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Synthesis of selectively deuterated nitrobenzene derivatives

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Dedicated to Professor Janusz Jurczak on the occasion of his 60th birthday.

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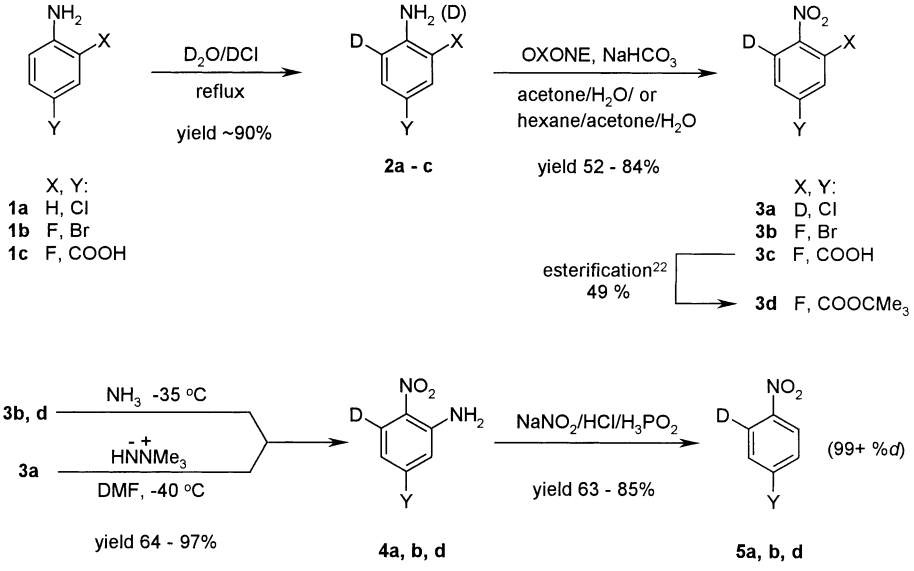
Abstract—Selectively *ortho*-deuterated nitroarenes of high isotopic purity are prepared via acid catalysed H→D exchange in *para*-substituted anilines followed by oxidation of the amino groups.

For studies of the kinetic isotope effects in the vicarious and oxidative nucleophilic substitution of hydrogen and other reactions of nucleophilic substitution of hydrogen we needed a series of model nitroarenes deuterated in well-defined positions—compounds **3a–d**, **5a,b,d** as indicated in Scheme 1.[1,2] In our previous studies we have prepared some similar deuterated nitroarenes via reduction of dry nitroaryl diazonium tetrafluoroborates with deuterated hypophosphorous acid; however, the isotopic purity of the deuterated nitroarenes prepared by this method usually did not exceed 94%.[3–5] When nitroaryl diazonium tetrafluoroborates exhibit relatively good solubilities in water and it is difficult to obtain such salts in the solid state, they can be reduced in a D_2O solution but with an unavoidably lower introduction of deuterium into the nitroaryl moiety. For example, 2-deutero-4-chloronitrobenzene (**5a**) 89.5% D was prepared from 5-chloro-2-nitroaniline in a one pot reaction by diazotization in DCl/D_2O followed by reduction of the diazonium salt with D_3PO_2.[6] A higher isotopic purity, up to 98% of the deuterium content, was obtained via reduction of the corresponding dry aryldiazonium hexafluorophosphate, when it was isolated in the solid form, but the procedure required the salt to be dried for a long time over P_2O_5. It seems to be difficult to reach a higher isotopic purity by this method because hydrogen is introduced 2–6 times faster than deuterium.[7] Alternative methods of synthesis of



Scheme 1.

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Table 1. The results of the reactions of Scheme 1

Product No	Product name	Yield[a] (%)	Isotopic purity[b] (%)
3a	4-Chloro-2,6-di-deuteronitrobenzene	59	99.06
3b	4-Bromo-2-deutero-6-fluoronitrobenzene	52	99.25
3d	4-*tert*-butoxycarbonyl-2-deutero-6-fluoronitrobenzene	84	99.02
4a	2-amino-4-chloro-6-deuteronitrobenzene	64	99.38
4b	2-amino-4-bromo-6-deuteronitrobenzene	97	99.14
4d	2-amino-4-*tert*-butoxycarbonyl-6-deuteronitrobenzene	85	99.32
5a	4-chloro-2-deuteronitrobenzene	63	99.42
5b	4-bromo-2-deuteronitrobenzene	85	99.98
5d	4-*tert*-butoxycarbonyl-2-deuteronitrobenzene	81	99.17

