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A practical synthesis of deuterated methylamine and dimethylamine

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Abstract

In recent years, several deuterated drugs have entered clinical trials and have been approved for use. Deuterated methylamine and dimethylamine as important intermediates play significant roles in the preparation of deuterated drugs. In this study, we have developed a new method to prepare deuterated methylamine and dimethylamine. This method employs Boc-benzylamine as the starting material and $TsOCD_3$ as the deuterated methylation reagent. Our method gives relatively high yields and involves simple purifications, which provide a favourable supplement for the development and synthesis of deuterated drugs in the future.

Keywords

deuterated drugs, deuteration, dimethylamine, methylamine, methylation

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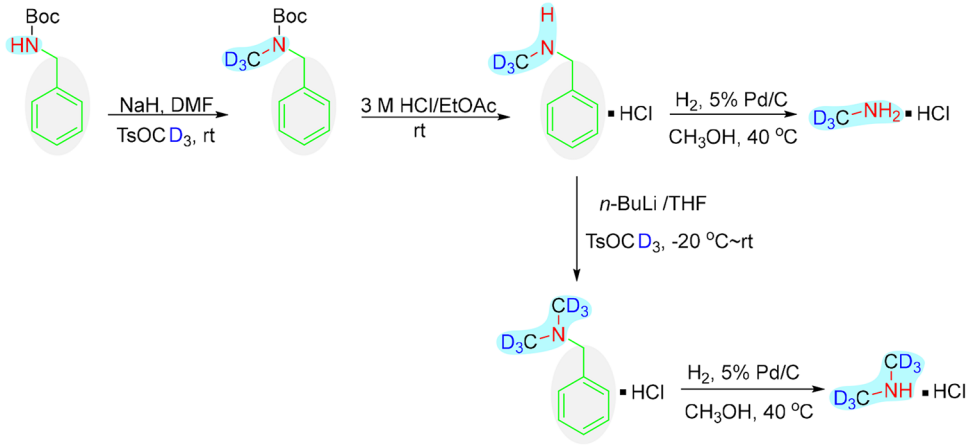

Introduction

Deuterated drugs are small molecule drugs in which the hydrogen atoms are replaced by the heavier stable isotope deuterium. In modern clinical medicine, deuterated drugs play an important role in the field of drug discovery and disease treatment. Compared with traditional drugs, deuterated drugs have better metabolic stability and improved efficacy.[1] Moreover, deuteration can slow down the system clearance rate and prolong the half-life of the drug in the body.[2,3] Therefore, deuterated drugs can reduce the toxicity and side effects by reducing the dose of a single administration while not affecting the pharmacological activity of the drug.[4,5] The first deuterated drug Austedo (deutetrabenazine), (Figure 1) was approved by

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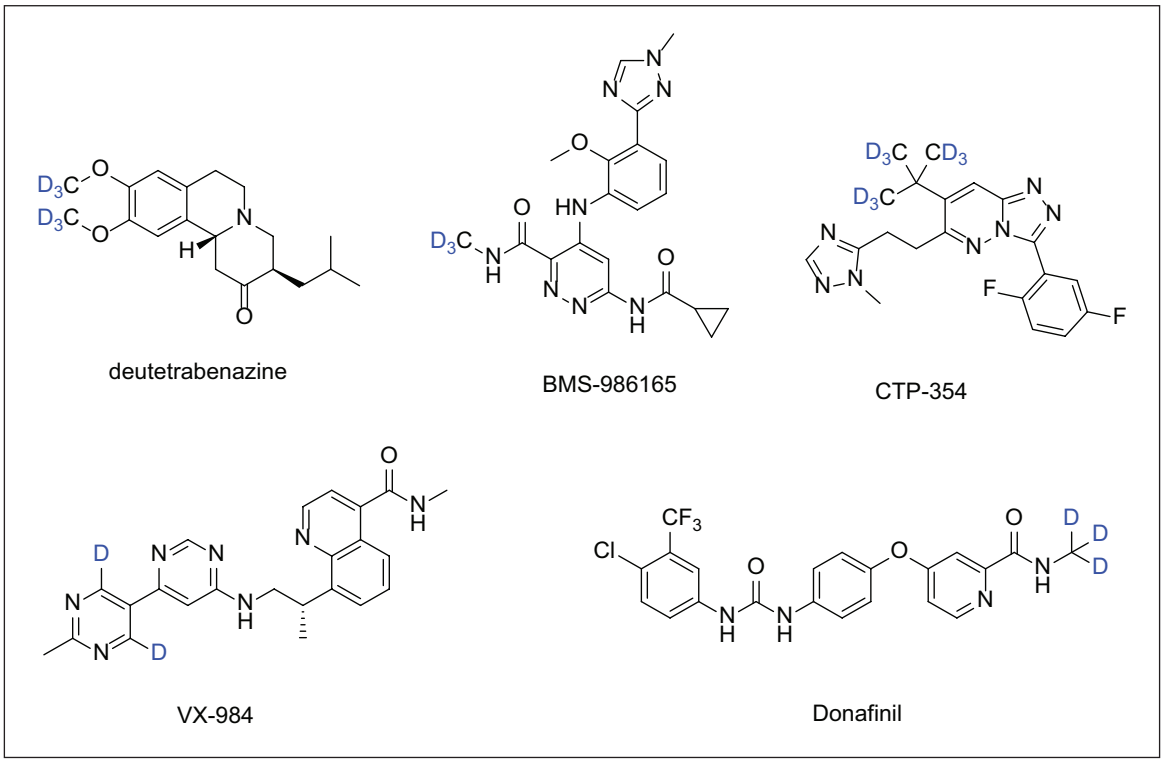


