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Synthesis of [^{15}N]t-butylamine hydrochloride

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This report presents an efficient synthesis of [^{15}N]t-butylamine hydrochloride. Acylation of [^{15}N]ammonia with pivaloyl chloride provided [^{15}N]pivalamide, this was converted to benzyl [^{15}N]N-t-butylcarbamate through a Hofmann rearrangement. Hydrogenolysis of benzyl [^{15}N]N-t-butylcarbamate and acidification afforded [^{15}N]t-butylamine hydrochloride in an overall yield of 79.2% in four steps.

Keywords: ^{15}N-labelling synthesis; [^{15}N]t-butylamine hydrochloride; Hofmann rearrangement

Introduction

t-Butylamine is a versatile and important building block for compounds with biological activities. Finasteride, a 5α-reductase inhibitor for use in treating acne, female hirsutism and benign prostatic hyperplasia, was prepared by the reaction of the carboxylate of 4-aza-5α-androst -1-ene-3-one with t-butylamine.[1] It was also built into an apoptosis inhibitor,[2] an HIV protease inhibitor,[3] various antibotics[4] and nucleosides.[5] Moreover t-butylamine residues are commonly in adrenergic drugs to increase affinity for β-adrenoceptors.[6–8]

Here we describe an efficient synthesis of [^{15}N]t-butylamine hydrochloride, which can be used as biomarker for biologically active compounds containing this motif or incorporated in the synthesis of drug candidates for use as analytical internal standards or for metabolic studies.

Results and discussion

Reports of the preparation of [^{15}N]t-butylamine are very rare. Previously Glueck *et al.* described the preparation of [^{15}N]t-butylamine hydrochloride.[9] Pivaloyl chloride reacted with [^{15}N]ammonia to give [^{15}N]pivalamide, which was converted to t-butyl [^{15}N]isocyanate with KOBr via a Hofmann rearrangement. t-Butyl [^{15}N]isocyanate was then reacted with HCl to give [^{15}N]t-butylamine hydrochloride in moderate yield. In this method [^{15}N]t-butylamine hydrochloride and its intermediate were insufficiently characterized. In order to improve the synthesis of [^{15}N]t-butylamine, we developed a new synthetic method with a higher labelling yield.

As shown in Scheme 1, acylation of [^{15}N]NH_3, which was derived from [^{15}N]NH_4Cl **1**, with pivaloyl chloride in Et_2O-H_2O gave [^{15}N]pivalamide **2** in 93.8% yield. [^{15}N]Pivalamide **2** was converted to benzyl [^{15}N]N-t-butylcarbamate **3** through a Hofmann rearrangement with *N*-bromosuccinimide, mercuric acetate and benzyl alcohol in DMF under nitrogen at room temperature in 90.5% yield. Jew *et al.* discussed the reaction mechanism in detail (Scheme 2).[10] When NBS was added to the solution of pivalamide, $Hg(OAc)_2$ and benzyl alcohol in DMF, the N-Br bond cleaved with the help of DMF and reacted with pivalamide to give [^{15}N]N-bromopivalamide **5**, which was converted to the t-butyl [^{15}N]isocyanate **6** with the aid of $Hg(OAc)_2$. Normally alkyl isocyanates reacted only slowly with benzyl alcohols at room temperature and did not react completely;[11] however, t-butyl [^{15}N]isocyanate **6** reacted with benzyl alcohol smoothly at room temperature and gave an excellent yield in this reaction. It is conceivable that the acetic acid produced *in situ* catalyzed the transformation. Finally catalytic hydrogenolysis of benzyl [^{15}N]N-t-butylcarbamate **3** and acidification with HCl gas gave [^{15}N]t-butylamine hydrochloride **4** in 79.2% overall yield in four steps.

Experimental

Materials and instruments

[^{15}N]Ammonium chloride (99.5 atom% ^{15}N) was purchased from Shanghai Engineering Research Center of Stable Isotope. Pivaloyl chloride was distilled before use. All other chemicals were of analytical grade. Melting points were determined on XT4A microscopic digital melting-point apparatus and are uncorrected. ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra were recorded on a JNM-ECA-400 NMR spectrometer in $CDCl_3$ or DMSO-d_6 (TMS as internal standard). FT-IR spectra were recorded on a Nicolet FT-IR 5700 spectrometer using KBr pellets. EI-MS Spectra were obtained with ZAB-HS spectrometer.