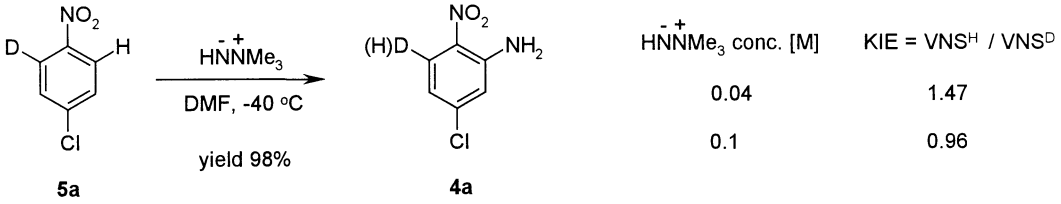
[a] Yields were calculated on the basis of amount of arene used in corresponding stage as the reactant.
[b] Isotopic purity was calculated on the basis of average multiscan MS EI spectra by applying the appropriate correction for the contribution of heavy isotopes in natural abundance, errors are below ±0.05%.

arenes deuterated in well-defined positions are oxidation of aryl hydrazines,[8] base induced decomposition of aryl (*N*-tosyl) hydrazines in D_2O media,[9] or quenching aryl lithium or aryl magnesium halides with D^+/D_2O.[10–12] All these methods do not assure high isotopic purities of the products, nor can they be applied for synthesis of deuterated nitroarenes.

Here we report an alternative simple method of synthesis of deuterated nitroarenes **3a–d** and **5a,b,d** of high isotopic purity, exceeding 99 atom % of D at the desired positions indicated in Scheme 1, Table 1.

The method consists of electrophilic substitution of H for D in *para*-substituted anilines in the *ortho* position to the amino group which occurs simply via treatment of the anilines with DCl/D_2O, followed by oxidation of the amino groups of the deuterated anilines under mild conditions. Thus repeated treatment (3–4 times) of substituted anilines **1a–c** with a solution of DCl in D_2O gave deuterated anilines **2a–c** with isotopic purity exceeding 99%.[11–13] Since partial D/H exchange in amino groups takes place during work-up the MS determination of the isotopic purity of the deuterated anilines is not possible. These values are based on the absence of the *ortho*-proton signals in ^1H NMR spectra of the deuterated anilines and particularly on the isotopic purity of the resulting nitroarenes. Deuterated anilines **2a–c** were oxidized to nitroarenes **3a–c** without loss of deuterium in a neutral acetone solution of dimethyldioxirane DMDO produced in advance[14] or generated in situ with OXONE/$NaHCO_3$ in acetone–water, or in hexane–water–acetone solvents. Under the oxidation conditions enabling DMDO to be generated in situ, the consumption of OXONE is several times lower than that in the procedure involving the use of the reagent prepared in advance. Other methods for transforming aromatic amines into nitro compounds, which use strong acidic conditions like Caro acid or percarboxylic acids,[15] are not applicable because the reaction can be accompanied by acid-catalyzed isotope exchange and loss of deuterium. Deuterated nitroarenes **5a,b,d** were prepared from **3a**, **3b** and **3d** which had been converted first into *ortho*-nitroanilines **4a,b,d** via vicarious nucleophilic amination of **3a** with *N,N,N*-trimethylhydrazonium iodide[16] or substitution of fluorine with ammonia in **3b** and **3d**. These anilines were reductively deaminated via diazotization and reduction of the diazonium salts with hypophosphorous acid in situ to give **5a,b,d**, again without loss of deuterium.