Figure 1. The chemical structures of deuterium-containing drugs.

the US Food and Drug Administration (FDA) in 2017 for the treatment of involuntary movements or chorea in patients with Huntington's disease.[6] Many pharmaceutical companies and research institutions have committed to the development of deuterium-containing drugs. Several deuterium-containing drugs have entered clinical trials, such as BMS-986165, VX-984, and CTP-354.[7–9] Recently, the clinical study of Donafinil showed significant overall survival in the treatment of advanced hepatocellular carcinoma, and this new drug application was formally accepted by the State Food and Drug Administration of China in May 2020.

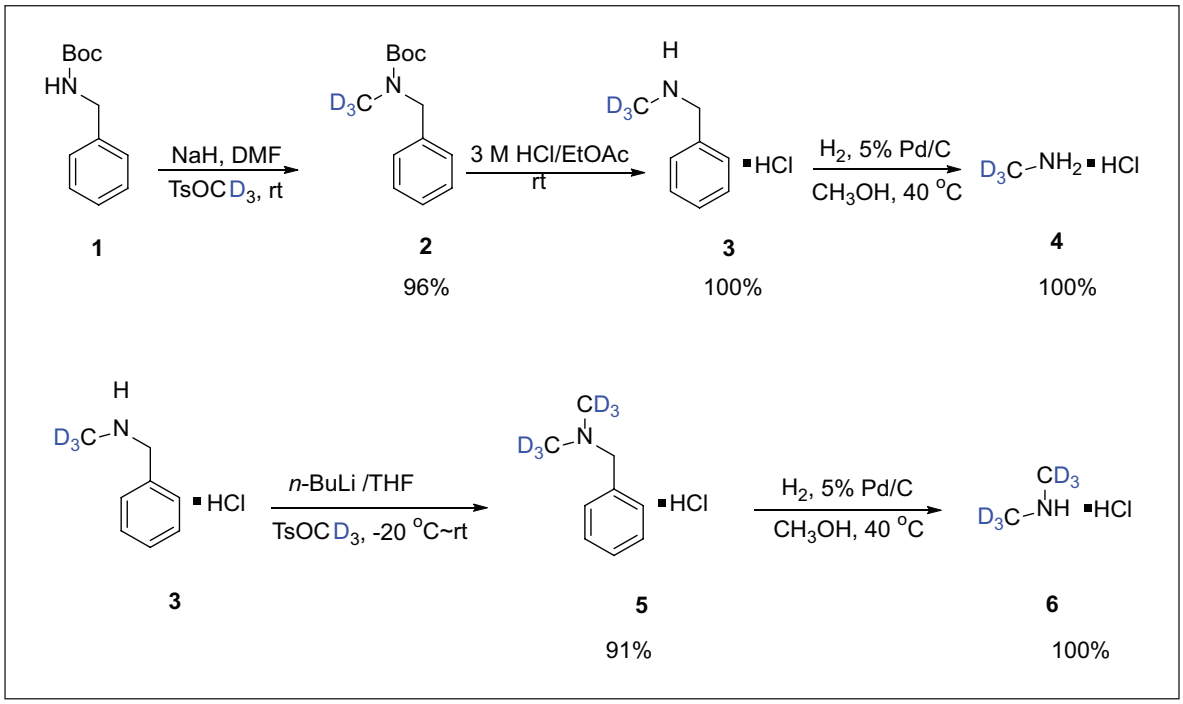
Among these deuterium drugs, the deuteration of methyl groups is a common method in the design of deuterated drugs.[10] Taking the JAK inhibitor BMS-986165 as an example, it exhibits a unique ability to selectively bind to the pseudokinase (JH2) domain of tyrosine kinase 2 (TYK2) and inhibits the TYK2 function through an allosteric mechanism.[11] The deuteration of the *N*-methyl group was shown to slow down the generation of a less selective primary amide metabolite *in vivo* by suppressing an *N*-demethylation metabolic pathway via a deuterium kinetic isotope effect (DKIE).[11] Similarly, Donafinil was designed from Sorafenib with a deuteriated methyl group. From the structures of BMS-986165 and Donafinil, we find that deuterated methylamine and dimethylamine, as the important intermediates, play significant roles in the preparation of deuterated drugs.

