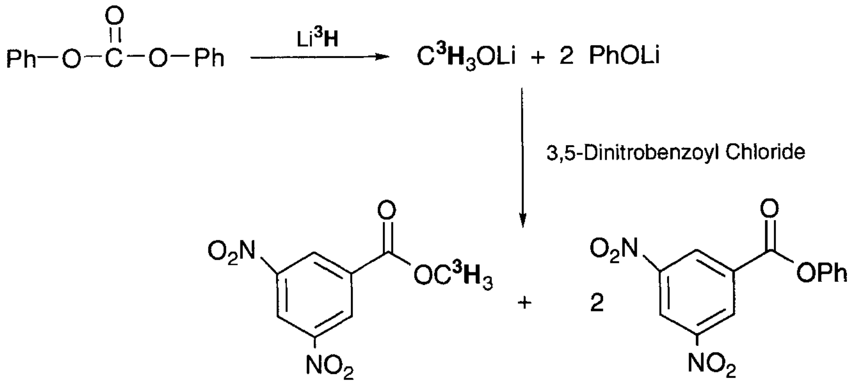
FIG. 1

^1H and ^3H NMR spectra of tritiated products, dissolved in C_6D_6. A. 300 MHz ^1H NMR spectrum (δ 4.95-4.75) of β-naphthalene methanol produced by reaction of Li^3H with 2-naphthaldehyde. B. Selective ^3H decoupled ^1H NMR spectrum of the product in (A). C. Proton decoupled 320 MHz ^3H NMR spectrum of the sample in (A). D. 300 MHz ^1H NMR spectrum (δ 4.95-4.75) of β-naphthalene methanol produced by reaction of $Li(CH_3O)_3B^3H$ with 2-naphthaldehyde. E. Selective ^3H decoupled ^1H NMR spectrum of the product in (D). F. Proton decoupled 320 MHz ^3H NMR spectrum of the sample in (D). G. 320 MHz ^3H NMR spectrum (δ 4.12-3.92) of methyl 3,5-dinitrobenzoate produced by reaction of Li^3H with diphenylcarbonate. H. Proton decoupled 320 MHz ^3H NMR spectrum of the product in (G). I. 320 MHz ^3H NMR spectrum (δ 2.54-2.34) of tritiated CQA produced by reaction of $Li(CH_3O)_3B^3H$ with CQA-Bt.

radioactivity was in the desired product. A chemical yield of 25% was attained with a S.A. of 24.6 Ci $mmol^{-1}$ compared to a value of 26.7 Ci $mmol^{-1}$ as calculated from NMR spectra. It was evident from NMR experiments that ~93% (by mass) of the alcohol product was labelled with one tritium while ~7% of the alcohol contained no tritium. Again, the unlabelled alcohol appears as a singlet at 4.87 ppm in the proton spectrum (Figure 1D) while the monolabelled alcohol occurs as a large doublet centered at 4.84 ppm ($J_{H\text{-}T}$ = 13.68 Hz). Selective ^3H decoupling experiments show that the doublet collapses to a singlet at 4.84 ppm (Figure 1E). There is no peak at 4.82 ppm in the ^3H NMR spectrum (Figure 1F), indicating that the concentration of ditritiated alcohol species was much less than 1%.

In addition to its use in generating $Li(CH_3O)_3B^3H$ and other tritides,[4] Li^3H has potential for production of tritiated methyl iodide. The standard preparation of C^3H_3I by way of C^3H_3OH involves both high temperatures and pressures, and is inefficient in the use of $^3H_2$.[9] In contrast, a rapid method for synthesizing $^{11}CH_3I$ has been developed which relies on the reduction of CO_2 with $LiAlH_4$.[10] By analogy, we propose a process for synthesizing C^3H_3I by the action of $LiAl^3H_4$ or Li^3H on diphenylcarbonate or CO_2 (Scheme 2).

When diphenylcarbonate was treated with Li^3H, the tritiated methoxide which formed was trapped with 3,5-dinitrobenzoyl chloride to allow for analysis as the tritiated methyl ester. Although the yield of the reaction was poor (ca. 5%), ^3H NMR analyses showed that the specific activity of the product was very high. Comparison of the ^3H with the ^1H decoupled ^3H NMR spectra in Figures 1G and 1H, respectively, allows calculation of a S.A. of 83.5 Ci $mmol^{-1}$ for the product (97% of theoretical). With appropriate optimization of the methoxide yields, reaction with HI will provide a rapid, convenient route to the synthesis of high specific activity C^3H_3I. Once again, the isotope effect on the ^3H chemical shift

