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A Simple and Cost-Effective Method for the Regioselective Deuteration of Phenols

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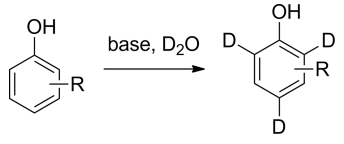
A highly effective and operationally simple method for the deuteration of phenols using NaOH as a catalyst and D_2O as the deuterium source is presented. A high regioselectivity for the *ortho* and/or *para* hydrogens relative to the oxygen atom was achieved, as well as a high degree of deuterium incorporation. The method also has a high functional-group tolerance, and allowed the deuteration of complex pharmaceutically interesting substrates.

Introduction

Deuterium-labelled compounds are essential tools for the study of reaction mechanisms and kinetics, analysis of drug metabolism, structural elucidation of biological macromolecules, and quantitative analysis of environmental pollutants and residual pesticides, and they may be used as functional materials and as internal standards in analytical methods.[1] Recently, deuterium-labelled drugs have attracted great interest within the pharmaceutical community, as the introduction of deuterium as a hydrogen bioisostere can significantly improve the pharmacokinetic properties (ADMET) of a great many drugs.[2] As such, deuterium incorporation has experienced a renaissance, partly as a result of this growing interest from the pharmaceutical industry.[2,3] Thus, the development of site-selective and post-synthetic deuterium-labelling methods is desired.

There are numerous methods for the preparation of deuterium-labelled aromatic molecules,[4] and they include pH-dependent[5a–5c] and transition-metal-mediated protocols.[5d–5h] A number of H–D exchange methods have been reported for the preparation of deuterium-labelled phenols. For example, the H–D exchange reactions catalysed by transition metals [Pt(C)/D_2O/H_2,[6a,6b] Pd(C)/Pt(C)/D_2O/H_2,[6c] Pt(C)/*i*PrOH,[6d] Ir[7] and Rh[8]], and microwave-enhanced metal-catalysed exchange reactions.[9] Also, a mixture of D_3PO_4, BF_3 and D_2O has been used for the deuteration of polyphenolic substrates such as flavonoids, isoflavonoids, and lignans at activated positions after several reaction cycles over a period of 1–4 d.[10] And recently, Pohjoispää et al. reported a method with capricious selectivity for the electrophilic deuteration of methylenedioxy-substituted aromatic compounds.[11] These methods often suffer from low efficiencies of deuterium exchange,[8] and they require expensive or difficult-to-access catalysts and deuterium sources.[7–9] Moreover, these published protocols often gave perdeuterated phenols without any selectivity, and they sometimes gave moderate to low degrees of deuteration. Therefore, a convenient, site-selective, and highly efficient labelling method is needed.

We surmised that phenols could be regioselectively deuterated through electrophilic aromatic substitution. As previously described, anilines were efficiently deuterated at the *ortho* and/or *para* positions relative to the nitrogen in the presence of concentrated HCl (1 equiv.) in D_2O.[5b] The aim of this investigation was to find an efficient similar method for the regioselective deuteration of phenols in basic D_2O (Scheme 1).



Scheme 1. Base-catalysed deuteration of substituted phenols.

Results and Discussion

Initially, NaOH (1 equiv.) was used as base together with D_2O (75 equiv.) as deuterium source for the deuteration of *o*-cresol. The reaction mixture was heated to 180 °C for 30 min under microwave irradiation, and the level of deuter-

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ium incorporation reached 96% at the *ortho* and *para* positions (Table 1, entry 1). When the reaction time was decreased to 15 min, this also led to a high deuterium content (Table 1, entry 2). However, decreasing the temperature led to a lower degree of deuteration (Table 1, entry 4). We were pleased to find that decreasing the amount of catalyst further to 50 mol-% resulted in a higher deuterium content (97%; Table 1, entry 5). Moreover, the use of 10 mol-% of NaOH still gave a high degree of deuterium incorporation (96.5%; Table 1, entry 6). As expected, increasing or lowering the amount of D_2O influenced the degree of deuteration (Table 1, entries 7 and 8). KO*t*Bu, another strong base, gave a deuterium incorporation of 96% (Table 1, entry 9). However, KOAc, a weak base, gave only a moderate level of deuterium labelling of *o*-cresol (Table 1, entry 10). Stoichiometric amounts of concentrated HCl, which was used for the deuteration of anilines under microwave irradiation at 180 °C,[5b] gave deuterium incorporation of 67–88% without selectivity (Table 1, entry 11). Neutral D_2O induces only partial deuteration of phenols even under near-critical conditions.[12] A comparable result was observed with conventional heating in an oil bath in a sealed tube (Table 1, entry 12). We tested the pH of the above reaction systems, and this indicated that basic conditions facilitate the H–D exchange reaction. Under basic conditions, the phenoxide ion might be generated, and this could result in a more regioselective transformation compared to the phenol.[13] We speculate that the phenols were deuterated in the phenoxide ion form. For reasons of convenience and cleanliness, the optimized conditions were taken to be: NaOH (50 mol-%) in D_2O (75 equiv.), heating to 180 °C under microwave irradiation for 15 min.

