Deuteriodediazoniation: A General Method for the Replacement of a Diazonium Group by Deuterium[1]
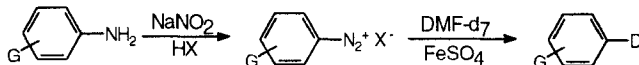
Frederick W. Wassmundt[*] and William F. Kiesman[2]

Department of Chemistry, University of Connecticut, Storrs, CT 06269-3060

Abstract: Aromatic amino groups are replaced with deuterium via a diazonium salt intermediate. Dimethylformamide-d_7 is the deuterium donor in this mild replacement method that yields aromatic-d_1 products in high isotopic purity. The presence of methyl groups lowers the isotopic purity of the products.

Key words: aromatic-d_1 compounds, dediazoniation, free-radical, deuterium.

Introduction. We have developed a procedure for the replacement of diazonium groups by deuterium atoms; the process serves as the second stage of deamination of aromatic amines.

Currently there are only a few simple methods available to introduce deuterium onto aromatic rings. Total replacement of ring hydrogens[3] by deuterium can be achieved by using deuterated acids in which D^+ acts as an electrophile or by using deuterium oxide with platinum black or other catalysts. Selective replacements have been more difficult. Deuterium can be attached to a specific position through the hydrolysis of organometallic reagents[4a] (Grignard reagents, organolithium compounds, etc.) with deuterium oxide. Unfortunately the incompatibility of organometallic reagents with many structural features limits its applicability. Earlier alternative methods via aryl diazonium salts formed replacement products of only modest isotopic purity.[5] Typical procedures involved the use of D_3PO_2 as a deuterium donor.[4b] The requisite D_3PO_2 was prepared from H_3PO_2 by a series of exchanges with D_2O. High isotopic purity in the aromatic compound was never achieved, possibly because D_3PO_2 underwent reversible exchange of hydrogen for deuterium in a subsequent step. In another approach,

Threadgill and Gledhill[6] synthesized, under carefully controlled anhydrous conditions, formamide-d_1 labelled with deuterium on the formyl unit, and used it as the deuterium donor in the reduction of *p*-nitrobenzenediazonium tetrafluoroborate. Apparently the experimental difficulties limited the method to a single use, and there is no description of the scope of the reaction.

During an investigation into the catalysis of free-radical hydrodediazoniations in DMF,[7] we demonstrated that, when DMF-d_7 was used in place of ordinary DMF, deuterium was incorporated into the aromatic compound. We have expanded upon this observation and developed a simple method with commercially available DMF-d_7 as the deuterium donor.
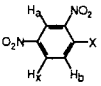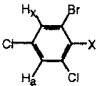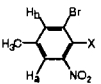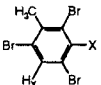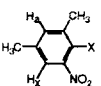
Results and Discussion. The diazonium salt was added to a stirred mixture of $FeSO_4 \cdot 7H_2O$ and DMF-d_7. The reaction was spontaneous and complete upon the final addition of the diazonium salt to the reductant mixture. Dilution of the reaction mixture with water caused the solid products to separate. Many of the products were of such quality that only filtration and washing with water were necessary to afford pure material. The lower yields on deuteriodediazoniation than on hydrodediazoniation are attributable to the fact that the former reactions were run on a much smaller scale.

For the convenience of the exploration of the scope of the reaction we chose reactions whose products (1) are known solids to simplify purification and identification, and (2) have ^{1}H NMR spectra which will reveal the position and the amount of replacement of hydrogen by deuterium.

