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A Simple, Cost-Effective Method for the Regioselective Deuteration of Anilines

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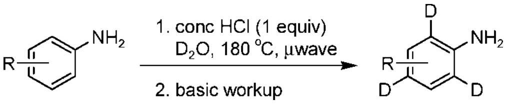
ABSTRACT



A highly effective and operationally simple method for the regioselective deuteration of anilines is presented. A variety of electron-rich and electron-deficient anilines are efficiently deuterated at the ortho and/or para position with respect to the nitrogen in the presence of 1 equiv of conc HCl in D_2O. Under the present conditions, aromatic methoxy groups do not facilitate deuteration, enabling a chemo- and regioselective deuteration of *p*-anisidine.

Isotopically labeled molecules are essential tools for the study of reaction mechanisms and metabolic pathways and as internal standards in analytical methods. The deuterium atom is the most common isotopic label and is the primary source for determining kinetic isotope effects in mechanistic studies. A wide variety of deuterated compounds are commercially available; however, they can be prohibitively expensive. Thus, synthetic chemists, most often in academic laboratories, must synthesize labeled compounds themselves.

There are numerous methods for the incorporation of deuterium into aromatic molecules,[1] and while many recent approaches employ the use of transition metals,[2] the complexes, ligands, or reagents employed may not be readily accessible or economically viable. Thus, a simple, cost-effective method for the deuteration of aromatic molecules is highly desirable. Herein we report a simple strategy for the synthesis of regioselectively deuterated anilines under microwave irradiation which uses HCl and D_2O.

While exploring the reaction mechanisms of palladium-catalyzed coupling reactions in our laboratories, we required an aryl iodide with a deuterium at the position ortho to the iodide. As anilines serve as convenient synthetic precursors to aryl iodides, we sought a method to make deuterated anilines. We came across a microwave-mediated method for the deuteration of 2-methylaniline[3] via formation of the anilinium hydrochloride salt, H−D exchange of the salt, and heating through several cycles in a domestic microwave. While our adaptation of this method to a commercial microwave worked exceedingly well for the substrate we tested,[4] we found that the procedure was tedious and time-consuming. We surmized that a simple alternative would be to simply heat an anilinium hydrochloride, formed in situ in acidic D_2O. As the deuteration is proposed to occur via electrophilic aromatic substitution upon deuteronium ions,[3] we postulated that the low concentration of hydronium ion with respect to deuteronium ion could enable nearly complete deuteration. Thus, we aimed to develop a general method for the deuteration of anilines.

Using 2-methyl-3-nitroaniline (**1a**) as our model substrate, we explored the use of both catalytic and stoichiometric amounts of a variety of Brønsted and Lewis acids in D_2O under microwave irradiation. While some catalytic Lewis

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(1) For an excellent review of modern methods of deuterium incorporation, see: Atzrodt, J.; Derdau, V.; Fey, T.; Zimmerman, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 7744–7765.

(2) Selected examples using (a) Ir: Golden, J. T.; Andersen, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2001**, *123*, 5837–5838. Garman, R. N.; Hickey, M. J.; Kingston, L. P.; McAuley, B.; Jones, J. R.; Lockley, W. J. S.; Mather, A. N.; Wilkinson, D. J. *J. Label Compd. Radiopharm* **2005**, *48*, 75–84. (b) Ru: Alexakis, E.; Hickey, M. J.; Jones, J. R.; Kingston, L. P.; Lockley, W. J. S.; Mather, A. N.; Smith, T.; Wilkinson, D. J. *Tetrahedron Lett.* **2005**, *46*, 4291–4293. (c) Pd: Derdau, V.; Atzrodt, J. *Synlett* **2006**, 1918–1922. Matsubara, S.; Yokota, Y.; Oshima, K. *Org. Lett.* **2004**, *6*, 2071–2073.

(3) Barthez, J. M.; Filikov, A. V.; Frederiksen, L. B.; Huguet, M.-L.; Jones, J. R.; Lu, S.-Y. *Can. J. Chem.* **1998**, *76*, 726–728.

(4) Martins, A.; Lautens M. Submitted for publication.

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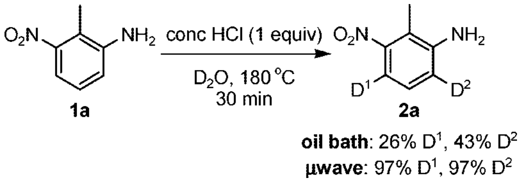
acids[5] gave considerable amounts of deuteration, we found that the best and most cost-effective results were obtained from using 1 equiv of HCl in D_2O, and heating to 180 °C under microwave irradiation for 30 min. We also found that microwave irradiation has a beneficial effect on the degree of deuteration, as conventional heating did not afford comparable results (Scheme 1).[6,7]