Some observations on deuterium distribution and on the kinetic isotope effect were made while searching for a method for the amination of **3a** to give **4a** without loss of deuterium. We have found the VNS amination of **3a** with *N,N,N*-trimethylhydrazonium iodide executed under standard conditions in the presence of an excess of *t*-BuOK[16] proceeds with an excellent yield; however, it is connected with some loss of deuterium, about 3%. Control experiments indicated that no detectable H/D exchange occurred in 2-amino-4-chloro-6-deuteronitrobenzene (**4a**) when it was subjected to the reaction conditions. On the other hand, an experiment in which 4-chloro-2,6-dideuteronitrobenzene **3a** was treated with *t*-BuOK in DMSO containing 20% *t*-BuOH resulted in a rapid isotope exchange so that the recovered nitro-compound lost the deuterium almost completely. This is in agreement with the results of studies on H/D exchange under basic conditions in nitrobenzene and in 1,3-dinitrobenzene.[17,18] When the amination of **3a** was carried out under similar conditions in the presence of an excess of *t*-BuOK in DMSO containing 10% *t*-BuOH, the loss of deuterium in the amination product was about 20%. It means that the H/D exchange in **3a** competes with amination and is promoted by the excess of *t*-BuOK and *t*-BuOH. In order to avoid the undesired isotope exchange during the amination, we applied the procedure in which *N,N,N*-trimethylhydrazonium iodide was used in excess to nitroarene and slight excess over *t*-BuOK. Under such conditions



Scheme 2.

the VNS amination of **3a** of 99.06% D isotopic purity[19] gave **4a** containing 99.38% of D. The increase of deuterium content during the amination seems at first glance surprising. It can be rationalized by taking into account that VNS reactions, particularly when carried out in the presence of a weak base, exhibit primary kinetic isotope effect $k_H/k_D>1$, often of substantial value.[1,2,4] In separate experiments, we have found that the amination of **5a** which is admixture in **3a**, under our conditions exhibits moderate KIE $k_H/k_D\cong1.5$ and close to 1.0 in the case of higher nucleophile concentrations (Scheme 2). Although this value of KIE is not significant, somewhat faster replacement of H than D in a mixture of **3a** and **5a** results in preferential replacement of H in the latter, hence the overall improvement of isotopic purity of **4a** and after deamination, in **5a**.

Considering the isotope exchange in **3a** and the isotope effect in the conversion of **5a** into **4a**, the conditions are an important factor that determines the isotopic purity of the product. Both methods of amination VNS in **3a** and S_NAr in **3b,d**, lead to the desired products of high isotopic purity. The substrates for the method starting from fluoroaniline are not easily available; however, this method is more convenient for the preparation of the product on a larger scale.

1. Experimental

Mass spectra were obtained on a AMD-604 and HP 5972A MSD spectrometers. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Gemini (200 MHz) and Brucker AM 500 (500 MHz) instruments. Chemical shifts are expressed in ppm referred to TMS, coupling constants in Hertz. Silica gel Merck 60 70-230 mesh was used for column chromatography.

3-Fluoro-4-nitrobenzoic acid was obtained by oxidation of methyl 2-(3-fluoro-4-nitrophenyl)propionate with $K_2Cr_2O_7$ in 50% H_2SO_4, crude product was treated with charcoal and recrystallized from 15% H_2SO_4 yield 58%, mp 170–174°C (lit.[21] 174–175°C).

Methyl 2-(3-fluoro-4-nitrophenyl)propionate was prepared via VNS.[20] To a solution of vigorously stirred *t*-BuOK (90 g, 0.8 mol) in 300 mL DMF a solution of 2-fluoronitrobenzene (28.2 g, 0.2 mol) and methyl 2-chloropropionate (24.5 g, 0.2 mol) in 500 mL DMF was added dropwise at −30°C within 3 min. Afterwards an additional portion of methyl 2-chloropropionate (12.3, 0.1 mol) was added within 1 min. The reaction mixture was stirred for 5 min., poured into ice–10% HCl and extracted with ethyl acetate. Evaporation and distillation gave methyl 2-(3-fluoro-4-nitrophenyl)propionate, bp 116–117°C (0.05 mmHg) yield 75% (lit.[20] 58%).

The remaining materials were commercial and were purified before use by recrystallisation or distillation, if necessary. DMF was dried over CaH_2, and distilled at reduced pressure (20 mmHg) and handled under argon all the time. THF was dried and distilled from sodium and benzophenone. DMSO was dried and distilled from CaH_2. Deuterium oxide, 99.9% atom D, was purchased from RC POLATOM PL-05-400 Otwock-Świerk, Poland. D_3PO_2 50 wt. % solution in D_2O 99+ % atom D was purchased from Aldrich.