The reaction of 2,4-dinitrobenzenediazonium tetrafluoroborate (**1a**) afforded the first illustration. Protiodediazoniation of **1a** gave 1,3-dinitrobenzene (**1b**)(Table 1.), which had a nicely resolved ^{1}H NMR spectrum. H_a flanked by the two nitro groups was highly deshielded and exhibited a singlet (1H) at 9.08 ppm. The two H_x protons, with a doublet splitting pattern (because of the splitting by H_b) had a chemical shift of 8.63 ppm. H_b was split by the adjacent H_x protons into a triplet with a chemical shift of 7.86 ppm. In the ^{1}H NMR spectrum of the deuteriodediazoniation product (**1c**, 51% yield), the magnitude of the H_x absorption decreased to 1 H, the H_a absorption remained unchanged and the H_b proton now showed up as a doublet (1H) because it was split by only one adjacent H_x proton. Confirmation of the deuterium incorporation was provided by mass spectral analysis which showed that at least 99% deuterium replacement had been achieved. Clearly one of the H_x positions was occupied by deuterium.

To determine if water interfered with the deuterium incorporation, we examined its influence upon the isotopic purity of the product. The filtrate from the preparation of deuterated

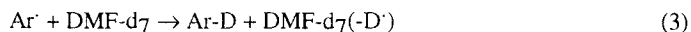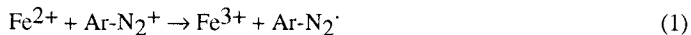## Table 1. Illustrations of Protio- and Deuterio-dediazoniations.

Cmpd No.	X	Yield, %	Deuterium Incorporation, %
1b	H_X	73	--
1c	D	51,54,61	>99.5
2b	H_X	87	--
2c	D	85	>99.5
3b	H	76	--
3c	D	53	85
4b	H_X	96	--
4c	D	84	94
5b	H_X	72	--
5c	D	51	70

dinitrobenzene (containing about 20% DMF-d_7 and 80% water by volume) was recycled twice more. The deuterated dinitrobenzene from the second (54% yield) and third (61% yield) uses of the filtrate had ^1H NMR spectra identical to the first deuteration product. No incorporation of hydrogen from the water was detected, even in the third iteration of the reaction. Mass spectral analysis of the deuteration products confirmed that each was at least 99% isotopically pure, and this high value shows that the sole deuterium (or hydrogen) donor is the DMF-d_7. Moreover, the expense of DMF-d_7 can be offset by recycling the filtrate.
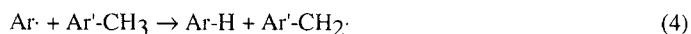
2-Bromo-4,6-dichlorobenzenediazonium tetrafluoroborate (**2a**) underwent deuteriodediazoniation quickly and cleanly giving **2c** in 85% yield. The ^1H NMR spectrum of **2c** showed that the diazonium group was replaced by deuterium. Analysis of **2c** by GC/MS failed to detect anything other than the deuterium compound.

We encountered a limitation of the method during the deuteriodediazoniation of the diazonium salt derived from 2-bromo-4-methyl-6-nitroaniline (**3a**). The ^1H NMR spectrum of **3c**, in comparison to that for **3b**, still exhibited a very small absorption at δ 8.16 which indicated that replacement by deuterium was incomplete. This indication was confirmed by mass spectrometric analysis which showed 85% incorporation of deuterium into the product. The only reasonable hydrogen atom source is the labile benzylic group.

These results can be explained on the basis of the mechanism. The mechanism of this deuteriodediazoniation is analogous to that of the catalyzed hydrodediazoniation[7] and proceeds as follows:

$$Fe^{2+} + Ar\text{-}N_2^+ \rightarrow Fe^{3+} + Ar\text{-}N_2^{\cdot} \qquad (1)$$

$$Ar\text{-}N_2^{\cdot} \rightarrow Ar^{\cdot} + N_2 \qquad (2)$$

$$Ar^{\cdot} + DMF\text{-}d_7 \rightarrow Ar\text{-}D + DMF\text{-}d_7(\text{-}D^{\cdot}) \qquad (3)$$

The electron donor reduces the diazonium cation to the diazenyl radical, which undergoes cleavage to form molecular nitrogen and the aryl radical. The aryl radical abstracts deuterium from the DMF-d$_7$. Benzylic hydrogen atoms are sufficiently reactive that they can compete with DMF-d$_7$ as the atom source.