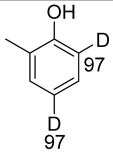
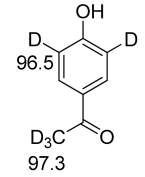
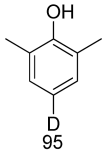
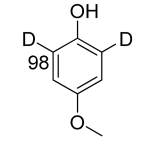
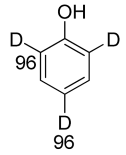
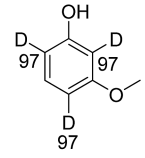
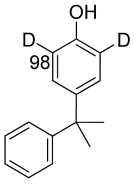
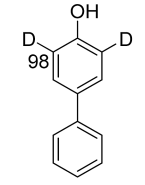
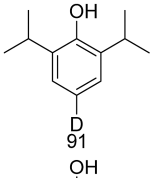
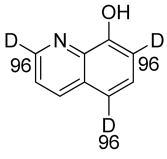
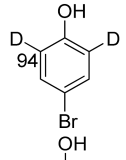
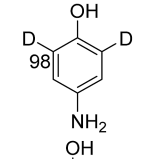
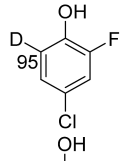
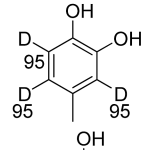
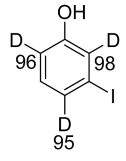
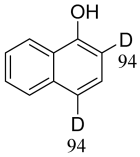
Table 1. Optimization of deuteration conditions on *o*-cresol.

Entry	Catalyst (mol-%)	pH	Time [min]	*T* [°C]	D content [%][a]
1	NaOH (100)	10.71	30	180	95
2	NaOH (100)	10.71	15	180	96
3	NaOH (100)	10.71	5	180	91
4	NaOH (100)	10.71	15	160	87
5	NaOH (50)	9.28	15	180	97
6	NaOH (10)	8.69	15	180	96.5
7	NaOH (50)	9.28	15	180	97.5[b]
8	NaOH (50)	9.28	15	180	94.5[c]
9	KO*t*Bu (50)	9.26	15	180	96
10	KOAc (50)	6.45	15	180	55[d]
11	HCl (100)	0.60	30	180	67–88[e]
12	NaOH (50)	9.28	15	180	96[f]

[a] Unless otherwise stated, reactions were conducted with *o*-cresol (2 mmol) in D_2O (3 mL) heated under microwave irradiation. The deuterium content was calculated on the basis of ^1H NMR spectroscopy. [b] 150 equiv. of D_2O. [c] 37.5 equiv. of D_2O. [d] Average deuterium content of the *ortho* and *para* positions. [e] *O*-cresol was labelled without selectivity. [f] Oil bath.

A variety of substituted phenols were subjected to the optimized conditions to evaluate the scope of the reaction (Table 2). Spectroscopically pure labelled phenols could easily be isolated by acidification and simple extraction, and no further purification was required. Traditional methods gave perdeuterated phenol without selectivity.[6–9] In contrast, this method allows the deuteration of phenol with high regioselectivity at the *ortho* and *para* positions (Table 2, entry 3). Electron-rich and electron-deficient phenols were efficiently deuterated, including 4′-hydroxyacetophenone (Table 2, entry 9), which was also deuterated at the α-position, and even sterically hindered substituents were tolerated (Table 2, entry 5). Various halogen-substituted phenols were successfully labelled. Due to the double-

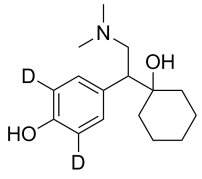
Table 2. Deuteration of phenols under microwave irradiation.[a]

Entry	D content [%]	Yield [%][b]	Entry	D content [%]	Yield [%][b]
1		94	9		89
2		91	10		90
3		89	11		90
4		97	12		94
5[c]		93	13[c]		87
6		93	14[c]		87
7		89	15		88
8		91	16		91

[a] Unless otherwise stated, reactions were carried out with the substrate (2 mmol) and NaOH (0.5 equiv.) in D_2O (3 mL) at 180 °C for 15 min under microwave irradiation. The deuterium content was calculated on the basis of ^1H NMR spectroscopy. [b] Isolated yield. [c] 1 equiv. of NaOH, 30 min.

