Convenient Deuteration of Bromo Aromatic Compounds by Reductive Debromination with Sodium Amalgam in CH_3OD

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Deuterated compounds provide conclusive information on the proton assignments of ^{1}H NMR and ESR spectra and play important roles in kinetic and mechanism studies and in the biochemical field.[1] However, the desired deuterated compounds, particularly partly deuterated compounds, with high isotopic purities are still difficult to prepare and require many steps in their preparation, starting from commercially available, but expensive deuterated compounds.[2] Deuteration by reductive dehalogenation of halo compounds is one of the most useful methods. For examples, hydrolysis of Grignard or organolithium reagents obtained from halo compounds in D_2O or CH_3COOD,[3] treatment of trialkylstannane compounds obtained from halo compounds in $CH_3COOD-D_2O$,[4] photolysis of halo compounds in CD_3OD,[5] and Raney alloy reduction of halo compounds in alkaline deuterium oxide solution[6] have served for the preparation of a variety of partly deuterated compounds. However, these methods have still severe problems in the isotopic purities or yields of the products, the easiness of the procedures, or the prices of the deuterated solvents used.

We have recently found that reductive debromination of bromo aromatic compounds with sodium amalgam in refluxing CH_3OD gives the corresponding deuterated compounds with high isotopic purities in high yields.[7] Since CH_3OD is commercially available at a relatively inexpensive price and the procedure is quite simple, this reductive debromination would provide a useful method for the preparation of partly deuterated compounds. Herein we report the preparation of deuterated aromatic compounds shown in Chart 1 by this method.

Results and Discussion

Reductive debromination of bromo aromatic compounds was carried out by heating them in refluxing MeOD over 4.8 wt % sodium amalgam for 2−24 h. The reaction mixtures were then poured into a large excess of water and the products were extracted with ether or benzene. In the case of **17a**, the reaction mixture was first evaporated and then acidified, and the product was extracted with ether. Upon removal of the solvent pure or almost pure products were obtained in high yields in most cases. The results of this deuteration reaction are summarized in Table 1, and the ^{1}H and ^{13}C NMR data shown in Table 2.

In the present reductive deuteration 10 mL (238 mmol) of MeOD was used to keep the reaction system in high isotopic purity. This amount corresponds to 33 times the molar amount for one bromine atom of the bromo compounds. Furthermore, aniline compounds were treated with MeOD prior to the reductive deuteration. Since some bromo compounds (**7a**, **10a**, **11a**, **16a**, and **17a**) are insoluble in such a small amount of MeOD even at the reflux temperature, 10−20 mL of dry benzene (**7a**, **10a**, **11a**, and **16a**) or 5 mL of D_2O (**17a**) was further added to dissolve the bromo compounds completely in CH_3OD solution. The purities of the separated products were evaluated by HPLC or TLC. For most products HPLC or TLC analyses showed only a single peak or one spot.[8]

