e-ISSN:2319-9849
p-ISSN:2322-00

Research & Reviews: Journal of Chemistry

Microwave Promoted Metal Free Deuteration of Anilines by I/D Exchange with D_2O as a Deuterium Source

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Research Article

Received date: 24/06/2016
Accepted date: 01/07/2016
Published date: 06/07/2016

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Keywords: Deuteration of anilines, I/D exchange, D_2O.

ABSTRACT

A microwave promoted I/D exchange deuteration of anilines method was developed. Under microwave condition, this exchange could be completed in a short time with D_2O as a deuterium source. Furthermore, only thionyl chloride was used as additive.

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, D_2O is the cheapest deuterium source, so far [1] several methods have been developed for the synthesis deuterium-labelling compounds through H/D exchange with D_2O, deuterium gas and deuterium solvents. The common pathways are pH-dependent H/D exchange [2-6] and metal catalyzed H/D exchange [7-13]. 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. [14] reported a tributyltin hydride promoted I/D exchange reaction for deuteration on pyrimidine and purine nuclei with THF-d_8 as deuterium source. After that, Lautens et al. [15] 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 [16,17]. Herein, we would report a microwave promoted I/D exchange method for getting deuterated aniline with D_2O as an inexpensive deuterium source.

EXPERIMENTAL

General information

Unless otherwise noted, commercial reagents were used as received. ^1H (400 MHz) and ^{13}C (100 MHz) NMR chemical shifts were reported in $CDCl_3$ 7.27 ppm for ^1H, 77 ppm for ^{13}C 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), D_2O (3 ml) and $SOCl_2$ (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 $NaHCO_3$, extracted with diethyl ether (50 mL × 3), the combined organic layer was washed with brine, and dried with anhydrous Na_2SO_4. 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; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.86 (s, 1H), 6.83 (s, 1H), 3.44 (br s, 2H), 2.22 (s, 3H) and 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.98, 131.15, 127.87, 127.27, 122.50, 114.93 (1:1:1 t, *J*=23.5 Hz), 20.45, 17.33; HRMS (EI) calcd. for $C_8H_{10}DN$ [M$^+$] 122.0954, found 122.0955; IR (KBr): cm^{-1}: 3266, 2920, 2866, 1687, 1635, 1510, 1482, 1300, 880.

4-deuterium-2,6-dimethylaniline (2b). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.94 (s, 2H), 3.57 (br s, 2H) and 2.81 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.66, 128.23, 121,86, 117.92 (1:1:1 t, *J*=24.5 Hz), 17.69; HRMS (EI) calcd. for $C_8H_{10}DN$ [M$^+$] 122.0954, found 122.0956; IR (KBr): cm^{-1}: 3260, 2960, 2850, 1730, 1620, 1545, 1260, 1080, 1025, 970, 803, 662.

2-deuterium-4-phenyl-6-methylaniline (2c). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{13}H_{12}DN$ [M$^+$] 184.1111, found 184.1115; IR (KBr): cm^{-1}: 3330, 3322, 3000, 2941, 2920, 2830, 1620, 1480, 1300, 1267, 1081, 1030, 897, 770, 699.

2-deuterium-4-methyl-6-phenylaniline (2d). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.40 (m, 4H), 7.34-7.30 (m, 1H), 6.96-6.95 (m, 2H), 3.55 (br s, 2H) and 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 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*=24 Hz), 20.45; HRMS (EI) calcd. for $C_{13}H_{12}DN$ [M$^+$] 184.1111, found 184.1117; IR (KBr): cm^{-1}: 3452, 3350, 2922, 1623, 14389, 1265, 872, 779, 742, 698, 587.

2-deuterium-6-bromo-4-methylaniline (2e) Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (s, 1H), 6.90 (s, 1H), 3.92 (br s, 2H) and 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.52, 132.74, 129.09, 128.92, 115.54 (1:1:1 t, *J*=24.5Hz), 109.34, 20.09; HRMS (EI) calcd. for C_7H_7BrDN [M$^+$] 185.9903, found 185.9904; IR (KBr): cm^{-1}: 2926, 2848, 1730, 1507, 1465, 1269, 1080.

