THE USE OF BORON TRIBROMIDE AS A CATALYST FOR THE RAPID TRITIUM LABELING OF AROMATIC COMPOUNDS

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SUMMARY

Boron tribromide has been assessed as a catalyst for rapid tritium labeling of organic compounds using tritiated water under mild conditions. Alkyl and halogen substituted aromatics labeled rapidly, the labeling being most pronounced in the ortho and para positions. Compounds containing electrophilic deactivating groups were found to be difficult to label. Very little byproduct formation was observed.

Key Words: Tritium labeling, Boron tribromide, Lewis acid

INTRODUCTION

It has previously been demonstrated (1,2) that alkylaluminium halides, in particular ethyl- and methylaluminium chloride, are useful catalysts for the rapid tritium labeling of aromatic and selected aliphatic compounds, using traces of high specific activity tritiated water as the isotope source. The technique results in labeling to high specific activity, the label being mostly confined to the aromatic ring where applicable (3,4), or to tertiary carbons of aliphatic compounds (5). In the case of aromatic compounds, tritium generally was found to be randomly distributed in the ring. A series of hydroxybenz[a]pyrenes (6) and cyclopenta[c,d]pyrene (7) were tritium labeled using ethylaluminium chloride. The chemical and radiochemical purity of the

labeled compounds was reported to be better than 95%, with the specific activity dependent upon the activity of the tritiated water used (either 5, 50 or 500 Ci/mL). In addition, 1,3,5-trimethylbenzene and 1,4-dimethylnaphthalene were labeled to high specific activity (8) by this method. The technique is also in common use for routine production of tritiated compounds (9).

We now report boron tribromide as a suitable rapid tritiation catalyst, as an alternative to the alkylaluminium halides, for use when the labeling required is more characteristic of electrophilic (ie. general acid catalysed) substitution.

Boron tribromide has been previously used (10,11) as a catalyst for tritium labeling of aromatic compounds, naphthalene and various steroids, using tritiated water as the isotope source. This work was preliminary in nature, and we now report a more systematic study of this labeling system. The conditions for efficient exchange in toluene were established, and a selection of alkylaromatics and substituted benzenes were labeled under these conditions.

EXPERIMENTAL

In a typical exchange experiment, the organic compound to be labeled (0.2g or 0.2mL) was placed in a constricted-neck pyrex reaction ampoule. Solids were dissolved in a minimum quantity of an inert solvent such as cyclohexane. The tube was flushed with dry nitrogen and placed in a drybox. Liquid boron tribromide (0.1mL approx.) was then introduced from a dry syringe. The tube was removed from the drybox and the contents quickly frozen in liquid nitrogen. Tritiated water of the required activity (0.1mL) was then frozen onto the inner wall of the tube. The tube was removed from the liquid nitrogen and, after a pause of several seconds to allow the escape of condensed atmospheric gases, the tube was flame-sealed. Samples were generally held at 70^0 for 24

hours before analysis. The organic compound was isolated from the reaction mixture by careful hydrolysis of the remaining boron tribromide using non-isotopic water, followed by removal of the organic layer using a Pasteur pipette or a microlitre syringe. The isolated organic was dried over anhydrous sodium carbonate or 5A molecular sieve, and analysed. The overall activity and sample purity was assessed by radio-gas chromatography, and the orientation of tritium was determined by ^{3}H NMR spectroscopy. The instrument used throughout was a Bruker WP60 NMR spectrometer, equipped with a 5mm tritium probe, and operating at a frequency of 64MHz.

RESULTS

The results of tritium labeling of alkylaromatics and substituted benzenes in the presence of boron tribromide are reported in the Table. Those compounds which displayed sufficient exchange were analysed by ^{3}H NMR to determine the distribution of tritium within the compound. The theoretical equilibrium activity was calculated by a determination of the mole ratio of hydrogen in the substrate to the total hydrogen content of the sample (tritiated water + substrate), and assuming a random distribution of tritium at equilibrium.

All alkylbenzenes studied underwent efficient exchange, and it was found that labeling was confined to the aromatic ring, the labeling being most pronounced in the ortho and para positions, with the meta positions severely deactivated in all cases. The chemical and radiochemical purity of the labeled compounds generally was found to be better than 95%. Traces of benzene were found in some cases, but not more than 5% abundance. The halobenzenes labeled predominantly in the para position, with an increasing amount of label in the ortho position as the size of the halogen substituent increased. Iodobenzene decomposed significantly on addition of BBr$_3$ and was not further investigated.