Chart 1

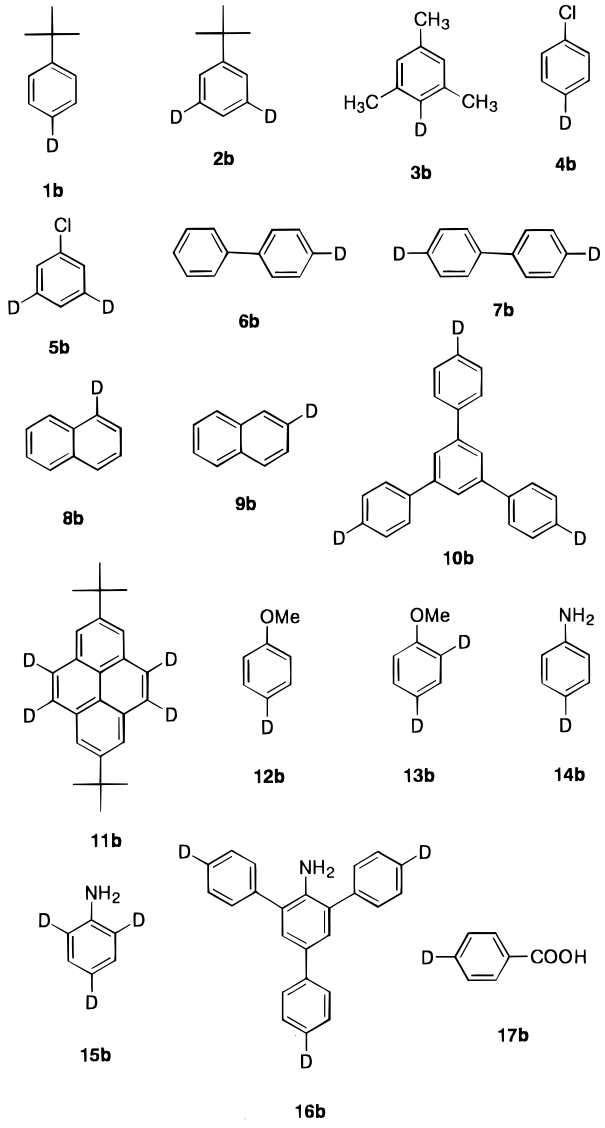

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Table 1. Results of Reductive Deuteration of Bromo Compounds with Sodium Amalgam in CH_3OD

entry	bromo compound (mmol)	solvent (mL)	time (h)	product	isolated yield (%)	isotopic purity (%)[a]
1	4-bromo-1-*tert*-butylbenzene (**1a**) (7.2)	MeOD (10)	2	*tert*-butylbenzene-4-*d* (**1b**)	93	98.5 (D_1), 1.5 (D_0)
2	3,5-dibromo-1-*tert*-butylbenzene (**2a**) (3.6)	MeOD (10)	2	*tert*-butylbenzene-3,5-d_2 (**2b**)	92	96 (D_2), 4 (D_1)
3	2,4,6-trimethyl-1-bromobenzene (**3a**) (7.2)	MeOD (10)	2	1,3,5-trimethylbenzene-2-*d* (**3b**)	94	D_1 (99), 1 (D_0)
4	1-chloro-4-bromobenzene (**4a**) (7.2)	MeOD (10)	2	chlorobenzene-4-*d* (**4b**)	76	98 (D_1), 2 (D_0)
5	1-chloro-3,5-dibromobenzene (**5a**) (3.6)	MeOD (10)	2	chlorobenzene-3,5-d_2 (**5b**)	97	98 (D_2), 2 (D_1)
6	4-bromobiphenyl (**6a**) (7.2)	MeOD (10)	2	biphenyl-4-*d* (**6b**)	98	1 (D_2), 98 (D_1), 1 (D_0)
7	4,4′-dibromobiphenyl (**7a**) (3.6)	MeOD (10)−benzene (5)	2	biphenyl-4,4′-d_2 (**7b**)	99	99 (D_2), 1 (D_1)
8	1-bromonaphthalene (**8a**) (7.2)	MeOD (10)	2	naphthalene-1-*d* (**8b**)	95	99 (D_1), 1 (D_0)
9	2-bromonaphthalene (**9a**) (7.2)	MeOD (10)	2	naphthalene-2-*d* (**9b**)	92	1 (D_2), 98 (D_1), 1 (D_0)
10	2,4,6-tris(4-bromophenyl)benzene (**10a**) (2.4)	MeOD (10)−benzene (10)	4	1,3,5-tri(phenyl-4-*d*)benzene (**10b**)	98	99 (D_3), 1 (D_2)
11	2,7-di-*tert*-butyl-4,5,9,10-tetrabromopyrene (**11a**) (1.8)	MeOD (10)−benzene (20)	4	2,7-di-*tert*-butylpyrene-4,5,9,10-d_4 (**11b**)	74	63 (D_4), 29 (D_3), 7 (D_2), 1 (D_1)
12	4-bromoanisole (**12a**) (7.2)	MeOD (10)	2	anisole-4-*d* (**12b**)	90	1 (D_2), 97 (D_1), 2 (D_0)
13	2,4-dibromoanisole (**13a**) (3.6)	MeOD (10)	2	anisole-2,4-d_2 (**13b**)	88	97 (D_2), 3 (D_1)
14	4-bromoaniline (**14a**) (7.2)	MeOD (10)	2	aniline-4-*d* (**14b**)	89	98 (D_1), 2 (D_0)
15	2,4,6-tribromoaniline (**15a**) (2.4)	MeOD (10)	2	aniline-2,4,6-d_3 (**15b**)	87	1 (D_4), 96 (D_3), 2 (D_2), 1 (D_1)
16	2,4,6-tris(4-bromophenyl)-1-nitrobenzene (**16a**) (2.4)	MeOD (10)−benzene (10)	24	2,4,6-tri(phenyl-4-*d*)aniline (**16b**)	85	97 (D_3), 2 (D_2), 1 (D_1)
17	4-bromobenzoic acid (**17a**) (7.2)	MeOD (10)−D_2O (5)	3	benzoic-4-*d* acid (**17b**)	94	97 (D_1), 3 (D_0)

[a] Determined by mass spectroscopy.