Generally, methylation of amino compounds can be achieved by nucleophilic substitution reactions with methyl iodide[12] or by reductive amination with aldehydes.[13,14] Therefore, the deuterated methylation of amino compounds can be achieved with deuterated methylating agents such as deuteroiodomethane and $TsOCD_3$.[15] However, the purity of the nucleophilic substitution reaction between the amine and deuteroiodomethane is relatively low due to the high activity of deuteroiodomethane. The amino compounds can go on to react with the deuterated methylation reagent to form a mixture of secondary, tertiary, and quaternary ammonium salts. Furthermore, the reductive amination of formaldehyde is another efficient and feasible method; however, this method did not lead to deuterated methylamine and dimethylamine because deuterated formaldehyde is difficult to obtain and very expensive.[16] Hence, there is a requirement to develop a new approach to the synthesis of deuterated methylamine and dimethylamine.

In this study, we report a novel synthetic method towards deuterated methylamine and dimethylamine. Boc-protected benzylamine as the starting material, reacted with the deuterated methylation reagent $TsOCD_3$ at low temperature in the presence of NaH or *n*-butyllithium. Next, the Boc and benzyl protecting groups were removed to afford the targeted deuterated methylamine and dimethylamine. This novel method exhibits relatively high yields, a simple operation, and satisfactory purity.

Results and discussion

Initially, we attempted to synthesize deuterated methylamine by utilizing benzylamine as the starting material and *n*-butyllithium as a strong base. Although there were no tertiary amine or quaternary ammonium salt by-products, the yield of deuterated methylamine was relatively low. Next, we selected Boc-benzylamine as the starting material for the reaction. As shown in Scheme 1, Boc-benzylamine reacted with $TsOCD_3$ to give intermediate **2** quantitatively in the presence of sodium hydride. The hydrochloride form



Scheme 1. The synthetic routes to deuterated methylamine hydrochloride 4 and deuterated dimethylamine hydrochloride 6.

of deuterated *N*-methylbenzylamine **3** was obtained by removal of the Boc group under acidic conditions. Finally, considering that methylamine and dimethylamine are gaseous at normal temperature and pressure, deuterated methylamine hydrochloride **4** was obtained by removing the benzyl group of compound **3** in the presence of Pd/C.

Similar to the deuterated methylamine hydrochloride **4**, deuterated dimethylamine hydrochloride **6** was synthesized from intermediate **3**. Reaction of compound 3 with *n*-butyllithium and $TsOCD_3$ afforded compound **5**. After the subsequent hydrogenation was completed, Pd/C was removed by filtration. Finally, the filtrate was concentrated to afford deuterated dimethylamine hydrochloride **6**.

Conclusion

Deuterated methylamine and deuterated dimethylamine are important deuterated intermediates that are employed in the synthesis of various deuterated drug molecules. Convenient and controllable methods for synthesizing deuterated methylamine and dimethylamine are of great significance. In this study, an efficient and practical route conducive to the reduction of production costs of deuterium methylamine hydrochloride and deuterium dimethylamine hydrochloride is described. This novel method exhibits relatively high yields, a simple operation, and satisfactory purity.