directing effects of 3-iodophenol, the 2-position was labelled preferentially. It has previously been reported that substituted anisoles were labelled under microwave-mediated conditions.[5a,5e] In contrast, an attempt to deuterate the anisole under the optimized conditions was unsuccessful, which indicates that the OH group is essential for the regioselectivity. As noted above, when methoxy-substituted phenols were subjected to the reaction conditions, deuterium was only observed *ortho* and/or *para* to the phenol oxygen (Table 2, entries 10 and 11). Interestingly, not only the 5- and 7-positions, but also the 2-position of 8-hydroxyquinoline was labelled, which might be due to the acidity of the 2-position (Table 2, entry 13). It has been reported that perdeuterated 4-aminophenol was obtained in the presence of concentrated HCl (1 equiv.) in D_2O under microwave irradiation at 180 °C.[5a] Surprisingly, by our method, this compound incorporated deuterium only at the positions *ortho* to the phenolic hydroxyl group (Table 2, entry 14). Moreover, the method also allowed the deuteration of 4-methylcatechol, which indicates that this protocol could be used for the deuteration of substrates containing multiple phenolic hydroxyl groups (Table 2, entry 15). Substrates with carboxy or nitro groups underwent little to no deuteration. Base-sensitive compounds containing amide, ester, or cyano groups decomposed under the reaction conditions.

To further evaluate the substrate scope of our new catalytic deuteration procedure, the FDA-approved drug desvenlafaxine, featuring a phenolic hydroxyl moiety, was chosen as a benchmark compound. Desvenlafaxine is used for the treatment of adult patients with major depressive disorder.[14] As expected, a deuterium incorporation of 98% was achieved with a yield of 93% using NaOH (0.5 equiv.) in D_2O (150 equiv.), and heating to 180 °C under microwave irradiation for 30 min (Scheme 2).



Scheme 2. Deuteration of Desvenlafaxine using the NaOH/D_2O system under microwave irradiation.

Conclusions

An efficient method for the synthesis of regioselectively deuterated phenols under microwave irradiation has been developed. The ease of operation of the reaction, the high levels of deuterium incorporation, and the low cost of the reagents make this a very valuable method for isotopic labelling. We envisage that this method could also be extended to the tritium labelling of pharmaceutically interesting compounds for medicinal applications.

Experimental Section

Representative Procedure for Deuteration Reactions: In a microwave reaction vial with a magnetic stirrer bar, *o*-cresol (1 equiv., 2 mmol) was added, followed by NaOH (0.5 equiv., 40 mg) and D_2O (75 equiv., 3 mL). The vial was sealed and heated in the microwave synthesis apparatus for 15 min at 180 °C. Then the mixture was cooled to room temperature, HCl (0.1 M aq.; 10 mL) was added, and the mixture was extracted with ethyl acetate (2 × 10 mL). The organic layer was washed with brine (5 mL), dried with anhydrous Na_2SO_4, and filtered. The filtrate was concentrated to give [D_2]*o*-cresol. The total incorporation yield was determined by ^{1}H NMR spectroscopy relative to the intensity of a nonexchangeable proton in the molecule, and was confirmed by ^{2}H NMR spectroscopy.

[^{2}H]*o*-Cresol (Table 1, entry 1): Brown liquid (94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12 (s, 1 H), 7.07 (s, 1 H), 6.84 (t, J = 7.4 Hz, 0.03 H), 6.76 (d, J = 8.0 Hz, 0.03 H), 4.79 (br. s, 1 H), 2.25 (s, 3 H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 6.91 (s), 6.83 (s) ppm.

[^{2}H]2,6-Dimethylphenol (Table 1, entry 2): Pale brown solid (91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97 (s, 2 H), 6.78–6.73 (m, 0.05 H), 4.61 (br. s, 1 H), 2.25 (s, 6 H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 6.86 (s) ppm.

[^{2}H]Phenol (Table 1, entry 3): Pale brown liquid (89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (s, 2 H), 6.92 (t, J = 7.4 Hz, 0.04 H), 6.83 (d, J = 8.5 Hz, 0.08 H), 5.42 (br. s, 1 H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 7.00 (s), 6.91 (s) ppm.

[^{2}H]4-Cumylphenol (Table 1, entry 4): White solid (97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.19 (m, 4 H), 7.16 (t, J = 6.7 Hz, 1 H), 7.09 (s, 2 H), 6.72 (d, J = 9.2 Hz, 0.04 H), 1.65 (s, 6 H) ppm. ^{2}H NMR (61.4 MHz, DMSO): δ = 6.74 (s) ppm.

[^{2}H]2,6-Diisopropylphenol (Table 1, entry 5): Pale yellow liquid (93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06 (s, 2 H), 6.90 (t, J = 7.6 Hz, 0.09 H), 4.79 (s, 1 H), 3.16 (dt, J = 13.7, 6.9 Hz, 2 H), 1.27 (d, J = 6.9 Hz, 12 H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 7.04 (s) ppm.

[^{2}H]4-Bromophenol (Table 1, entry 6): Pale brown solid (93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (s, 2 H), 6.72 (d, J = 9.2 Hz, 0.12 H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 6.79 (s) ppm.

[^{2}H]4-Chloro-2-fluorophenol (Table 1, entry 7): Pale brown liquid (89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09 (dd, J = 10.3, 2.4 Hz, 1 H), 7.00 (s, 1 H), 6.92 (t, J = 8.9 Hz, 0.05 H), 4.84 (br. s, 1 H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 6.94 (s) ppm.

[^{2}H]3-Iodophenol (Table 1, entry 8): Pale brown solid (91%). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 9.76 (br. s, 1 H), 7.16–7.14 (m, 0.05 H), 7.12 (s, 0.02 H), 6.97 (s, 1 H), 6.80–6.75 (m, 0.04 H) ppm. ^{2}H NMR (61.4 MHz, DMSO): δ = 7.11 (s), 6.73 (s) ppm.

[^{2}H]4′-Hydroxyacetophenone (Table 1, entry 9): Pale brown solid (89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (br. s, 1 H), 7.91 (s, 2 H), 6.96 (d, J = 9.2 Hz, 0.07 H), 2.56 (s, 0.08 H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 7.02 (s), 2.58 (s) ppm.

[^{2}H]4-Methoxyphenol (Table 1, entry 10): Off-white solid (90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.79 (s, 2 H), 4.98 (br. s, 1 H), 3.76 (s, 3 H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 6.84 (s) ppm.

[^{2}H]3-Methoxyphenol (Table 1, entry 11): Pale brown liquid (90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (s, 1 H), 6.50 (d, J = 8.3 Hz, 0.03 H), 6.44–6.42 (m, 0.06 H), 5.19 (br. s, 1 H), 3.78 (s, 3 H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 6.50–6.57 (m) ppm.

[^{2}H]4-Phenylphenol (Table 1, entry 12): White solid (94%). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 9.55 (br. s, 1 H), 7.57 (d, J =

7.5 Hz, 2 H), 7.49 (s, 2 H), 7.41 (t, J = 7.7 Hz, 2 H), 7.27 (t, J = 7.3 Hz, 1 H), 6.86 (d, J = 9.1 Hz, 0.04 H) ppm. ^{2}H NMR (61.4 MHz, DMSO): δ = 6.93 (s) ppm.

[^{2}H]8-Hydroxyquinoline (Table 1, entry 13): Pale brown solid (87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.78 (d, J = 3.2 Hz, 0.04 H), 8.16 (d, J = 8.3 Hz, 1 H), 7.49–7.38 (m, 2 H), 7.33 (d, J = 8.3 Hz, 0.04 H), 7.18 (d, J = 7.7 Hz, 0.04 H) ppm. ^{2}H NMR (61.4 MHz, DMSO): δ = 8.85 (s), 7.41 (s), 7.12 (s) ppm.

[^{2}H]4-Aminophenol (Table 1, entry 14): Pale brown solid (87%). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 8.34 (br. s, 1 H), 6.48 (d, J = 4.8 Hz, 0.04 H), 6.42 (s, 2 H), 4.36 (br. s, 2 H) ppm. ^{2}H NMR (61.4 MHz, DMSO): δ = 6.50 (s) ppm.

[^{2}H]4-Methylcatechol (Table 1, entry 15): Pale yellow powder (88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.75 (s, 0.05 H), 6.69 (s, 0.05 H), 6.60 (s, 0.05 H), 5.13 (br. s, 2 H), 2.24 (s, 3 H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 6.80–6.65 (m) ppm.

[^{2}H]1-Naphthol (Table 1, entry 16): Pale brown solid (91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22–8.13 (m, 1 H), 7.85–7.77 (m, 1 H), 7.53–7.45 (m, 2 H), 7.44 (d, J = 8.5 Hz, 0.06 H), 7.31 (s, 1 H), 6.82 (d, J = 7.4 Hz, 0.06 H), 5.37 (s, 1 H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 7.52 (s), 6.89 (s) ppm.

[^{2}H]Desvenlafaxine (Scheme 2): Off-white solid (91%). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 6.96 (s, 2 H), 6.63 (d, J = 8.9 Hz, 0.04 H), 2.99 (dd, J = 12.2, 8.9 Hz, 1 H), 2.73–2.69 (m, 1 H), 2.33 (dd, J = 12.4, 6.2 Hz, 1 H), 2.13 (s, 6 H), 1.56–0.99 (m, 10 H) ppm.

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