TABLE

Exchange of Alkylaromatics and Substituted Benzenes
with HTO in the Presence of Boron Tribromide

Compound	% App.[•]	% Incorporation/H			
		ortho	meta	para	alkyl
Benzene	4.8	-	-	-	-
Toluene	58.7	31.5	5.1	26.9	<0.1
n-Propyl-Φ	57.3	30.5[ι]	4.2	30.5[ι]	<0.1
iso-Propyl-Φ	20.3	31.0	2.7	32.7	<0.1
iso-Butyl-Φ	15.8	21.4	<0.1	57.3	<0.1
t-Butyl-Φ	48.6	30.2	4.3	31.0	<0.1
Cyclohexyl-Φ	9.1	30.2	3.4	32.8	<0.1
$CH_2\Phi_2$	7.8	33.3[ι]	<0.1	33.3[ι]	<0.1
F-Φ	11.8	15.8	<0.1	68.4	-
Cl-Φ	7.3	27.3	<0.1	45.5	-
Br-Φ	7.4	26.0	<0.1	48.0	-
I-Φ			DECOMPOSED		
CH_3O-Φ			DECOMPOSED (see text)		
OCH-Φ	<0.1	-	-	-	-
CF_3-Φ	<0.1	-	-	-	-

[•] % Approach to theoretical equilibrium

[ι] ortho and para positions unresolved in n-propylbenzene and diphenylmethane

Gas chromatographic analysis of the crude reaction mixture from the
anisole sample showed that complete conversion to phenol had occurred.
This result is in accord with the findings of Benton et al (12), and
McOmie et al (13,14), who found that phenols were formed on cleavage of
aryl ethers by boron tribromide. No detectable exchange was recorded in
benzaldehyde and benzotrifluoride. With the exception of anisole, the
formation of active byproducts was not observed.

DISCUSSION

The tritium labeling of aromatic compounds in the presence of boron tribromide, as described above, appears to be governed by the rules of electrophilic substitution. Labeling in the ortho and para positions of the alkyl- and halobenzenes, and the lack of labeling in benzaldehyde and benzotrifluoride, all indicate an electrophilic mechanism.

The extent of overall labeling, as measured by % approach to equilibrium, is only an indication of the reactivities of the various compounds, since the reaction appears to be very rapid, and up to 20% variation in replicate samples has been found. The indications are, however, that for the compounds studied the reactivities are of the same order as the comparable reaction using ethylaluminium chloride (3,4). The orientations of isotope, in contrast, are quite different from those obtained with ethylaluminium chloride. Comparison of the two systems shows that, whilst their overall reactivities are of the same order, the tritium distributions are quite different. For ethylaluminium chloride the labeling in the aromatic ring of alkylbenzenes was close to random (2), whereas when boron tribromide is used the meta contribution is very small.

Labeling of halobenzenes with BBr_3 is also in contrast to that with $EtAlCl_2$. The latter gave close to random exchange, whereas BBr_3 showed an apparent preference for the para position, with no meta labeling recorded. The dependence of the ortho contribution on the size of the halogen substituent is further evidence in favour of an acid mechanism, since this effect is well documented in standard works on the subject of general electrophilic substitution reactions.

The reason for the apparent difference in the mode of operation of the two catalysts is not clear. The appearance of strongly coloured, electrically conductive solutions, together with the apparently random distribution of isotope, indicates that charge transfer complexation may be a significant aspect of reactions of aromatics with $EtAlCl_2$ (2).

Solutions of aromatics with boron tribromide are also generally strongly coloured, but boron tribromide, on reaction with water, may act simply as a powerful electrophilic reagent, since tritium labeling of toluene can be effected even when the BBr_3 has been previously hydrolysed with tritiated water.

It is likely that the exchange mechanism is similar to that proposed elsewhere (2) for other Lewis acid-type catalytic systems.

Clearly then, the technique is attractive for compounds which would be expected to undergo electrophilic substitution. Aromatics which contain highly deactivating groups such as -CHO (benzaldehyde) are difficult to label by this method. The main advantage, however, is that compounds can be labeled with tritium by an acid mechanism under mild conditions, as an alternative to the conventional electrophilic tritiation catalysts such as $HTSO_4$ (15,16), CF_3COOT (17) and the complex acid $T(F_3BOPO_3H_2)$ (18), all of which require much harsher conditions with accompanying formation of byproducts.

The technique gives a distribution of isotope different from that obtained using precipitated metals, ethyl aluminium chloride and other similar Lewis acids, and thus represents a very valuable alternative to these methods in cases where specifically electrophilic labeling is required.

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