[^{15}N]Pivalamide (2)

Pivaloyl chloride (3.0 mL, 24 mmol) in Et_2O (10 mL) was layered onto a solution of $^{15}NH_4Cl$ (1.0 g, 18.3 mmol) in H_2O (4 mL) in a 25 mL flask so the layers did not mix. The flask was cooled to 0°C and NaOH (4.4 g, 110 mmol) in H_2O (6 mL) was added slowly by

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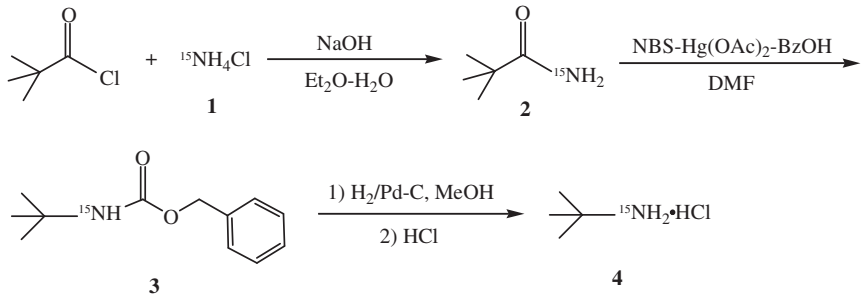
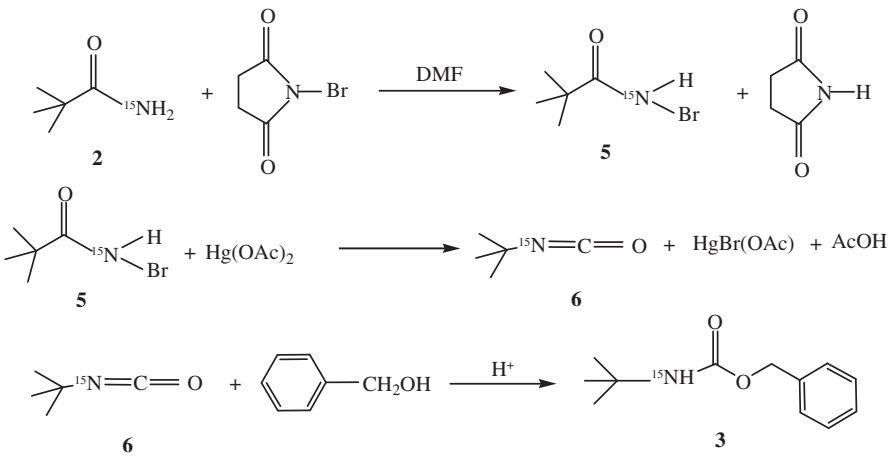


Scheme 1.



Scheme 2.

pipette to the aqueous layer with slow stirring to avoid mixing of the layers. A white precipitate formed during addition. The flask was warmed to room temperature and stirred for 15 min, and then the mixture was stirred violently for additional 10 min. The white solid was collected by filtration and washed with diethyl ether. After drying under vacuum, the white solid was purified by flash chromatography (petroleum ether: ethyl acetate = 1:1and 5% methanol was added) to afford [^{15}N]pivalamide **(2)** (1.75 g, 93.8%), m.p.: 154–155°C (Lit. 155–156°C for the unlabelled analogue[12]). ^{1}H-NMR (DMSO-d_6)δ: 1.06 (s, 9H); ^{13}C-NMR (DMSO-d_6)δ: 27.5 (s), 37.8(d, $^2J_{13C-15N}$ = 6.8 Hz), 179.8(d, $J_{13C-15N}$ = 13.8 Hz); FT-IR (KBr) cm^{-1}: 3390, 3199, 2961, 2923, 2756, 1648, 1485, 1455, 1408, 1376, 1356, 1221, 1103, 863, 816, 732, 615; EI-MS *m/z* : 102 (M^+, 18), 87(10), 69(5), 57(100), 47(18), 45(23), 41(66), 29(43).