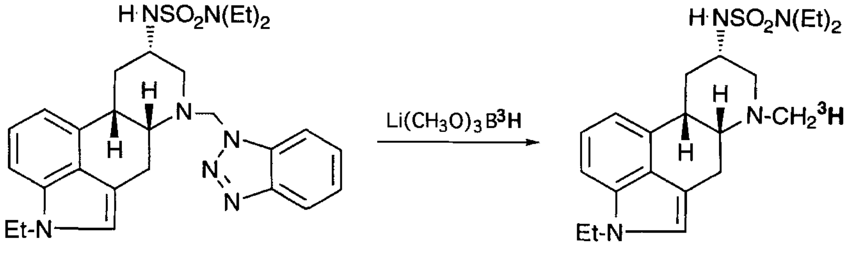


Scheme 2

for $ROCH^3H_2$ and ROC^3H_3 signals ($\Delta\delta = 8.30 \pm 0.21$ Hz) in Figure 1H is consistent with past measurements of multitritiated methyl signals at lower field (2.5 Hz at 96 MHz).[8a]

As an alternative to the N-^{3}H-methylation of amines using tritiated methyl iodide, $Li(CH_3O)_3B^3H$ can be used efficiently in a novel labelling reaction based on Katritzky's benzotriazole-mediated alkylation of amines.[11] Reaction of the ergoline derivative, NOR-CQA, with 1-hydroxymethylbenzotriazole[12] gave the crude benzotriazolylmethyl-substituted ergoline, CQA-Bt. This material was readily reduced by freshly prepared $Li(CH_3O)_3B^3H$ (Scheme 3), made from 10% $^3H/^1H$, in tetrahydrofuran (THF) at room temperature to cleanly afford ^{3}H-CQA (26% yield; S.A. = 3.3 Ci mmol^{-1}; ^{3}H NMR analysis in Figure 1I; $J_{H\text{-}T}$ = 12.70 Hz). It is noteworthy that $LiBH_4$ was ineffective under these reaction conditions.

Both Li^3H and $Li(CH_3O)_3B^3H$ provide new methods for tritium labelling of carbonyl compounds as demonstrated by the reduction of 2-naphthaldehyde. While Li^3H serves as an excellent intermediate for the formation of a large range



Scheme 3

of specialty hydride reagents,[4] we have shown that it is also a valuable reagent in its own right. We have also demonstrated the usefulness of these reagents in two completely new approaches to tritium labelling: (i) the reduction of diphenylcarbonate as a precursor for C^3H_3I, and (ii) the reduction of a benzotriazole derivative as a precursor to a labelled secondary amine. While the benzotriazole reaction is also possible with $NaBH_4$ and $LiAlH_4$,[11] neither of these is routinely available at maximum specific activity and their synthesis is more involved[4] than the straightforward approach we have outlined for $Li(CH_3O)_3B^3H$.

Experimental:

All glassware, syringes and needles were oven-dried prior to use. The NMR spectra were recorded on an IBM Instruments AF-300 MHz NMR spectrometer as previously described,[4,7] using $CDCl_3$ as both the solvent and internal chemical shift reference. HPLC analyses were performed[4] on a Supelco LC-18 column with a mobile phase of CH_3OH/H_2O. A general tritiation procedure is reported below with 2-naphthaldehyde as substrate.

Tritiated β-Naphthalene methanol. A side-arm flask containing a Teflon stirbar was filled with tritium gas to a final pressure of 80 kPa. A solution of n-butyllithium in hexanes (1.6 M; 0.2 mmol; 125 μL) was added, followed by injection of TMEDA (0.2 mmol; 36 μL). The formation of Li^3H over the next 40 minutes gave a white, creamy precipitate. For the preparation of $Li(CH_3O)_3B^3H$, trimethyl borate (0.2 mmol; 24 μL) was then added to the Li^3H suspension producing a clear solution, followed by slow precipitation of the hydride. A solution of 2-naphthaldehyde (0.2 mmol; 31.2 mg) in THF was added to each reagent, and the reactions were allowed to continue for 2 h before the addition of methanolic HCl to quench any excess hydride. After extraction with ethyl acetate the organic phase of each reaction was lyophilized, the products were dissolved in $CDCl_3$, and aliquots were analyzed by radio-HPLC, and by ^1H and ^3H NMR spectroscopy. Chemical yields were 35% (Li^3H) and 25% [$Li(CH_3O)_3B^3H$]; $^1H[^3H]$ NMR ($CDCl_3$): δ 7.84 (m, 4H, naphthyl ring B H's), 7.50 (m, 3H, naphthyl ring A H's), 4.87 (s, Naph-C$\underline{H}_2$OH) and 4.84 (s, Naph-C$\underline{H}{}^3$HOH); $[^1H]^3H$ NMR ($CDCl_3$): δ 4.84 (s, Naph-CH$^3\underline{H}$OH) and 4.82 (s, Naph-C$^3\underline{H}_2$OH).

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