1.1. Deuteration of anilines 1a–c to 2a–c; General procedure

To the stirred D_2O (25 mL), freshly distilled $SOCl_2$ (5 mL) was added dropwise at room temperature under argon. The solution was heated to reflux and cooled to room temperature. Aniline (30 mmol), was added and the resulting solution or suspension was refluxed overnight under argon. The solvent was evaporated in vacuo and the residue was dried for 2 h in vacuo over P_2O_5. The residue was then dissolved in 20 mL of D_2O, and $SOCl_2$ (3 mL) was added dropwise at room temperature under argon. The mixture was refluxed overnight. The exchange was monitored by ^{1}H NMR. After disappearance of the signal of appropriate proton, the procedure was repeated. Usually, after 4 repetitions, the percentage of D atom in the appropriate position was higher than 99%. After the last exchange, the reaction mixture was cooled to room temperature and neutralised with $NaHCO_3$, extracted with AcOEt, treated with Na_2SO_4, the solvent was evaporated and a crude product (yield about 90%) was used in the oxidation step.

1.2. Oxidation of anilines 2b–c to nitroarenes 3b–c with OXONE in acetone/water; General procedure

To a stirred solution of aniline (1 mmol) in acetone/water (1:1, 35 mL) $NaHCO_3$ (9 g) and OXONE (23 g) were added portionwise within 2 h at −15°C. The suspension was diluted with acetone/water (1:1, 35 mL) and $NaHCO_3$ (9 g) and OXONE (23 g) were added portionwise within 2 h. After being stirred overnight, the suspension was filtered off and the solid was washed with AcOEt or CH_2Cl_2. The combined organic layers were evaporated and the product was distilled with steam, filtered and recrystallised: **3b** from MeOH, **3c** was not distilled, instead the crude product was recrystallised from H_2SO_4 (15% in H_2O) and used for preparing of **3d**.

1.3. Oxidation of 4-chloro-2,6-dideuteroaniline 2a to 4-chloro-2,6-dideuteronitrobenzene 3a with OXONE in hexane/water/acetone

To a stirred solution of **2a** (1 mmol) in hexane/water/acetone (6.7:5:1, 6 mL) $NaHCO_3$ (0.4 g) and OXONE (1.05 g) were added at 0°C. After 20 min., a second portion of $NaHCO_3$ (0.4 g) and OXONE (1.05 g) was added and after 20 min., the final portion of $NaHCO_3$ (0.4 g) and OXONE (1.05 g) was added. After being stirred for 1h, the suspension was diluted with water, the organic layer was extracted with CH_2Cl_2. The combined organic layers were evaporated and the product was distilled with steam, filtered and recrystallised from hexane. From the distillation residue a by-product was obtained: *N,N′*-bis-(4-chloro-2,6-dideutero-phenyl)-diazene *N*-oxide (yield 13%, δ_H $CDCl_3$, 200 MHz: 7.43 (s, 2H), 7.47 (s, 2H); δ_C $CDCl_3$, 50 MHz: 123.40 (t, J=25.8), 126.75 (t, J=25.5), 128.82 (s), 128.87 (s), 135.22 (s), 138.02 (s), 142.03 (s), 146.38 (s) MS EI m/z (%): 270(M^+, 25), 207 (8), 172 (6), 141 (15), 127 (37), 113 (100); TLC identical to *N,N′*-bis-(4-chloro-phenyl)-diazene *N*-oxide).

1.4. Amination of 3a to 4a

To a solution of $NH_2N^+Me_3I^-$ (808 mg, 4 mmol) in DMF (90 mL) vigorously stirred and cooled to −40°C, a solution of *t*-BuOK (450 mg, 4 mmol) in DMSO (4 mL) was added. To the resulting homogeneous solution, a solution of 4-chloro-2,6-dideuteronitrobenzene **3a** (160 mg, 1 mmol) in DMSO (2 mL) was added at −40°C. Immediately after that, a solution of *t*-BuOK (337 mg, 3 mmol) in DMSO (4 mL) was added dropwise within 3 min.

After being stirred for 10 min., the mixture was poured into water (0.6 L) and carefully acidified with AcOH to pH≈6, extracted with CH_2Cl_2, washed with brine, dried with Na_2SO_4 and purified by column chromatography. Yield 111 mg (64%), of **4a** as yellow crystals.

1.5. Aminolysis of 3b,d to 4b,d

Liquid NH_3 (ca. 2 mL) was added to 1 mmol of 4-bromo-2-deutero-6-fluoronitrobenzene (**3b**) or 4-*tert*-butoxycarbonylo-2-deutero-6-fluoronitrobenzene (**3e**) placed in an ampoule with a teflon stopper equipped with a magnetic stirrer at −35°C, and the mixture was stirred for 2.5 h at 0°C. Ammonia was evaporated, and the residue was extracted with ethyl acetate, evaporated, and used without further purification.

