Lithium Triethylborotritide (Super-tritide): a Useful Reagent for Tritium Labelling

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Lithium triethylborotritide prepared from lithium tritide and triethylborane was used to introduce tritium label by reduction of carbonyl compounds, epoxides, alkyl halides, and alkyl toluene-*p*-sulphonates.

Lithium triethylborohydride (super-hydride) was introduced as a reducing agent by H. C. Brown and his associates in 1972[1] and since then has been used widely in organic synthesis.[2] This hydride donor is far more nucleophilic than other reducing reagents such as LiAlH$_4$ or LiBH$_4$,[3] and is capable of reducing hindered alkyl halides, toluene-*p*-sulphonates, and epoxides. The reductive dehalogenation of alkyl halides with super-hydride involves a clean inversion at the reaction site.[3] Reduction of epoxides with this reagent is also remarkably regio- and stereo-specific leading to the more highly substituted alcohol.[4] The broad spectrum of reducing properties of super-hydride, coupled with the possibility of introducing tritium label stereospecifically in some reactions, prompted us to investigate the tritiated equivalent of super-hydride, LiEt$_3$B^{3}H.†

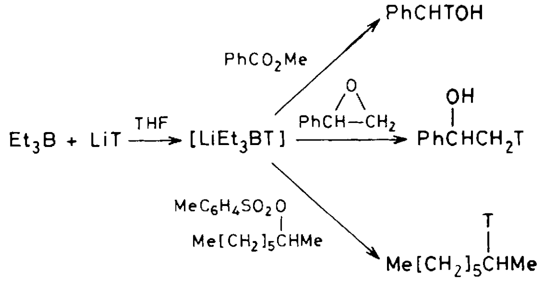
Since the efficient utilization of tritide might depend upon an intermolecular isotope effect, a series of competitive reductions with super-hydride and super-deuteride was carried out to estimate the magnitude of the deuterium isotope effect. Benzaldehyde, acetophenone, methyl benzoate, styrene oxide, 1-bromononane, n-hexadecyl toluene-*p*-sulphonate, or cholestanyl toluene-*p*-sulphonate were reduced with two equivalents of 1 : 1 super-hydride–super-deuteride [1 M in tetrahydrofuran (THF), 2 h at 25 °C] and the deuterium content of the product was determined by mass spectrometry. Since deuterium incorporations corresponding to 88—96% of the theoretical value were observed in each case, it is clear that the kinetic isotope effects associated with these reductions are small (k_H/k_D = 1.08—1.4)[5] and that there should be little kinetic discrimination against tritium in tracer preparations.[6]

A 1 M stock solution of lithium triethylborotritide in THF with a specific activity (s.a.) of *ca.* 50 mCi/mmol was prepared in a nitrogen-filled glove bag by the following procedure.[7] To an ampoule containing *ca.* 0.4 mg of lithium tritide (100 mCi, *ca.* 2000 mCi/mmol) was added 1 ml of 1 M triethylborane in THF and *ca.* 0.5 mmol of lithium hydride. The suspension was stirred at room temperature for 48 h. The almost clear solution was transferred under nitrogen to a screwcap test tube and diluted with another 1 ml of 1 M triethylborane in THF. The calculated amount (*ca.* 1.5 mmol) of lithium hydride was added and the mixture was heated at 80—90 °C for 2 h. The resulting stock solution of super-tritide was diluted to 50—100 μCi/mmol with 1 M super-hydride in THF for the reductions shown in Table 1. The specific activity was assayed by reducing cinnamaldehyde and determining the radioactivity of the h.p.l.c.-purified [^{3}H]-cinnamyl alcohol by liquid scintillation counting in toluene (7 g 2,5-diphenyloxazole per litre) using the channels ratio method. The super-tritide solution appears to be quite stable since the specific activity of one 2 ml stock solution (40 mCi/mmol) remained unchanged after storage under nitrogen for 9 months at room temperature.

The following procedure for the reduction of carbonyl compounds and epoxides is representative. A dry 10 ml flask was flushed with nitrogen and charged with 2 ml of 1 M super-tritide (2 mmol, s.a. = 50–100 μCi/mmol) in THF. The solution was stirred as 2 mmol of the carbonyl compound or epoxide in 2 ml of THF was added *via* a syringe. After 2 h at ambient temperature, the excess of hydride was destroyed by addition of water, and the reaction mixture was diluted with 2 ml of ether. The organic layer was dried (K$_2$CO$_3$) and concentrated under reduced pressure. The products were purified by preparative g.c., h.p.l.c., or recrystallization, and the specific activities were determined by liquid scintillation counting (see Table 1). The reductions of the alkyl halides and toluene-*p*-sulphonates were carried out in the same manner using 4 mmol (2 equiv.) of super-tritide.

The data in Table 1 indicate that high chemical and radiochemical yields can be easily achieved by this method. However, since the amounts and specific activities of the lithium tritide used were not precisely known, the actual overall incorporations of radioactivity were not directly measured. The radiochemical yields are based upon an assumed 100% incorporation of radioactivity in the reduction of cinnamaldehyde (assay procedure). Analysis of the reaction mixtures from reduction of benzaldehyde and methyl benzoate by radio h.p.l.c. established that the majority of the radioactivity coincided with the peak for benzyl alcohol; thus only minor amounts of radioactive by-products were formed in these two reductions.

Super-tritide promises to be a very useful reagent for tritium labelling of organic compounds. It is a much stronger hydride donor than NaB^{3}H$_4$ which is generally incapable of reducing esters, epoxides, and toluene-*p*-sulphonates (Scheme 1). LiAl^{3}H$_4$ is available at only moderate specific activities (*ca.* 100 mCi/mmol) and has a limited shelflife. A further potential disadvantage of these tetrahydrido ate complexes is incomplete utilization of all four hydride equivalents. The application of super-tritide to the preparation of stereospecifically tritiated compounds is under investigation in our laboratories. Reaction of lithium tritide with other trialkylboranes may similarly lead to other novel tritiating reagents.



Scheme 1

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† A preliminary announcement of the results was presented by C. J. P. at the International Symposium on the Synthesis and Applications of Isotopically Labelled Compounds, Kansas City, Missouri, June 10, 1982.

Table 1. Representative reductions with lithium triethylborotritide (super-tritide) in THF at 25 °C.

Reactant	$[^3H]$ Product	Chemical yield (%)[a]	Radiochemical yield (%)[b]
Benzaldehyde	Benzyl alcohol	85	93
Acetophenone	1-Phenylethanol	92	66
Methyl benzoate[c]	Benzyl alcohol	88	58[d]
Styrene oxide	1-Phenylethanol	86	81
Benzyl bromide[c]	Toluene	93	66
Octyl toluene-*p*-sulphonate[c]	n-Octane	90	72
1-Methylheptyl toluene-*p*-sulphonate[c]	n-Octane	88	67
Nonyl bromide[c]	n-Nonane	93	91
3β-Cholestanyl toluene-*p*-sulphonate[c]	Cholestane[e]	82	90
Cinnamaldehyde	Cinnamyl alcohol	96	(100)

[a] Chemical yields were determined by g.c. analysis with an internal standard. [b] Radiochemical yield = (d.p.m. product/d.p.m. cinnamyl alcohol) × 100. The radiochemical yield of cinnamyl alcohol (assay procedure) was assumed to be 100%. [c] Two equivalents of super-tritide were used. [d] Based on theoretical incorporation of two equivalents of super-tritide. [e] Yield after recrystallization.

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