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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 5195–5197

Microwave mediated hydrogen deuterium exchange: a rapid synthesis of ^{2}H-substituted benzimidazole

Srirajan Vaidyanathan and Bruce W. Surber*

Abbott Laboratories, Dept. R46V, AP9, 100 Abbott Park Road, IL 60064, USA

Received 20 April 2005; revised 24 May 2005; accepted 25 May 2005
Available online 15 June 2005

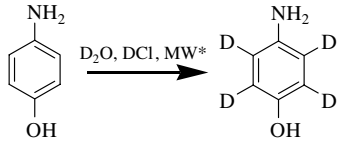
Abstract—Deuterium aromatic substituted compounds were prepared by microwave irradiation of the parent unlabeled compounds in the presence of deuterium oxide and deuterium chloride. The percentage of deuterium incorporation was investigated under various reaction conditions. A rapid synthesis of ^{2}H-substituted benzimidazole under microwave irradiation is described.

Deuterium labeled drug entities are widely used as internal standards in Mass Spectrometry in the pharmaceutical industry.[1] Synthesis of these drug entities requires an appropriate deuterium labeled starting material. Though there are many commercially available deuterium labeled starting materials known, synthetic chemists often face many constraints because of the limitation of availability of the labeled reagents as well as the number of mass units that must be added. So there is a great need to devise new methodologies for deuterium labeling. In the literature, there are very few reports for deuterium labeling and very often the reaction conditions are extreme, time consuming, and low yielding.[2]

In recent years, microwave technology received wide attention in organic chemistry because of the versatility, speed, and cleaner reaction products.[3] Varma and co-workers have reported the use of microwaves in solvent-free reactions.[4] The use of microwave for deuterium labeling in heterocyclic and carbohydrate chemistry was reported.[5] In our ongoing research in CNS (erectile dysfunction, ED), we faced the challenge of preparing a higher mass ED isotopomer by deuterium incorporation. This prompted an exploration of new synthetic methodologies for deuterium incorporation with an emphasis in microwave mediation. Herein, we wish to report the synthesis of deuterium labeled aromatic compounds using microwave irradiation and simple reaction conditions and its application to the preparation of the ED analogue, ^{2}H-ABT-724.

Readily available *p*-aminophenol was used as model compound for our study. This was dissolved in 35% deuterium chloride in deuterium oxide[6] and the reaction mixture was irradiated in a CEM microwave oven at 9 W and 100 °C for 30 min (Scheme 1). This resulted in deuterium incorporation of varying percentage between M+1 and M+4 with 25% unreacted starting material. Encouraged by this result, we carried out systematic correlation studies and optimal conditions were found to be 175 °C at 140 W for 20 min. Under these reaction conditions, we obtained 84% of M+4 and 16% of M+3 and there was no unreacted starting material[7] (Table 1). The deuterium incorporation on the aromatic ring was proved by ^{1}H NMR spectroscopy. MS analysis of the crude sample **1** treated with water to remove labile deuterium showed a mass peak at *m/e* 114, which corresponds to the M+4 product with four deuteriums on the aromatic ring.

As a comparative case study between the conventional heating and microwave irradiation, *p*-amino phenol was dissolved in 35 wt % deuterium chloride in



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Scheme 1.

Keywords: Microwave; Deuterium.
* Corresponding author. Tel.: +1 8479373880; fax: +1 8479382336; e-mail: bruce.surber@abbott.com

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doi:10.1016/j.tetlet.2005.05.110

Table 1. Optimization of the conditions for deuteration of *p*-aminophenol

Experiment	Temp (°C)	MW (W)	Time (min)	Mass spectroscopy results
1	100	9	30	M+1 (46%), M+2 (29%), M+3 and M+4 traces and starting material (25%)
2	150	50	5	M+1 (7%), M+2 (34%), M+3 (41%) and M+4 (18%)
3	150	50	15	M+1 (12%), M+2 (10%), M+3 (35%) and M+4 (42%)
4	175	140	15	M+1 (6%), M+2 (13%), M+3 (27%) and M+4 (53%)
5	175	140	20	M+3 (16%) and M+4 (84%)
6	175	140	60	M+3 (24%), M+4 (76%) and considerable decomposition

deuterium oxide and heated in an oil bath at 175 °C for 24 h. MS analysis showed 6% of M+4 and 28% of M+3 with major M+2 as 59%. MS analysis of the sample after 72 h at 175 °C showed 51% of M+4 and 35% of M+3. Thus, microwave irradiation provides a higher order of deuterium incorporation in higher percentage in shorter time.