$$Ar^{\cdot} + Ar'\text{-}CH_3 \rightarrow Ar\text{-}H + Ar'\text{-}CH_2^{\cdot} \qquad (4)$$

A similar limitation also applied to the deuterium replacement in 3-methyl-2,4,6-tribromobenzenediazonium tetrafluoroborate (**4a**). ^{1}H NMR analysis of the product (**4c**) was not sensitive enough and showed that the H$_x$ absorption dropped by about one hydrogen when compared to the protio compound (**4b**). Mass spectral analysis, however, showed that only 94% deuterium incorporation was achieved. The presence of a methyl group in the substrate again lowered the isotopic purity of the replacement product.

The last example was provided by the deuteriodediazoniation of a compound with two methyl substituents. Diazotization of 2,4-dimethyl-6-nitroaniline (**5a**) required a mixture of concd HCl and acetic acid. The ^{1}H NMR spectrum of the deuterium replacement product **5c** showed that the absorption of H$_x$ was slightly larger than one H when compared to the protio compound **5b**. Mass spectral analysis demonstrated that 70% deuterium incorporation resulted. Again, the presence of a methyl group lowered the isotopic purity on replacement, possibly, the presence of two methyl groups was responsible for the worst example.

Conclusion. Our method of introducing deuterium via diazonium salts is general and simple to use. The yields of deuterated product range from moderate to good, and replacement products are of high isotopic purity even in the presence of water. A limitation to this method is due to the reactivity of the aryl radical intermediates generated from the diazonium salts. Aromatic rings with methyl groups have lower deuterium incorporation values.

Experimental

General. Melting points are uncorrected. ^{1}H NMR spectra were run with a Bruker AC-270 FT NMR using CDCl$_3$ solutions with Me$_4$Si as an internal standard. GC/MS were run with a Hewlett Packard 5890 Series II GC coupled to a HP 5971 Series Mass Selective Detector.

3-Methyl-2,4,6-tribromobenzenamine. This amine was prepared by the method described by Pedemonte.[8] Bromine (22.91 g, 143 mmol) was added dropwise with stirring to 5.00 g (47

mmol) of 3-methyl-2,4,6-tribromoaniline in 40 mL of acetic acid. When the addition was complete, the reaction mixture was stirred for an additional 30 min and then poured into 100 mL of ice-water. The off-white precipitate was collected by suction filtration, washed with water, and dried to give a quantitative yield of the crude product, mp 100-101 °C (lit.[9] mp 100-101 °C).

2-Bromo-4-methyl-6-nitrobenzenamine (3a). This amine was prepared in a manner similar to 3-methyl-2,4,6-tribromobenzenamine from 2-nitro-4-methylaniline. The light orange product was formed in 97% yield, mp 63.5-64.5 °C (lit.[10] mp 64.5 °C).

3-Methyl-2,4,6-tribromobenzenediazonium Tetrafluoroborate (4a). This compound was prepared by the method described by Doyle[11] with minor modifications. To a 100 mL 3-neck flask equipped with a magnetic stirrer, condenser, and two addition funnels was added 2.3 mL (8.73 mmol) of $BF_3 \cdot Et_2O$. The $BF_3 \cdot Et_2O$ was chilled to -10 to -15 °C in an ice-acetone bath and to it was added a solution of 2.00 g (5.82 mmol) of 3-methyl-2,4,6-tribromobenzenamine in 13 mL of CH_2Cl_2. A precipitate formed; to facilitate mixing an additional 10 mL of CH_2Cl_2 was added to the reaction mixture. A solution of 0.72 g (6.98 mmol) of butyl nitrite in 10 mL of CH_2Cl_2 was added dropwise with stirring over a 10 min period. The reaction mixture was stirred for an additional 30 min at -15 °C and then allowed to warm, over a 20 min period, to 5 °C in an ice-water bath. The reaction mixture was poured into 100 mL of pentane to fully precipitate the product. The white solid was collected, washed with ether, and dried to give 1.216 g (47%) crude product. TLC of the product (silica, CH_2Cl_2) indicated the presence of amine. The product was purified by the acetone-ether method to yield 0.926 g (36%) of the white diazonium salt; mp 230.5-231.5 °C (dec). Anal. Calcd for $C_7H_4BBr_3F_4N_2$: C, 18.99; H, 0.91; N, 6.33. Found: C, 19.43; H, 0.50; N, 6.35.