The only two exceptions were **11b** and **16b** which contained some byproducts in small amounts. However, pure **11b** and **16b** were easily obtained by column chromatography.

As found in Table 1, the product yields are high (74−99%), and the isotopic purities, determined by mass spectra, are satisfactorily high in any case (89−99%). Deuteration of **11a** was previously undertaken using similar reaction conditions (**11a**, 1.59 mmol; 4.2 wt % sodium amalgam, 33 g; CH_3OD, 10 mL; benzene, 20 mL; reflux time, 4 h),[7] giving similar results to the current work (the previous yield and isotopic purity, 80 and 87%, the current yield and isotopic purity, 74 and 89%).

The structures of the products were confirmed by ^1H and ^{13}C NMR spectra. In the ^{13}C NMR spectra the deuterium-bounded carbons were recorded as a 1:1:1 triplet with $J = 24.8$ or 23.2 Hz, with a ~0.3 ppm upfield chemical shift relative to the corresponding nonlabeled compounds. On the basis of the ^1H and ^{13}C NMR results, it was confirmed that the deuteration occurred at the expected positions, and no migration of bromine atoms or deuterium atoms during the reductive debromination was observed.

As found in Table 1, reductive deuteration of **4a** and **5a** gave interesting results. Although the bromo atoms were rapidly subjected to this reductive deuteration, the chloro atoms were inert for this reduction. This selective dehaloganation was further examined in more detail. Compound **4a** was treated for 6 h in refluxing MeOD over 4.8% sodium amalgam, and the reaction mixture was analyzed by HPLC. After 1 h, **4a** disappeared completely and only a peak due to **4b** appeared. After 6 h, the reaction mixture was again inspected, and the situation was observed to be entirely the same.[9] Since **4b** and **5b** can be converted to a variety of deuterated compounds via the Grignard reagent, they will be useful intermediates for the syntheses of deuterated compounds.

In Table 3 the present reductive deuteration method (method A) is compared with the Raney alloy method (method B) developed by Tashiro *et al.*[6] Method B has many advantages over the other methods mentioned above.[3−5] That is, the procedure is quite convenient and has a wide appreciation. The yields and isotopic purities of the products are very high in most cases. However, in the sodium amalgam method even better results are observed in the yields and isotopic purities of the products, as found in Table 3. Since our current method is quite convenient and CH_3OD is less expensive, this method would be useful for the preparation of deuterated compounds from bromo aromatic compounds.

Experimental Section

^1H and ^{13}C NMR spectra were obtained with a JEOL α-400 NMR spectrometer (400 MHz), and mass spectra were recorded on a JEOL JMS-HX 100 instrument at 70 eV by the GC mass method. The isotopic purities of the products were determined by comparison with the mass spectra of the deuterated com-

(8) In the cases of **4b** and **5b**, the products were obtained as a mixture with the solvent MeOH (derived from MeOD) because the solvents ether and MeOH were removed at atmospheric pressure to avoid the loss of the low boiling point products. The yields were determined by the integration ratio of the protons of ^1H NMR spectra of the mixtures weighed.

(9) We further investigated reductive dechlorination of some chloro aromatic compounds in a similar manner. While 1,4-dichlorobenzene was not subject to reductive dechlorination, 1,3-dichloro- and 1,3,5-trichlorobenzenes underwent slow reductive dechlorination to give a mixture of 1,3-dichloro- and chlorobenzenes and a mixture of 1,3,5-trichloro-, 1,3-dichloro-, and chlorobenzenes, respectively.