2,6-dideuterium-4-methylaniline (2f) Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 (s, 2H), 3.51 (br s, 2H) and 2.24 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.72, 129.66, 127.79, 115.01 (1:1:1 t, *J*=23.5 Hz), 20.47; HRMS (EI) calcd. for $C_7H_7D_2N$ [M$^+$] 109.0861, found 109.0866; IR (KBr): cm^{-1}: 3290, 2970, 2930, 2870, 1734, 1678, 1600, 1477, 1274, 1203, 1090, 985, 905, 775, 502.

2,4,6-trideuteriumaniline (2g) [6] Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (s, 2H) and 3.62 (brs, 2H).

1-(4-amino-3,5-dideuterophenyl)-2,2,2-trideuteroethanone (2h) [17] Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (s, 2H) and 4.33 (br s, 2H).

RESULTS AND DISCUSSION

Our work was initialed by using 2-iodo-4, 6-dimethylaniline 1a as substrate, which was refluxed in CD_3OD in the presence of thionyl chloride for 12 h, 2-deuterium-4,6-dimethyl -aniline was obtained at 20% yield **(Table 1).** When CD_3OD was replaced with cheaper D_2O, 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 D_2O in combination with $SOCl_2$ at 100°C for 15 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[a]

Entry	Solvent	Reaction condition	Yield(%)[b]
1	$CD_3OD/SOCl_2$	reflux, 12 h	20
2	$D_2O/SOCl_2$	reflux, 12 h	25
3	$D_2O/SOCl_2$	reflux, 24 h	26
4	$D_2O/SOCl_2$	MW(100°C, 15 min)	56
5	$D_2O/SOCl_2$	MW(100°C, 30 min)	84

[a]The reaction was carried out using 2-iodo-4,6-dimethy-laniline (1 mmol), $SOCl_2$ (0.2 ml), CD_3OD or D_2O (2 ml).
[b]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 be observed, singe 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.

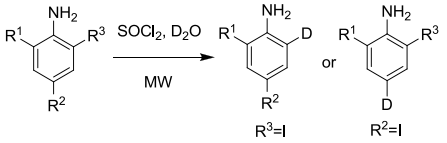
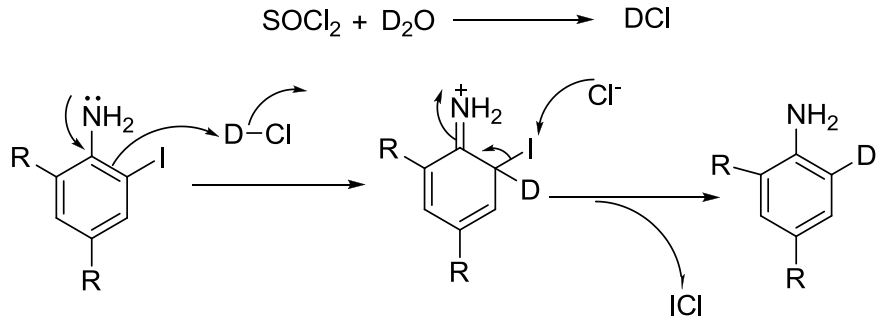


Table 2. I/D exchange on aniline using D_2O as a deuterium source.

Entry	Substrate	R^1	R^2	R^3	Product	D content[a] (%)	Yield (%)[b]
1	1a	Me	Me	I	2a	99	84
2	1b	Me	I	Me	2b	98	80
3	1c	Me	Ph	I	2c	98	85
4	1d	Ph	Me	I	2d	98	85
5	1e	Br	Me	I	2e	97	26
6	1f	I	Me	I	2f	99	73
9	1g	H	H	I	2g	98	67
10	1h	H	Ac	I	2h	98	80

[a]Determined by ^1H NMR spectroscopy in $CDCl_3$
[b]Isolated yield

The possible mechanism can be proposed as **Scheme 1**. First, thionyl chloride reacted with D_2O 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 attacksiodine to form ICl.



Scheme 1. The possible mechanism of I/D exchange.

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 D_2O as a deuterium source.

