

Research Article

Borohydride exchange resin as an alternative method for deuterium labelling: selective reduction of aryl bromides

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Summary

Transition metal-activated borohydride exchange resin and borodeuteride exchange resin have been prepared and used for the selective reductive deuteration of aryl bromides. This methodology, which utilizes deuterated methanol as the primary source of label, provides an alternative method for the introduction of deuterium. Investigation of which bond in the solvent donates the deuterium and model reductions on *ortho*-bromo-*N,N*-dimethylbenzamide suggest that an organocopper(III) intermediate is most likely involved. The immobilized hydride on resin also provides an easy workup and gives products of high purity. This methodology is far more selective than typical catalytic deuteration and, in most cases, provides products with high levels of deuterium incorporation. Copyright © 2001 John Wiley & Sons, Ltd.

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Introduction

Borohydride exchange resin (BER)¹ is a quaternary ammonium borohydride supported on an ion exchange resin (typically Amberlite

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IRA-400). BER is a milder reducing agent than sodium borohydride²⁻⁴ and allows for workup by simple filtration.

BER reactivity can be modified via addition of a transition metal salt which greatly increases its reducing power. These salts include Ni(OAc)₂,⁵⁻⁷ CuSO₄⁸ and Pd.⁹ Modified BER resin has been used for selective olefin reductions,⁵ alkyne to alkene reductions,¹⁰ aryl nitro reductions to anilines¹¹ and reductive aminations.¹²

Labelling an aromatic ring with deuterium is typically accomplished by dehalogenation using deuterium or tritium gas over a Pd catalyst, or by isotopic exchange with labelled water or deuterium or tritium gas.¹³ Often, these reductions need to be selective since many compounds of interest bear chlorine. Copper sulfate-activated BER, in particular, is thus of interest for isotopic labelling due to its selectivity in reducing bromoaromatics in the presence of chloroaromatics such as 4-bromochlorobenzene to chlorobenzene.⁸

Narisada¹⁴ has previously noted that a solution phase copper(I) chloride–sodium borohydride system can effect labelling when deuterated solvent is used. Since the primary source of the proton in these BER reductions must also be from the solvent rather than from the resin, use of a deuterated solvent would provide a deuteron for quenching the active intermediate. This would thus offer an alternative way to introduce a deuterium label into a molecule.

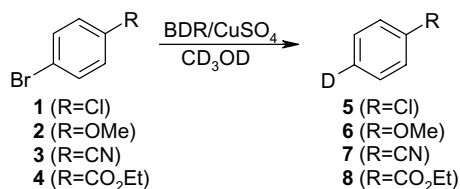
Results and discussion

Preparation of BER and BDR

The BER is easily prepared by treating the chloride form of Amberlite IRA-400 with a 1 M aqueous solution of sodium borohydride as described by Yoon.¹⁵ Borodeuteride resin (BDR) was prepared in a similar manner by treating the chloride form of Amberlite IRA-400 with a 1 M aqueous solution of sodium borodeuteride (in H₂O, not D₂O). Excess borohydride or borodeuteride was rinsed from the resin with water and the resin was dried under vacuum.

Model reductive deuterations

A thorough examination of the labelling capability of the BER/BDR–copper sulfate system was carried out using 4-bromobenzene derivatives as model substrates (Scheme 1). The data are summarized in Table 1.



Scheme 1.

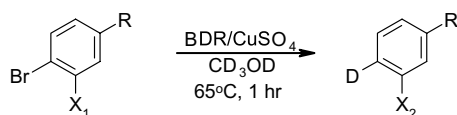
Table 1. Reduction of 4-bromobenzenes 1–4 with BER–CuSO₄ or BDR–CuSO₄ in methanol or methanol-d₄

Resin	Solvent	R	% d ₀	% d ₁
1. BER	CD ₃ OD	Cl	30	70
2. BER	CD ₃ OD	OMe	34	66
3. BER	CD ₃ OD	CN	17	83
4. BER	CD ₃ OD	CO ₂ Et	33	67
5. BDR	CD ₃ OD	Cl	15	85
6. BDR	CD ₃ OD	OMe	8	92
7. BDR	CD ₃ OD	CN	5	95
8. BDR	CD ₃ OD	CO ₂ Et	5	95
9. BDR	CH ₃ OH	Cl	95	5
10. BDR	CH ₃ OH	OMe	96	4
11. BDR	CH ₃ OH	CN	95	5
12. BDR	CH ₃ OH	CO ₂ Et	95	5

Entries 1–4 represent our initial attempts at the reduction using BER and deuterated methanol as solvent. Yields were moderate until the resin was extracted with methylene chloride which gave yields of 90–100%. All four substrates were selectively reduced and had deuterium incorporations of 0.66–0.83 d/molecule. However, this incorporation was substantially less than theoretical and indicated that there must be a significant source of isotopic dilution which occurred during reduction.

One potential source of isotopic dilution was the resin itself. Switching to BDR and still using methanol-d₄ as solvent increased deuterium incorporation to 0.85–0.96 d/molecule (entries 5–8). It thus appeared that the hydride protons on the resin itself were entering into the reduction.