Table 2. ^{1}H and ^{13}C NMR Data for Deuterated Compounds

compound	^{1}H chemical shifts (ppm)[a]	^{13}C chemical shifts (ppm)[a]
1b	1.32 (s, 9 H), 7.30 (d, J = 7.8 Hz, 2 H), 7.40 (d, J = 7.8 Hz, 2 H)	31.3, 34.6, 125.1 (t, J = 24.8 Hz), 125.3, 127.9, 151.1
2b	1.32 (s, 9 H), 7.17 (s, 1 H), 7.39 (s, 2 H)	31.4, 34.6, 125.1, 125.2, 127.7 (t, J = 24.8 Hz), 151.1
3b	2.28 (s, 9 H), 6.80 (s, 2 H)	21.1, 21.2, 126.6 (t, J = 24.8 Hz), 126.9, 137.6, 137.7
4b	7.29 (d, J = 8.3 Hz, 2 H), 7.34 (d, J = 8.3 Hz, 2 H)	126.1 (t, J = 24.8 Hz), 128.6, 129.6, 134.2
5b	7.25 (s, 1 H), 7.34 (s, 2H)	126.2, 128.5, 129.4 (t, J = 24.8 Hz), 134.2
6b	7.34 (t, J = 7.8 Hz, 1 H), 7.428 (d, J = 7.8 Hz, 2 H), 7.430 (t, J = 7.8 Hz, 2 H), 7.59 (d, J = 7.8 Hz, 4 H)	126.9 (t, J = 24.8 Hz), 127.15, 127.23, 128.6, 128.7, 141.2
7b	7.42 (d, J = 7.8 Hz, 4 H), 7.58 (d, J = 7.8 Hz, 4 H)	126.9 (t, J = 24.8 Hz), 127.2, 128.6, 141.2
8b	7.44 - 7.47 (m, 4 H), 7.81 - 7.83 (m, 3 H)	125.7, 125.8, 127.5 (t, J = 23.2 Hz), 127.8, 127.9, 133.37, 133.44
9b	7.45 - 7.47 (m, 3 H), 7.82 - 7.84 (m, 4 H)	125.5 (t, J = 23.2 Hz), 125.7, 125.8, 127.7, 127.9, 133.4
10b	7.47 (d, J = 7.8 Hz, 6 H), 7.70 (d, J = 7.8 Hz, 6 H), 7.78 (s, 3 H)	125.2, 127.2 (t, J = 24 Hz), 127.3, 128.7, 141.1, 142.3
11b	1.57 (s, 18 H), 8.18 (s, 4 H)	32.0, 35.2, 121.9, 122.9, 127.0 (t, J = 24.8 HZ), 130.7, 148.5
12b	3.81 (s, 3 H), 6.91 (d, J = 7.8 Hz, 2 H), 7.29 (d, J = 7.8 Hz, 2 H)	55.0, 113.8, 120.3 (t, J = 24.8 Hz), 129.3, 159.5
13b	3.81 (s, 3 H), 6.91 (d, J = 8.8 Hz, 1 H), ~ 7.29 (br. m, 2 H)	55.1, 113.6 (t, J = 24.8 Hz), 113.9, 120.3 (t, J = 24.8 Hz), 129.2, 129.3, 159.5
14b	3.58 (br. s, 2 H), 6.68 (d, J = 8.3 Hz, 2 H), 7.16 (d, J = 8.3 Hz, 2 H)	114.9, 118.1 (t, J = 24.8 Hz), 129.0, 146.3
15b	3.63 (s, 2 H), 7.16 (s, 2 H)	114.8 (t, J = 24.8 Hz), 118.2 (t, J = 24.8 Hz), 129.0, 146.2
16b	3.91 (s, 2 H), 7.38 (d, J = 8.3 Hz, 2 H), 7.41 (s, 2 H), 7.47 (d, J = 8.3 Hz, 4 H), 7.56 (d, J = 8.3 Hz, 4 H), 7.59 (d, J = 8.3 Hz, 2 H)	126.0 (t, J = 24.8 Hz), 126.4, 127.1 (t, J = 24.8 Hz), 128.25, 128.34, 128.53, 128.8, 129.3, 131.0, 139.6, 140.3, 140.8
17b	7.50 (d, J = 8.3 Hz, 2 H), 8.13 (d, J = 8.3 Hz, 2H)	128.4, 129.3, 130.2, 133.5 (t, J = 24.8 Hz), 172.4

[a] Solvent, $CDCl_3$. Chemical shifts refer to tetramethylsilane.