ACKNOWLEDGEMENTS

We are grateful to Shanxi Natural Science Foundation Committee (Project No.: 2012011002-3), Shanxi High School Development Project of Science and Technology Research (Project No.: 20101154; 2013168), Luliang University Science and Research Foundation (Project No.: ZRXN201211). The authors are also very grateful for the English and manuscript suggestions by Prof. Bai, J.M. and Bogan, A. from department of foreign language, Luliang University.

REFERENCES

1. Atzrodt J, et al. Synthesis of isoflavonoid deuterium labeled polyphenolic phytoestrogens. Tetrahedron 1999; 55: 3445-3454.
2. Seibles JC, et al. Synthesis of perdeuteriobenzo[a]pyrene, Pyranocoumarin. Angew Chem 1977; 89: 667-668.
3. Wähälä K and Rasku S. Synthesis of D4-genistein, a stable deutero labeled isoflavone, by a perdeuteration-Selective dedeuteration approach. Tetrahedron Lett. 1997; 38: 7287-7290.
4. Rasku S, et al. Synthesis of isoflavonoid deuterium labeled polyphenolic phytoestrogens. Tetrahedron 1999; 55 3445-3454.

5. Boix C and Poliakoff M. Efficient H-D Exchange of Aromatic Compounds in Near-Critical D_2O Catalysted by a Polymer-Supported Sulphonic Acid. Tetrahedron Lett 1999; 40: 4433-4436.

6. Bank S, et al. Electronic and Ion-Pairing Effects of a Methyl Group on a Diphenylmethyl Anion Determined by Restricted Aryl Rotation. J Org Chem 1984; 49: 5901-5093.

7. Kingston LP, et al. Parallel chemistry investigations of *ortho*-directed hydrogen isotope exchange between substituted aromatics and isotopic water: novel catalysis by cyclooctadienyliridium(I)pentan-1,3-dionates. Tetrahedron Lett 2000; 41: 2705-2708.

8. Küger J, et al. Iridium-Catalyzed H/D Exchange. Eur J Org Chem 2005; 2005: 1402-1408.

9. Hickey MJ, et al. Iridium-catalysed labelling of anilines, benzylamines and nitrogen heterocycles using deuterium gas and cycloocta-1,5-dienyliridium(I)1,1,1,5,5,5-hexafluoropentane-2,4-dionate. Tetrahedron Lett 2003; 44: 3959-3961.

10. Golden JT, et al. Exceptionally low-temperature carbon-hydrogen/carbon-deuterium exchange reactions of organic and organometallic compouds catalyzed by the $cp^*(pme_3)irh(clch_2cl)^+$ cation. J Am Chem Soc 2001; 123: 5837-5838.

11. Matsubara S, et al. Palladium-Catalyzed Decarboxylation and Decarbonylation under Hydrothermal Conditions: Decarboxylative Deuteration. Org Lett 2004; 6: 2071-2073.

12. Hardacre C, et al. A highly efficient synthetic procedure for deuteriating imidazoles and imidazolium salts. Chem Commun 2001; 2001: 367-368.

13. Zhan M, et al. A convenient method for the Ru(0)-catalyzed regioselective deuteration of N-alkyl-substituted anilines. Tetrahedron Lett 2014; 55: 5070-5073.

14. Mutsumi T, et al. Alternative I–D Exchange Reaction on Pyrimidine and Purine Nuclei Mediated by Tributyltin Hydride Using THF-d_8 as a Deuterium Source. Synlett 2008; 18: 2811-2814.

15. Martins A, et al. Palladium-Catalyzed Reductive ortho-Arylation: Evidence for the Decomposition of 1,2-Dimethoxyethane and Subsequent Arylpalladium(II) Reduction. Org Lett 2010; 22: 5186-5188.

16. Vaidyanathan S and Surber BW. Microwave mediated hydrogen deuterium exchange: a rapid synthesis of 2H-substituted benzimidazole. Tetrahedron Lett 2005; 46: 5195-5197.

17. Martins A and Lautens M. A Simple, Cost-Effective Method for the Regioselective Deuteration of Anilines. Org Lett 2008; 19: 4351-4353.