1.6. Esterification of 3c to 3d

The esterification proceeded according to the literature method,[22] yield 49% after purification by column chromatography and recrystallization from MeOH.

1.7. Determination of kinetic isotope effect in reactions in Scheme 2

Variant 1. To a vigorously stirred solution of freshly sublimed *t*-BuOK (168 mg, 1.5 mmol) in DMF (36 mL) thermostated for 3 min. at −40±0.2°C, $NH_2N^+Me_3I$ (303 mg, 1.5 mmol) was added, and after 1 min. stirring, a homogeneous solution (0.04 M conc. of KHN–NMe_3) was obtained and a solution of 4-chloro-2-deuteronitrobenzene 98.1% atom D (16 mg, 0.1 mmol) in DMF (1 mL) was added; a red colour appeared gradually. After being stirred for 5 min., the reaction mixture was poured into water (0.3 L), the product was extracted with CH_2Cl_2, washed with brine, dried with Na_2SO_4, and purified by column chromatography. The resulting product **4a** was obtained as yellow crystals, yield 17 mg (98%), 58.4% atom D.

Variant 2. According to the same procedure but using a higher concentration (0.1 M) of the nucleophile (1 mmol of NH_2NMe_3I and 9 mL of DMF was used) gave **4a** containing 48.2% D.

1.8. Synthesis of 4-chloro-2-deuteronitrobenzene 98.1% atom D

To a cooled (−2°C) and stirred suspension of 5-chloro-2-nitroaniline (4.5 g, 26.2 mmol) in 6 M HCl (20 mL), a solution of $NaNO_2$ (2.5 g, 40 mmol) in water (3 mL) was added dropwise. The mixture was stirred for 15 min. at 0°C and filtered. The filtrate was placed in a beaker and a solution of NH_4PF_6 (5.05 g, 32 mmol) in water (10 mL) was added portionwise with stirring. A white hydrophobic precipitate of 2-nitro-5-chlorobenzenediazonium hexafluorophosphate was filtered, washed with water and dried over P_2O_5 in vacuo to constant weight (one week) and used for the reaction with D_3PO_2. A sample of the resulting dry salt (4.63 g, 14 mmol) was placed in a 50-mL round-bottom flask equipped with an empty rubber balloon, D_2O (16.5 mL) was added and stirred for 5 min. followed by addition of 3.8 mL of 50% D_3PO_2 in D_2O and the mixture was stirred overnight at room temperature. The product was isolated by extraction with CH_2Cl_2 and purified by steam distillation followed by recrystallisation from 90% MeOH to give 4-chloro-2-deuteronitrobenzene, 1.35 g, mp 83–84°C, 98.1% atom D. Evaporation of the mother liquor and chromatography of the residue gave an additional 250 mg of product with essentially the same isotopic purity and overall yield 1.6 g, 71%. The reduction reaction was relatively slow. Attempts to increase the rate of the reduction by addition of dry ethyl ether or THF resulted in a drop in the isotopic purity of the product to 64% and 11% respectively. A similar reduction of arene diazonium salt by deuterated THF has been observed.[23]

Deuterated nitrobenzene derivatives (Table 1). The melting points cited here from the literature relate to non-deuterated analogues.

1.8.1. 4-Chloro-2,6-dideuteronitrobenzene (3a). Mp 85°C, MeOH (lit.[24] 83.6°C), ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60 (s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 124.64 (t, J=25,9), 129.43 (s), 141.33 (s), 146.33 (s); MS (EI) m/z (rel. intensity) 159 (100), 143 (2.9), 129 (45), 113 (86), 101(27), 77 (39).

1.8.2. 4-Bromo-2-deutero-6-fluoronitrobenzene (3b). Mp 87–88°C (lit.[25] 85–86°C, EtOH), ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (dd, J=10.1 J=2.0, 1H), 7.47 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 121.99 (d, J=23.5), 126.85 (td, J=26.2 J=2.1), 127.97 (d, J=16.8), 129.4 (dt, J=8.9 J=1.8), 136.4 (m), 155.27 (d, J=269.7); MS (EI) m/z (rel. intensity) 222 (99.6), 220 (100), 206 (6), 204 (6), 192 (81), 190 (82), 176 (32), 174 (33), 164 (37), 162 (38), 95 (73).