Table 3. Comparison of the Sodium Amalgam Method (A) with the Raney Cu−Al Alloy Method (B)

		method A		method B	
entry	reaction	yield (%)	isotopic purity (%)	yield (%)	isotopic purity (%)
1	**8a** → **8b**	95	99 (D_1), 1 (D_0)	37	99 (D_1), 1 (D_0)
2	**13a** → **13b**	88	97 (D_2), 3 (D_1)	56	1 (D_3), 95 (D_2), 4 (D_1)
3	**15a** → **15b**	87	1 (D_4), 96 (D_3), 2 (D_2), 1 (D_1)	71	3 (D_4), 77 (D_3), 20 (D_2)
4	**17a** → **17b**	94	97 (D_1), 3 (D_0)	86	1.3 (D_3), 1.4 (D_2), 94.9 (D_1), 2.4 (D_0)

pounds of the corresponding nondeuterated compounds obtained under the same instrument conditions. TLC analyses were carried out on Merck Kieselgel 60 F_{254} plates. HPLC analyses were performed with a Shimadzu LC-9A instrument equipped with a Shimadzu SPD-6A UV spectrophotomeric detector using MeOH as eluant.

CH_3OD (99.5% isotopic purity) and D_2O (99.9% isotopic purity) were purchased from Aldrich and used without any further purification. Sodium amalgam (4.8 wt %) was prepared according to the usual method:[10] 20 g of mercury was placed in a 100 mL flask; 1.0 g of sodium was cut to small pieces and added directly to the mercury under a nitrogen stream. After completion of the addition, it was cooled under a nitrogen stream and used in the following reaction.

Compounds **2a**,[11] **5a**,[12] **10a**,[13] and **11a**[7] were obtained by the reported method. Compound **16a**[14] was prepared by the analogous procedure as for 2,4,6-triphenylaniline. Other bromo compounds were commercially available.

General Procedure for Deuteration of Bromoarenes, Bromoanisoles, and Bromonitrobenzenes. Onto 21 g of 4.8% sodium amalgam were put 2.4−7.2 mmol of a bromo compound and 10 mL of CH_3OD. The mixture was then refluxed for 2−24 h under dry nitrogen. If the bromo compounds were not completely dissolved in the refluxing methanol, 5−20 mL of dry benzene was added. After cooling, the methanol solution was poured into a large amount of water, and the sodium amalgam was rinsed twice with CH_3OH, ether, or benzene. The organic products were extracted twice with ether or benzene, and the combined extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave a deuterated compound as an oil or crystals. HPLC analyses showed a single peak for the deuterated compounds except 2,7-di-*tert*-butylpyrene-4,5,9,10-d_4 (**11b**) and 2,4,6-tri(phenyl-4-*d*)aniline (**16b**). Compounds **11b** and **16b** were separated by column chromatography on silica gel (Wako gel, C200) with hexane (**11b**) or 1:1 benzene−hexane (**16b**) as eluant.

Deuteration of Bromoanilines. 4-Bromoaniline (2.4−7.2 mmol) was dissolved in 5 mL of CH_3OD on warming. For 2,4,6-tribromoaniline (2.4 mmol) 5 mL of dry benzene was further added to dissolve the bromo compound. The solvent was then completely removed in vacuum, and this cycle was again repeated. The resulting amino proton deuterated aniline was refluxed in CH_3OD (10 mL) over 4.8% sodium amalgam (21 g) for 2 h under dry nitrogen. After cooling, the methanol solution was poured into a large amount of water, and the sodium amalgam was rinsed twice with CH_3OH. The organic products were extracted with ether, and the combined ether extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave a deuterated aniline. HPLC analyses gave a single peak for the deuterated anilines.

Deuteration of 4-Bromobenzoic Acid. 4-Bromobenzoic acid (7.2 mmol) was refluxed in 10 mL of MeOD and 5 mL of D_2O over 4.8% sodium amalgam (21 g) for 3 h under dry nitrogen. After cooling, the reaction mixture was decanted and the sodium amalgam was rinsed twice with MeOH. The combined methanol solutions were evaporated and the residue was acidified with 10% HCl. The colorless crystals deposited were extracted with ether, and the ether extract was washed with brine and dried ($MgSO_4$). Evaporation of the solvent gave pure benzoic-4-*d* acid.

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