The following materials were prepared in a similar manner.

2,4-Dinitrobenzenediazonium Tetrafluoroborate (1a), from 2,4-dinitroaniline; dimethoxyethane was the solvent of choice for this diazotization, 56% yield, mp 165-167 °C (dec) (lit.[12] mp 156 °C (dec)).

2-Bromo-4,6-dichlorobenzenediazonium Tetrafluoroborate (2a), from 2-bromo-4,6-dichloroaniline, 64% yield, mp 225-225.8 °C (dec) (lit.[8] mp 196-197 °C (dec)).

Deuteriodediazoniations--1,3-Dinitro[4-D]benzene (1c). Solid 2,4-dinitrobenzenediazonium TFB (0.100 g, 0.35 mmol) was added to a mixture of $FeSO_4 \cdot 7H_2O$ (0.99 g, 0.35 mmol), and 1 mL of DMF-d_7. The reaction mixture was poured into 4 mL of water and the product was collected by suction filtration; 0.030 g, 51% yield after sublimation, mp 89-89.5 °C. ^1H NMR δ

9.08 (s, 1H$_a$), 8.62 (d, 1H$_x$), 7.86 (d, 1H$_b$).[17] MS m/z (M$^+$) calcd 169.01, obsd 169.00; 99.5%
deuterium incorporation. The filtrate was recycled for two more reductions giving 0.032 g (54%)
and 0.036 g (61%) respectively of sublimed product with identical NMR spectra. ^{1}H NMR δ
9.09 (s, 1H$_a$), 8.62 (d, 1H$_x$), 7.86 (d, 1H$_b$). MS m/z (M$^+$) calcd 169.01, obsd 169.00; both
99.5% deuterium incorporation.

The following materials were prepared in a similar manner.

1-Bromo-3,5-dichloro[2-D]benzene (2c), from 2-bromo-4,6-dichlorobenzenediazonium TFB
(0.150 g, 0.44 mmol) suspended in 1 mL of water, FeSO$_4$·7H$_2$O (0.122 g, 0.44 mmol), and 1 mL
of DMF-d$_7$; 0.085 g (85%), mp 74-75 °C. ^{1}H NMR δ 7.41 (s, 1H$_x$) and 7.31 (s, 1H$_a$).[17] MS
m/z (M$^+$) calcd 224.88, obsd 224.85; 99.5% deuterium incorporation.

1-Methyl-2,4,6-tribromo[3-D]benzene (4c), from 3-methyl-2,4,6-tribromobenzenediazonium
TFB, (0.100 g, 0.226 mmol) suspended in 1 mL of water,   FeSO$_4$·7H$_2$O (0.062 g, 0.226
mmol), and 1 mL of DMF-d$_7$; 0.062 g (84 %), mp 65-67.5 °C. ^{1}H NMR δ 7.65 (s, 1H$_x$), 2.5 (s,
3H). MS m/z (M$^+$) calcd 326.80, obsd 326.80; 94% deuterium incorporation.