Benzyl [^{15}N]N-t-butylcarbamate (3)

Benzyl alcohol (1.107 g, 10.25 mmol) was added to a solution of [^{15}N]pivalamide (0.209 g, 2.05 mmol) and Hg(OAc)$_2$ (0.795 g, 2.45 mmol) in DMF (8 mL), followed by the addition of a solution of NBS (0.48 g, 2.7 mmol) in DMF (2 mL) at room temperature under nitrogen. After reaction at this temperature for 30 h, the reaction mixture was poured into water and extracted with CH_2Cl_2 (15 mL × 3). The combined extracts were washed with water, saturated $NaHCO_3$, dried over anhydrous magnesium sulfate and evaporated. The crude product was purified by flash chromatography (petroleum ether: ethyl acetate = 40:1) to give yellow oil benzyl [^{15}N]N-t-butylcarbamate **(3)** (0.385 g, 90.5%). ^{1}H-NMR ($CDCl_3$)δ: 1.18(d, 9H, $^3J_{1H-15N}$ = 2.8 Hz), 4.83(d, 1H, J_{1H-15N} = 88.9 Hz), 4.91(s, 2H), 7.14–7.19(m, 5 H); ^{13}C-NMR ($CDCl_3$)δ: 28.6(s), 50.0(d, $J_{13C-15N}$ = 9.3 Hz), 65.6(s), 127.6(s), 127.7(s), 128.1(s), 136.6(s), 154.4(d, $J_{13C-15N}$ = 27 Hz); FT-IR (KBr) cm^{-1}: 3341, 2969, 1713, 1498, 1454, 1394, 1365, 1266, 1210, 1072, 914, 776, 738, 696; EI-MS *m/z* : 208 (M^+, 3), 193(4), 149(9), 108(47), 91(100), 89(3), 79(5), 57(11).

[^{15}N]t-Buytlamine hydrochloride (4)

Benzyl [^{15}N]N-t-butylcarbamate (1.04 g, 5 mmol) and 10% Pd-C (1.0 g) were dissolved in absolute methanol (10 mL) at room temperature. A gentle stream of hydrogen was passed through the reaction mixture. The reaction proceeded for 4 h and the mixture was then filtered and washed with methanol. The filtrate was cooled to 0°C and gaseous HCl was bubbled slowly through the solution. The reaction mixture was evaporated to give [^{15}N]t-butylamine hydrochloride **(4)** (0.515 g, 93.3%), m.p.: 230–240°C (sublimation)(Lit. 275–280°C for the unlabelled analogue[13]). ^{1}H-NMR (DMSO-d_6)δ: 1.25(d, 9 H, $^3J_{1H-15N}$ = 2.8 Hz), 7.93(d, 3 H, J_{1H-15N} = 71.6 Hz); ^{13}C-NMR (DMSO-d_6)δ: 27.1(s), 50.9(d, $J_{13C-15N}$ = 4.2 Hz); FT-IR (KBr) cm^{-1}: 2977, 2887, 2789, 2696, 2583, 2493, 2078, 1661, 1503, 1401, 1376, 1298, 1215, 994; EI-MS *m/z* : 59 (M-15, 100), 57(13), 53(3), 43(51), 41(61), 36(100), 31(33), 27(15).

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References

[1] G. H. Rasmusson, G. F. Reynolds, US 4760071 AI, Merck, **1988**.
[2] I. Kazuhito, T. Tohru, N. Chikao, W0 0064430 AI, Sumitomo Pharma, **2000**.
[3] S. R. Turner, *Curr. Med. Chem. Antiinfect. Agents* **2002**, *1*, 141–162.
[4] G . G . Zhanel, K. Honenuik, K. Nichol, A. Noreddin, L. Vercaigne, J. Embil, A. Gin, J. A. Karlowsky, D. J. Hoban, *Drug* **2004**, *64*, 63–88.
[5] E. Sochacka, D. Smuga, *Nucleosides, Nucleotides and Nucleic Acids* **2008**, *27*, 1045–1060.
[6] B. Waldeck, *Eur. J. Pharmacol.* **2002**, *445*, 1–12.
[7] R. R. Ruffolo Jr, W. Bondinell, J. P. Hieble, *J. Med. Chem.* **1995**, *38*, 3681–3716.
[8] D. B. Evans, R. Fox, F. P. Hauck, *Ann. Rep. Med. Chem.* **1979**, *14*, 81–90.
[9] D. S. Glueck, J. Wu, F. J. Hollander, R. G. Bergman, *J. Am. Chem. Soc.* **1991**, *113*, 2041–2054.
[10] S. S. Jew, H. G. Park, H. J. Park, M. S. Park, Y. S. Cho, *Tetrahedron Lett.* **1990**, *31*, 1559–1562.
[11] A. Benalil, P. Roby, B. Carboni, M. Vaultier, *Synthesis* **1991**, 787–788.
[12] K. T. Liu, M. H. Shih, H. W. Huang, C. J. Hu, *Synthesis* **1988**, 715–717.
[13] G. M. Loudon, A. S. Radhakrishna, M. R. Almond, J. K. