INTRODUCTION

Isotopic labelling is a technique, which has been widely used in chemistry and biochemistry to help understand chemical reactions and interactions, as well as stable isotopes in pharmacokinetic studies as biological internal standards. Usually, D₂O is the cheapest deuterium source, so far several methods have been developed for the synthesis deuterium-labelling compounds through H/D exchange with D₂O, deuterium gas and deuterium solvents. The common pathways are pH-dependent H/D exchange and metal catalyzed H/D exchange. Most of these methods have some disadvantages, such as time consuming, lower efficacy, very high reaction temperature, and expensive deuterium source, as well as precious metal was used as catalyst in most of these cases. Other methods for achieving deuterium-labelling compound through including decarboxylative deuteration, I/D exchange. It is well-known that deuterium-labelling anilines are a type of important intermediate due to its good reactivity, and a few of methods for synthesizing deuterium-labelling anilines have been reported. In 2008, Mutsumi et al. reported a tributyltin hydride promoted I/D exchange reaction for deuteration on pyrimidine and purine nuclei with THF-d₈ as deuterium source. After that, Lautens et al. developed a palladium mediated coupling-reductive method for obtaining meta-substituted biaryls. In both above mentioned method for deuterating aromatic compounds are highly expected. On the other hand, high-speed microwave synthesis has attracted a considerable amount of attention in the last two decades. Compared with conventional heating, microwave irradiation displayed a number of advantages, not only in heating effect, but also good selectivity and higher yield in many microwave promoted reactions. Herein, we would report a microwave promoted I/D exchange method for getting deuterated aniline with D₂O as an inexpensive deuterium source.

EXPERIMENTAL

General information

Unless otherwise noted, commercial reagents were used as received. ²H (400 MHz) and ¹³C (100 MHz) NMR chemical shifts were reported in CDCl₃ 7.27 ppm for ¹H, 77 ppm for ¹³C as standards and coupling constants(J) are reported in hertz (Hz). The following abbreviations are used to designate signal multiplicity: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad.
General procedure

In a 25 ml of seal tube, aniline (2 mmol), D₂O (3 ml) and SOCl₂ (0.2 ml) was added successively. Then this tube was irradiated under microwave at 130°C for 30 min. After cooled to room temp., the reaction was diluted with water, and neutralized with NaHCO₃, extracted with diethyl ether (50 mL × 3), the combined organic layer was washed with brine, and dried with anhydrous Na₂SO₄. Removal of all volatiles by vacuum evaporation left a residue, which was purified by flash chromatography to afford product.

2-deuterium-4,6-dimethylaniline (2a). Colorless oil; ¹H NMR (400 MHz, CDCl₃): δ 6.86 (s, 1H), 6.83 (s, 1H), 3.44 (br s, 2H), 2.22 (s, 3H) and 2.13 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 142.66, 128.23, 121.86, 117.92 (1:1:1 t, J=24.5 Hz), 17.69; HRMS (EI) calcd. for C₁₃H₂₀DN [M⁺] 226.1265, found 226.1264; IR (KBr): cm⁻¹: 2926, 2848, 1730, 1507, 1465, 1269, 1080.

4-deuterium-2,6-dimethylaniline (2b). Colorless oil; ¹H NMR (400 MHz, CDCl₃): δ 7.54-7.52 (m, 2H), 7.40-7.36 (m, 2H), 7.31-7.22 (m, 3H), 3.63 (br s, 2H) and 2.22 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 144.07, 141.39, 131.70, 129.26, 128.66, 126.50, 126.20, 125.59, 122.59, 115.00 (1:1:1 t, J=23.5 Hz), 17.55; HRMS (EI) calcd. for C₁₃H₂₀DN [M⁺] 184.1111, found 184.1110; IR (KBr): cm⁻¹: 3330, 3322, 3000, 2941, 2920, 2830, 1480, 1300, 1267, 1081, 1030, 897, 770, 699.

2-deuterium-4-phenyl-6-methylaniline (2c). Colorless oil; ¹H NMR (400 MHz, CDCl₃): δ 7.45-7.40 (m, 4H), 7.34-7.30 (m, 1H), 6.96-6.95 (m, 2H), 6.86-6.85 (m, 2H), 6.83-6.79 (m, 2H), 3.92 (br s, 2H) and 2.22 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 141.52, 132.74, 129.09, 128.92, 115.54 (1:1:1 t, J=24.5 Hz), 109.34, 20.99; HRMS (EI) calcd. for C₁₉H₁₄BrDN [M⁺] 185.9903, found 185.9904; IR (KBr): cm⁻¹: 2926, 2848, 1730, 1507, 1465, 1269, 1080.

2-deuterium-4-bromo-4-methyl-6-phenylaniline (2d). Yellow oil; ¹H NMR (400 MHz, CDCl₃): δ 7.23 (s, 1H), 6.90 (s, 1H), 3.92 (br s, 2H) and 2.22 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 140.94, 139.73, 131.00, 129.12, 128.95, 128.78, 127.88, 127.78, 127.11, 115.56 (1:1:1 t, J=23.5 Hz), 20.45; HRMS (EI) calcd. for C₁₉H₁₃BrDN [M⁺] 184.1111, found 184.1110; IR (KBr): cm⁻¹: 3452, 3350, 2922, 1623, 14389, 1265, 872, 779, 742, 698, 587.