1-Bromo-3-methyl-5-nitro[6-D]benzene (3c). To a solution of 2-bromo-4-methyl-6-
nitroaniline (0.150 g, 0.648 mmol) in 0.33 mL of concd H$_2$SO$_4$ was added 0.10 mL of water.
The amine suspension was chilled in an ice bath and solid NaNO$_2$ (0.744 g, 0.052 mmol) was
added slowly while stirring. The reaction mixture was diluted with 0.5 mL of water and allowed
to stir for an additional 2 h. The solution of the diazotized amine was then added dropwise with
stirring to a mixture of FeSO$_4$·7H$_2$O (0.180 g, 0.648 mmol) in 1 mL of   DMF-d$_7$. The reaction
solution was negative to 2-naphthol immediately after the last addition. Pouring into 5 mL of
water precipitated a yellow product which was collected by suction filtration, washed with water,
dried and sublimed to give 0.055 g (53% based on unrecovered amine) of yellow needles, mp 78-
79 °C. ^{1}H NMR δ 8.16 (s, 0.05H), 7.98 (s, 1H$_a$), 7.66 (s, 1H$_b$), 2.46 (s, 3H). When the filtrate
was made basic, 39 mg of unchanged amine was recovered. MS m/z (M$^+$) calcd 215.96, obsd
215.90; 85% deuterium incorporation.

1,3-Dimethyl-5-nitro[6-D]benzene (5c). A solution of 2,4-dimethyl-6-nitroaniline (0.150 g,
0.90 mmol) in 0.6 mL of acetic acid was added to a mixture of 0.30 mL of concd HCl and 1.8 g
of ice. A concentrated solution of NaNO$_2$ (0.068 g, 0.97 mmol) was added dropwise with
stirring. The reaction mixture was stirred for an additional 15 min and then sulfamic acid was
added to destroy any remaining nitrous acid. The solution of the diazotized amine was added
dropwise with stirring to a mixture of FeSO$_4$·7H$_2$O (0.250 g, 0.90 mmol), and 1 mL of DMF-d$_7$

and 1 mL of water. The reaction solution was negative to 2-naphthol immediately after the last addition. Pouring into 60 mL of water precipitated a red product which was collected by suction filtration, washed with water, dried, and sublimed to give 0.070 g (51%) of yellow needles of 1,3-dimethyl-5-nitro[6-D]benzene, mp 70-70.5 °C. ^{1}H NMR δ 7.81 (s, 1.1H$_x$), 7.30 (s, 1H$_a$), 2.40 (s, 6H). MS m/z (M$^+$) calcd 152.06, obsd 152.10; 70% deuterium incorporation.

The following non-deuterated materials were prepared in a similar manner[7] and used as comparison samples.

1,3-Dinitrobenzene (1b). ^{1}H NMR δ 9.08 (s, 1H$_a$), 8.63 (d, 2H$_x$), 7.86 (t, 1H$_b$). MS m/z (M$^+$) calcd 168.01, obsd 168.00. Mp 89-89.5 °C (lit.[13] mp 88 °C).

1-Bromo-3,5-dichlorobenzene (2b). ^{1}H NMR δ 7.41 (d, 2H$_x$) and 7.39 (t, 1H$_a$). MS m/z (M$^+$) calcd 223.88, obsd 223.85. Mp 74-75 °C (lit.[14] mp 74 °C).

1-Bromo-3-methyl-5-nitrobenzene (3b). ^{1}H NMR δ 8.16 (s, 1H), 7.98 (s, 1H$_a$), 7.66 (s, 1H$_b$), 2.47 (s, 3H). MS m/z (M$^+$) calcd 214.96, obsd 214.95. Mp 78-79 °C (lit.[16] mp 81.4-81.8 °C).

1-Methyl-2,4,6-tribromobenzene (4b). ^{1}H NMR δ 7.65 (s, 2H$_x$), 2.5 (s, 3H). MS m/z (M$^+$) calcd 325.79, obsd 325.70. Mp 67.5-68 °C (lit.[9] mp 68.5 °C).

1,3-Dimethyl-5-nitrobenzene (5b). ^{1}H NMR δ 7.83 (s, 2H$_x$), 7.31 (s, 1H$_a$), 2.41 (s, 6H). MS m/z (M$^+$) calcd 151.06, calcd 152.10. Mp 70.5-71 °C (lit.[15] mp 72 °C).

References and Notes

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(2) NSF Predoctoral Fellow (1993-present).

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(17) At higher resolution, the splitting becomes more complex because of the ability to observe *meta* coupling.