The methodology was tested with different aromatic compounds (Table 2). When *p*-bromoaniline was irradiated at medium power for 40 min, we observed M+2 increase in mass and the deuterium incorporation was assigned based on GC/MS, presumably on both positions[8] ortho to the amino group. MS analysis also showed traces of the singly deuterated isotopomer. Irradiating the reaction mixture for longer period of time did not improve the incorporation of deuterium in the molecule. Interestingly, we found the same phenomenon for *p*-bromoanisole, in which the hydrogens were exchanged with deuterium ortho to methoxy and this was confirmed by GC/MS and NMR analysis.[8]

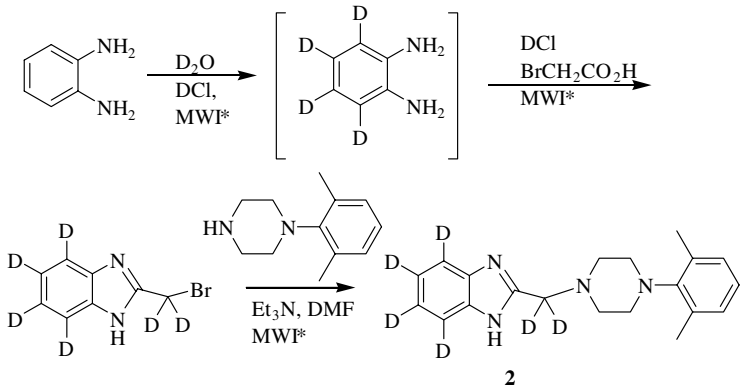
In the case of aniline, we observed M+3 as the major product and the deuterium incorporation was found to be at both ortho and para positions. On cooling the reaction mixture, the product precipitated out and was filtered. When *N*-methyl aniline was used as substrate, the reaction was carried out for 2 h to give 100% incorporation of M+3. The deuterium incorporation was assigned at ortho and para positions based on ^{1}H NMR and GC–MS. This methodology was successfully extended to the synthesis of deuterium labeled 2-[4-(2,6-dimethylphenyl)piperazin-1-yl-methyl]1*H*-benzimidazole **2**, a potent dopamine agonist for erectile dysfunction. The compound **2** was purified by flash chromatography using ethyl acetate/hexane as 1:1 eluant and characterized by NMR and MS spectroscopy.[9,10] Deuterated *o*-phenylenediamine was irradiated with bromoacetic acid in the presence of DCl for 60 min. MS analysis showed a mixture of M+3 (9%), M+4 (18%), M+5 (40%), M+6 (17%), and M+7 (16%). The crude reaction mixture was neutralized with potassium carbonate and extracted with ethyl acetate. The crude product, on microwave irradiation in the presence of triethylamine and 2,6-dimethylphenyl piperazine in DMF for 35 min, provided **2** (Scheme 2) as a mixture of M+3 (2%), M+4 (16%), M+5 (36%), M+6 (38%), and M+7 (8%) in 30% yield with no M+0.[8]

Table 2. Scope of acid-catalyzed, mircowave-mediated aromatic hydrogen/deuterium exchange

Substrate	Minutes	Number and percentage of deuterium
4-Bromoaniline	80	M+2 (100%)
Aniline	80	M+3 (80%) and M+2 (20%)
4-Bromoanisole	80	M+2 (100%)
N-Methyl aniline	160	M+2 (29%) and M+3 (71%)
o-Phenylenediamine	20	M+4 (78%) and M+2 (22%)

When attempts were made to extend this methodology to other aromatic compounds such as phenol and resorcinol, there was no deuterium incorporation observed, apparently because of the low miscibility of the substrate with aqueous medium. Addition of few drops of DMSO-d_6 to these reactions did not provide any appreciable improvement.

In summary, we have discovered an efficient labeling methodology for deuteration of water-miscible electron-rich aromatic compounds by the use of microwave irradiation. This methodology was extended to the



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Scheme 2.

stable label synthesis of ABT-724, a potent dopamine agonist for erectile dysfunction.

Acknowledgments

We thank Jeff Wang for mass and David Whittern for NMR spectral data. We also thank Dr. Stanley A. Roberts for his encouragement.

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6. Commercially available from Aldrich.
7. Preparation of [$^2H_4$]-*p*-aminophenol: *p*-aminophenol (1 mmol) was dissolved in 35% DCl in D_2O (1 mL) and irradiated in a CEM robot microwave oven at 175 °C for 20 min at medium power (140 W). The precipitate obtained by cooling the reaction mixture was filtered and dried to afford **1** in quantitative yield.
8. The regioselective deuterium incorporation was assigned based on ^1H NMR and GC/MS.
9. Mp 204–205 °C, lit.[10] 203–205 °C. ^1H NMR ($CDCl_3$, 300 MHz): 2.38 (s, 6H); 2.74 (m, 4H); 3.21 (m, 4H); 7 (m, 3H); 9.9 (br s, 1H). MS (ESI): 327 $(MH)^+$.
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