2,6-dideuterium-4-methylaniline (2f). Yellow oil; ¹H NMR (400 MHz, CDCl₃): δ 7.23 (s, 1H), 6.90 (s, 1H), 3.92 (br s, 2H) and 2.22 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 7.60-7.55 (m, 2H), 7.54-7.45 (m, 2H), 7.23-7.15 (m, 4H), 6.90-6.85 (m, 2H), 6.83-6.79 (m, 2H), 5.95-5.90 (m, 1H), 4.38-4.33 (m, 1H), 3.44 (br s, 2H), 2.24 (s, 3H); ¹⁹F NMR (400 MHz, CDCl₃): δ -155.97; HRMS (EI) calcd. for C₁₂H₁₂D₄N [M⁺] 190.0861, found 190.0866; IR (KBr): cm⁻¹: 3290, 2970, 2930, 2870, 1734, 1678, 1600, 1477, 1274, 1203, 1090, 985, 905, 775, 502.

1-(4-amino-3,5-dideuterophenyl)-2,2,2-trideuterethane (2h). Yellow oil; ¹H NMR (400 MHz, CDCl₃): δ 7.79 (s, 2H) and 4.33 (br s, 2H).

RESULTS AND DISCUSSION

Our work was initiated by using 2-iodo-4, 6-dimethylaniline 1a as substrate, which was refluxed in CD₃OD in the presence of thionyl chloride for 12 h, 2-deuterium-4,6-dimethyl -aniline was obtained at 20% yield (Table 1). When CD₃OD was replaced with cheaper D₂O, and the reaction was refluxed for 12 h, I/D exchanged product was obtained in 24% yield (Table 1). Further prolonging the reaction time could not increase the yield (Table 1). Next, the microwave irradiation was applied to promote this reaction, to our great delight, when 4-iodo-2,6-dimethylaniline was heated in a sealed tube by microwave irradiation with D₂O in combination with SOCl₂ at 100°C for 30 min. I/D exchanged product was obtained in 56% yield (Table 1). When the reaction time was prolonged to 30 min., 84% yield was obtained (Table 1).

### Table 1. Optimization of the reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Reaction condition</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CD₃OD/SOCl₂</td>
<td>reflux, 12 h</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>D₂O/SOCl₂</td>
<td>reflux, 12 h</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>D₂O/SOCl₂</td>
<td>reflux, 24 h</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>D₂O/SOCl₂</td>
<td>MW(100°C, 15 min)</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td>D₂O/SOCl₂</td>
<td>MW(100°C, 30 min)</td>
<td>84</td>
</tr>
</tbody>
</table>

*The reaction was carried out using 2-iodo-4,6-dimethylaniline (1 mmol), SOCl₂ (0.2 ml), CD₃OD or D₂O (2 ml). *Isolated yield.
With this optimized reaction condition, other iodine substituted anilines were also extended. Most of these iodine substituted anilines could be transferred to corresponding I/D exchanged products with moderate to good yield (Table 2). The Br/D exchange could be observed, since I/D exchanged product and double deuterium product were obtained (Table 2) led to lower yield of 2e. As shown in Table 2, I–D exchange reaction of all reactants to achieve a high D content.

![Scheme 1. The possible mechanism of I/D exchange.](image)

Table 2. I/D exchange on aniline using D₂O as a deuterium source.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Product</th>
<th>D content (%)</th>
<th>Yield (%)²</th>
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<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>Me</td>
<td>Me</td>
<td>I</td>
<td>2a</td>
<td>99</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>Me</td>
<td>I</td>
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<td>2b</td>
<td>98</td>
<td>80</td>
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<tr>
<td>3</td>
<td>1c</td>
<td>Me</td>
<td>Ph</td>
<td>I</td>
<td>2c</td>
<td>98</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>Ph</td>
<td>Me</td>
<td>I</td>
<td>2d</td>
<td>98</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>Br</td>
<td>Me</td>
<td>I</td>
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<td>97</td>
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<td>1g</td>
<td>H</td>
<td>H</td>
<td>I</td>
<td>2g</td>
<td>98</td>
<td>67</td>
</tr>
<tr>
<td>10</td>
<td>1h</td>
<td>H</td>
<td>Ac</td>
<td>I</td>
<td>2h</td>
<td>98</td>
<td>80</td>
</tr>
</tbody>
</table>

* Determined by ¹H NMR spectroscopy in CDCl₃
* Isolated yield

The possible mechanism can be proposed as Scheme 1. First, thionyl chloride reacted with D₂O to produce DCl in situ, which act as an electrophile. The amino group in aniline is strongly activating and ortho/para-directing group, when the electrophile DCl attacks the ortho positions of aniline, the nitrogen atom can donate electron density to the π system to form an iminium ion, then chloro ion attacks iodine to form ICl.

CONCLUSION

In conclusion, a microwave promoted I/D exchange deuteration of anilines method was developed. Under microwave condition, several iodo anilines could be rapidly and efficiently deuterated in a short time with D₂O as a deuterium source.

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REFERENCES