Scheme 1. Conventional Heating versus Microwave Irradiation



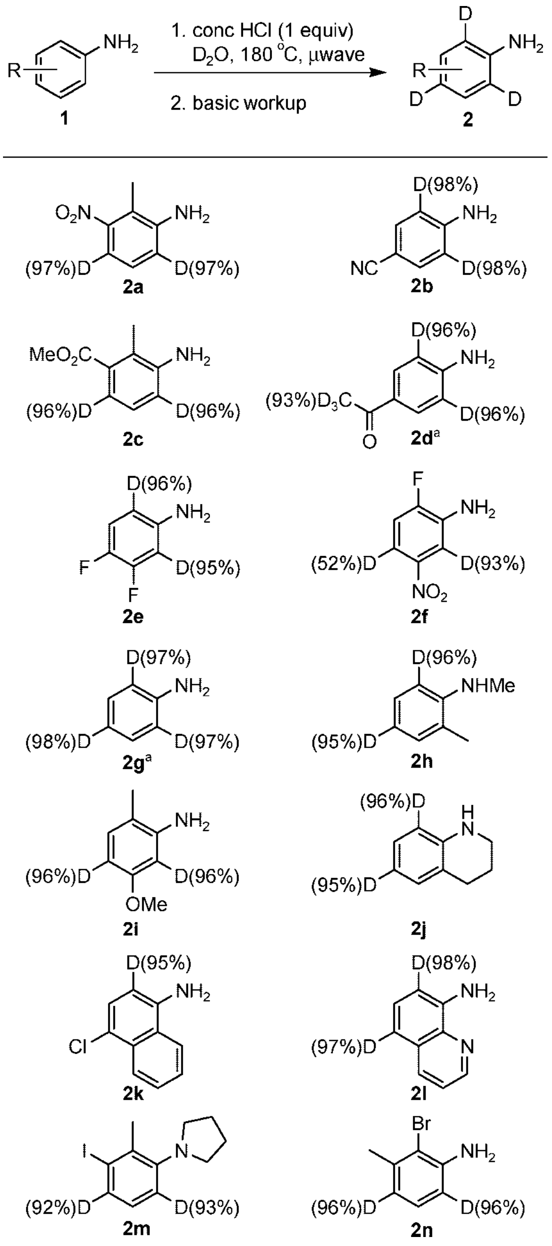
oil bath: 26% D^1, 43% D^2
µwave: 97% D^1, 97% D^2

Under the optimized reaction conditions, a variety of anilines were cleanly converted to the deuterated isotopologues with high levels of deuterium incorporation (Table 1). Electron-rich and electron-deficient anilines were efficiently deuterated, including **2d**, which was also deuterated at the α-position.[8] However, when the electron-withdrawing substitutent is ortho to the aniline nitrogen, the degree of deuterium incorporation is diminished para to the nitrogen (as in **2g**). The presence of several functional groups severely inhibit deuterium incorporation; for instance, phenols, even when containing an aniline nitrogen, undergo little to no deuteration,[9] while the presence of a pyridyl nitrogen led to little to no deuterium incorporation on the parent ring.[10]

An interesting result emerged when *p*-anisidine (**1o**) was subjected to the reaction conditions: while we expected that the additional electron donation of the methoxy group would enable complete deuteration of the aromatic ring, deuterium was only observed ortho to the aniline nitrogen (Scheme 2). Thus, under our reaction conditions, deuteration is regio- and chemoselective for the aromatic positions activated by aniline nitrogens.[11]

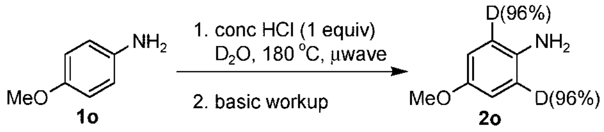
As previously mentioned, anilines serve as precursors to aryl iodides. To show the synthetic utility of deuterated anilines and to synthesize the required deuterated aryl iodide for our mechanistic studies, we were able to convert aniline **2a** to the corresponding aryl iodide **3** (Scheme 3). No erosion of deuterium content was observed under the reaction conditions.

Table 1. Deuteration of Anilines under Microwave Irradiation



[a] Run on 4 mmol scale.

Scheme 2. Chemoselective Deuteration of *p*-Anisidine



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(5) While $Cu(OTf)_2$, $Zn(OTf)_2$, and $La(OTf)_3$ fared quite poorly (∼15% D incorporation), 10 mol % of $Sc(OTf)_3$ under microwave irradiation (180 °C, 30 min) gave considerable amounts of deuterated product (40% D ortho, 58% D para).

(6) Oil bath temperature was 180 °C, internal temperature not monitored. Microwave temperature was internally monitored by the apparatus.

(7) Surber also reported the benefits of microwave irrradiation using concentrated DCl for the deuteration of 4-aminophenol. See: Vaidyanathan, S.; Surber, B. W. *Tetrahedron Lett.* **2005**, *46*, 5195–5197.

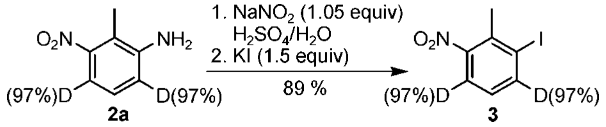
(8) Aside from α-deuteration, the levels of aromatic deuterium incorporation are much higher than the levels obtained by metal-catalyzed methods.

(9) 3-(*N*,*N*-Dimethyamino)phenol afforded <15% deuterium incorporation at the ortho and para positions.

(10) Following this trend, amidino or guanidino functional groups (such as 2-aminopyridines or 2-aminopyrimidines) showed little to no deuterium incorporation under the optimized conditions.

(11) To further test this hypothesis, basic aromatic compounds containing multiple methoxy groups such as veratrylamine, brucine, and quinine were tested and showed little to no deuterium incorporation.

Scheme 3



In summary, we have developed an efficient method for the synthesis of regioselectively deuterated anilines under microwave irradiation. The simple reaction conditions, high levels of deuterium incorporation, and low cost of the reagents make this a highly useful method for isotopic labeling which in the future could be extended to the incorporation of radioactive isotopes.[12]

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Supporting Information Available: Experimental procedures and characterization data for all new compounds are available free of charge via the Internet at http://pubs.acs.org.

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(12) For reviews of microwave-assisted radiochemistry, see: (a) Elander, N.; Jones, J. R.; Lu, S.-Y.; Stone-Elander, S. *Chem. Soc. Rev.* **2000**, 239–250. (b) Stone-Elander, S.; Elander, N. *J. Labelled Compd. Radiopharm.* **2002**, *45*, 715–746.