Experimental

Materials and instruments

All chemicals and reagents used in this work were of analytical grade and obtained from commercial suppliers without further purification. ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were recorded on a Bruker AM-400 NMR spectrometer in $CDCl_3$ or dimethyl sulfoxide (DMSO)-d_6. The chemical shifts are reported in δ (ppm) relative to tetramethylsilane (TMS) as the internal standard. Electrospray ionization mass spectrometry (ESI-MS) spectra were recorded on a Thermo MSQ PLUS mass spectrometer. High-resolution mass spectroscopy (HRMS) spectra were obtained on a Bruker Solarix 94 FT mass spectrometer.

tert-Butyl benzyl(methyl-d_3*)carbamate (***2***).* At 0 ℃, compound **1** (24.12 mmol) was added to dimethylformamide (DMF) (25 mL) under a nitrogen atmosphere. Next, NaH (60% in mineral oil, 26.54 mmol) was added dropwise to the solution, and after 30 min, $TsOCD_3$ (24.12 mmol) in DMF (5 mL) was added dropwise. The reaction mixture was warmed to room temperature. After completion of the reaction as determined by thin layer chromatography (TLC) analysis, the reaction was quenched with saturated ammonium chloride (40 mL) at room temperature. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to obtain the crude product. Compound 2 was obtained by flash chromatography over silica gel (EtOAc: petroleum ether, 1:10). Yield 96%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47 (s, 9H, -CH_3), 4.41 (s, 2H, -CH_2), 7.23–7.35 (m, 5H, -ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.5, 51.9, 52.5, 79.1, 127.2, 127.7, 128.5, 138.1.

N-Benzylmethan-d_3*-amine hydrochloride (***3***).* Compound **2** (12.06 mmol) in EtOAc was added dropwise to a solution of HCl/EtOAc (3 M, 15 mL) at 0 ℃. The reaction mixture was warmed to room temperature and a completion of the reaction as determined by TLC analysis, the mixture was concentrated to afford the hydrochloride of compound **3**

(12.06 mmol, yield 100%).[17] 1H NMR (400 MHz, D_2O): δ 4.08 (s, 2H, -CH_2), 7.36–7.39 (m, 5H, -ArH); ^{13}C NMR (100 MHz, D_2O): δ 31.4, 52.2, 129.2, 129.6, 129.7, 130.7. HRMS(ESI): m/z $[M+H]^+$ calcd for $C_8H_8D_3N$: 125.1158; found: 125.1152.

Methan-d_3*-amine hydrochloride (***4***).* Compound **3** (12.06 mmol) and 5% Pd/C (200 mg) were added to 25 mL of MeOH under a hydrogen atmosphere. The reaction was heated to 40 ℃, After completion of the reaction as determined by TLC analysis, the reaction mixture was filtered and evaporated to obtain compound **4** (12.06 mmol, yield 100%).[18] 1H NMR (400 MHz, DMSO-d_6):δ 8.10 (s, 2H, -NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ: 23.5.

N-benzyl-N-(methyl-d_3*)methanamine-*d_3 *hydrochloride (***5***).* At -20℃, *N*-benzylmethan-d_3-amine hydrochloride **3** (16.10 mmol) was added in 16 mL of anhydrous tetrahydrofuran (THF) under a nitrogen atmosphere. Next, *n*-butyllithium (16.10 mmol) was added dropwise to the solution, and after 30 min, $TsOCD_3$ (16.10 mmol) in anhydrous THF (20 mL) was added dropwise. The reaction was stirred for another 30 min. Then the reaction mixture was warmed to room temperature and reacted overnight. After completion of the reaction as determined by TLC analysis, the mixture was quenched with saturated ammonium chloride (20 mL) at room temperature. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to obtain the crude product. After purified by flash chromatography over silica gel (CH_2Cl_2: MeOH 20:1), the obtained compound was dissolved in 15 mL of EtOH. Then HCl/EtOH (3 M, 2 mL) was added to the solution. After removing the solvents, compound **5** was achieved (Yield 91%). 1H NMR (400 MHz, D_2O): δ 4.2 (s, 2H, -CH_2), 7.40–7.43 (m, 5H, -ArH); ^{13}C NMR (100 MHz, D_2O): δ 41.5, 60.9, 129.3, 130.2, 130.8. HRMS(ESI): m/z $[M+H]^+$ calcd for $C_9H_7D_6N$: 142.1503; found: 142.1497.

Bis(methyl-d_3*)amine hydrochloride (***6***).* Compound **5** (14.68 mmol) and 5% Pd/C (230 mg) were added to 25 mL of MeOH under a hydrogen atmosphere. The mixture was reacted at 40 ℃. After completion of the reaction as determined by TLC analysis, filtered and evaporated to give the compound **6** (yield 100%).[18] 1H NMR (400 MHz, D_2O): δ no other hydrogen was found except solvent D_2O; ^{13}C NMR (100 MHz, D_2O): δ 33.8.

Declaration of conflicting interests

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Supplemental material

The Supporting Information is available free of charge at HRMS spectrum and ^1H and ^{13}C (PDF).

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