Based on entries 1–4, it was clear that deuterium was primarily coming from the solvent, although a still significant portion was derived from the borodeuteride on the resin (entries 5–8). Entries 9–12 confirmed this where the only source of deuterium was the resin itself.

Table 2. Reductive deuteration of various aryl bromides

R	X ₁	X ₂	Average d/molecule ^a
OMe	Br	D	1.88 ^b
H	CONMe ₂	CONMe ₂	0.86

^a Isotope incorporation was determined by mass spectroscopy. Yields were >95% in all cases and were determined by HPLC.

^b 88.7% d₂, 10.9% d₁, 0.4% d₀.

A deuterium incorporation of 0.05 d/molecule was still observed with BDR in methanol.

We also investigated the reduction of 3,4-dibromoanisole and 2-bromo-*N,N*-dimethylbenzamide (Table 2). Deuterium incorporation was again quite high.

Mechanism

Some reports invoke a radical based mechanism for BER halide reductions.⁸ Under these conditions, 1-chlorooctane is not reduced but 1-bromooctane is. Reduction of bromocyclohexane gives a small amount of cyclohexene, and reduction of benzyl chloride gives an 8% yield of 1,2-diphenylethane along with the expected high yield of toluene (83%). However, these observations were for BER reductions of aliphatic systems. Narisada, on the other hand, in his work on copper(I) chloride/sodium borohydride reductions in solution, has suggested the intermediacy of a copper hydride.¹⁴ We chose to evaluate the mechanism by examining the reductive deuteration of 4-bromochlorobenzene (**1**) with copper sulfate-activated BER or BDR in methanol-*d*₄ to give 4-deuterochlorobenzene (**5**).

All possible sources of the deuterium label in the final product were assessed by using CD₃OD, CD₃OH, CH₃OD and CH₃OH as solvent. This enabled the deuterium donating capabilities of the C–D and O–D bonds to be separately evaluated.

A radical based mechanism would predict the HOCD₂–D bond, and not the CD₃O–D bond, as the primary donator of deuterium to the final product. This order is predicted based on the bond dissociation energies

Table 3. Source of deuterium in 4-bromochlorobenzene (1) reductions

	Resin	Solvent	Ave. D incorporation	% d ₀	% d ₁
1	BDR	CD ₃ OD	0.85	15	85
2	BDR	CD ₃ OH	0.11	89	11
3	BDR	CH ₃ OD	0.86	14	86
4	BDR	CH ₃ OH	0.05	95	5
5	BER	CD ₃ OD	0.70	30	70
6	BER	CD ₃ OH	0.02	98	2
7	BER	CH ₃ OD	0.65	35	65

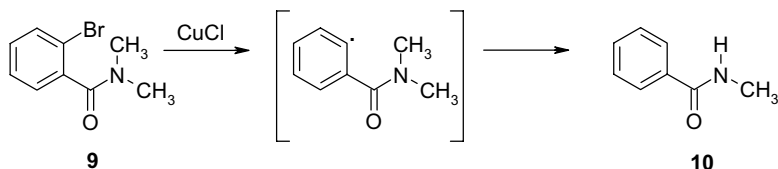
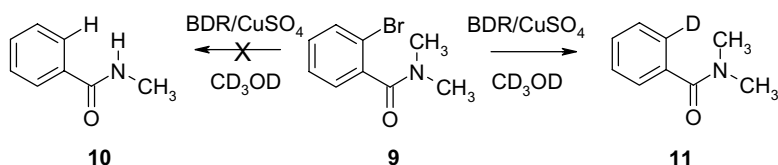
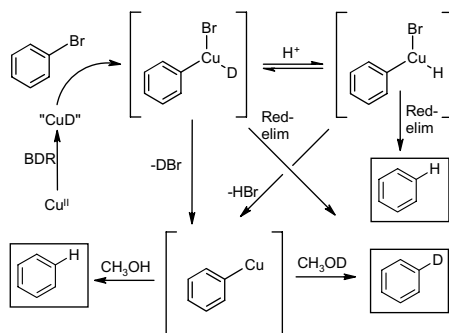
of the two species. The HOCH₂–H bond dissociation energy is 92 kcal/mol¹⁶ whereas the CH₃O–H bond dissociation energy is 102 kcal/mol.¹⁷ Cohen¹⁸ observed that the expected selectivity from the radical intermediate in the copper(I) induced aryldiazonium decomposition of diazobenzamides. Labelling studies demonstrated that the radical intermediate abstracted a hydrogen from the methyl group of methanol. An ion based mechanism, on the other hand, should show predominant deuterium contribution from the acidic O–D deuteron. Our results, which are summarized in Table 3, clearly show the O–D deuteron to be the primary source of label.

Deuterium incorporation is virtually the same regardless of whether CD₃OH or CH₃OH was used as solvent with BDR resin (entries 2 and 4). In the experiment, where the only possible source of label was the CD₃ group (entry 6), deuterium incorporation was only 0.02 d/molecule. In contrast, deuterium incorporation was always high when an acidic O–D group was present (entries 1, 3, 5 and 7). Thus, the primary source of label is the O–D bond with a small amount of label deriving from the BDR resin itself (entry 4).