1.8.3. 4-*tert*-Butoxycarbonyl-2-deutero-6-fluoronitrobenzene (3d). Mp 73–74°C (lit.[26] 68–70°C), ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 (s, 9H), 7.87–7.90 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.98 (s), 83.19 (s), 19.39 (d, J=22.3), 125.17 (d, J=4.3), 125.67 (dt, J=26 J=2.4), 155.01 (d, J=265.4), 162.49 (d, J=2.1); MS (EI) m/z (rel. intensity) 242 (1.2), 227 (3), 212 (1), 169 (60), 156 (7), 139 (13), 123 (16), 95 (13), 57 (100).

1.8.4. 2-Amino-4-chloro-6-deuteronitrobenzene (4a). Mp 122–124°C (lit.[27] 124–125.4°C), ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.15 (s, 2H), 6.64–6.69 (m, 1H), 8.84 (d, J=2.2, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 117.44 (s), 117.73 (s), 127.39 (t, J=26), 130.81 (s), 141.94 (s), 145.12 (s); MS (EI) m/z (rel. intensity) 175 (32), 173 (100), 145 (23), 143 (72), 129 (14), 127 (44), 115 (39), 100 (47), 91 (45).

1.8.5. 2-Amino-4-bromo-6-deuteronitrobenzene (4b). Mp 153–154°C (lit.[24] 151–152°C), ^{1}H NMR (200 MHz, $CDCl_3$/DMSO-d_6) δ 6.71 (d, J=2.0, 1H), 7.10 (s, 2H), 7.21 (d, J=2.0, 1H); ^{13}C NMR (50 MHz, $CDCl_3$/DMSO-d_6) δ 118.28 (s), 120.51 (s), 126.27 (t, J=26.0), 129.52 (s), 145.86; MS (EI) m/z (rel. intensity) 219 (98.3), 217 (100), 189 (14), 187 (14), 173 (24), 171 (25), 159 (11), 161 (10), 146 (14), 144 (10).

1.8.6. 2-Amino-4-tert-butoxycarbonyl-6-deuteronitrobenzene (4d). Mp 135°C (hexane/cyclohexane), ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.60 (s, 9H), 6.08 (s, 2H), 7.24 (d, J=1.7, 1H), 7.47 (d, J=1.8, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.02 (s), 82.31 (s), 116.77 (s), 120.40 (s), 125.99 (t, J=25.3), 133.75 (s), 138.06 (s), 144.07 (s), 164.00 (s); MS (EI) m/z (rel. intensity) 239 (19), 183 (100), 166 (25), 137 (12). HRMS: Found 239.10112; Calcd. for $C_{11}H_{13}O_4N_2D$ 239.10163.

1.8.7. 4-Chloro-2-deuteronitrobenzene (5a). Mp 83–84°C, MeOH–H_2O (lit.[24] 83.6°C), ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.50–7.56 (m, 2H), 8.17–8.21 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 124.65 (t, J=25.9), 124.88 (s), 129.43 (s), 129.52 (s), 141.31 (s), 146.38 (s); MS (EI) m/z (rel. intensity) 160 (26), 158 (82), 130 (22), 128 (69), 114 (32), 112 (100), 102 (17), 100 (37), 76 (62).

1.8.8. 4-bromo-2-deuteronitrobenzene (5b). Mp 124–125°C, MeOH (lit.[24] 127°C), ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.67–7.74 (m, 2H), 8.08–8.13 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 124.71 (t, J=25.0), 124.95 (s), 129.92 (s), 132.47 (s), 132.56 (s), 146.92 (s); MS (EI) m/z (rel. intensity) 204 (99.7), 202 (100), 174 (54), 172 (55), 158 (76), 156 (77), 146 (29), 144 (30), 77 (88), 76 (82), 75 (42), 74 (160).

1.8.9. 4-tert-Butoxycarbonyl-2-deuteronitrobenzene (5d). Mp 113–114°C (lit.[22] 115–116°C), ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.63(s, 9H), 8,12–8.17 (m, 2H), 8.24–8.29 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.06 (s), 82.57 (s), 123.08 (t, J=26.0), 123.31 (s), 130.36 (s), 130.46 (s), 137.39 (s), 150.17 (s), 163.70 (s); MS (EI) m/z (rel. intensity) 224 (2.5), 209 (2.2), 169 (30, 151 (79), 105 (12), 77 (17), 57 (100).

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