More direct evidence for an ion based, rather than a radical based mechanism, was obtained by studying the BDR reduction of *ortho*-bromo-*N,N*-dimethylbenzamide (**9**). It is known that a radical generated in the *ortho* position of *N,N*-dimethylbenzamide will lead to formation of *N*-methylbenzamide (**10**) via hydrogen abstraction from one of the methyl groups (Scheme 2).¹⁹

However, reduction of *ortho*-bromo-*N,N*-dimethylbenzamide (**9**) with BDR/CuSO₄ in methanol-d₄ gave, as the sole product, 2-deutero-*N,N*-dimethylbenzamide (**11**). Deuterium incorporation was 0.86 d/molecule. None of the monomethyl benzamide (**10**) was observed (Scheme 3).

One mechanism consistent with these observations is shown below (Scheme 4). Reduction of Cu^{II} to Cu^I is followed by oxidative-addition

**Scheme 2.****Scheme 3.****Scheme 4.**

to the aryl halide to give a Cu^{III} intermediate. This Cu^{III} intermediate could undergo either reductive elimination or decomposition to an aryl cuprate, which then reacts with solvent. Direct reaction with the Cu^{I} species with CuI and CuBr in the absence of hydride showed no reduction. It has been suggested that this Cu^{I} intermediate, in solution reactions, is copper deuteride.¹⁴ If copper deuteride were formed as the key intermediate, oxidative addition followed by the loss of DBr would give an aryl cuprate that would rapidly be quenched by the O–D proton of the solvent. A small amount of labelled product could also be derived by reductive elimination from the Cu^{III} intermediate. This would explain why a small amount of label seems to derive solely from the resin and not the solvent (Table 1). H–D exchange from the Cu^{III} intermediate would also be expected to occur.

Cohen²⁰ and Meyers²¹ has made similar observations in the Ullman coupling of aryl bromides where the likely mechanism involves initial addition of a copper(I) halide to the aryl bromide producing an aryl copper(III) intermediate. They have shown this intermediate to be sensitive to protonation. Such is the case in these BDR/CD₃OD reductions where the large excess of CD₃OD protonates the organo-copper(III) intermediate giving the observed deuterium labelled products.

Conclusion

In conclusion, copper sulfate-activated borodeuteride exchange resin reductions, when carried out in methanol-d₄, selectively reduces bromoaromatics with high incorporation of deuterium. This represents an easy alternative method for the introduction of deuterium into aromatic molecules. The method is rapid, mild, highly selective and is compatible with a wide variety of functional groups. Simple filtration gives products of high purity.

Experimental

Amberlite IRA-400 resin (40 mesh), sodium borohydride and sodium borodeuteride were purchased from Aldrich. CD₃OD was purchased from Isotec and was 99.96 atom % D. CH₃OD was purchased from Aldrich and was 99.5 atom % D. CD₃OH was purchased from Aldrich and was 99 atom % D. Reduction experiments were conducted using 5 equivalents (based on boron) of BER or BDR with the resin first treated with 0.05 mmol CuSO₄ · 5H₂O/0.1 mmol aryl bromide for 2 minutes at room temperature in either methanol or methanol-d₄ (1 mL/0.1 mmol aryl bromide). After 2 minutes the aryl bromide was added all at once (either neat or as a solution in methanol or methanol-d₄). Reactions were monitored and yields determined by either HPLC or GC (mesitylene as an internal standard). All product identities were confirmed by ¹H-NMR and HPLC, GC or TLC. GC-MS (Finnigan) with chemical ionization (ammonia) was used to determine deuterium incorporation.

Preparation of BDR

Amberlite IRA-400 (Cl⁻ form, 100 g) was washed with water, ethanol and then water. The wet resin was stirred with a solution of 19 g of sodium borodeuteride in 500 ml water for 60 min. The mixture was filtered and the borodeuteride resin washed with water to remove residual sodium borodeuteride (monitored by addition of the filtrate to dilute hydrochloric acid). The resin was dried under vacuum at 56°C. Borohydride exchange resin (BER) was prepared in the same manner with sodium borohydride.

Typical reduction

The experiments were conducted using 5 equivalents (based on boron) of BER or BDR. Reduction of 4-bromoanisole is representative. BDR resin (162 mg) was treated with 12.5 mg CuSO₄ · 5H₂O (0.5 equivalents/0.1 mmol aryl bromide) for 2 min at room temperature in 1 ml of methanol-d₄. Vigorous bubbling was seen and the resin turned black. After 2 min, the bubbling had ceased and 4-bromoanisole (18.7 mg, 12 µl, 0.1 mmol) was added. The reaction was heated at 65°C for 1 h. The reaction was filtered and concentrated under vacuum. This procedure gave 10 mg of anisole (93%). Proton NMR was identical with an authentic standard except for the absence of signals where deuterium was incorporated. Deuterium incorporation was determined by GC/MS (Table 1).

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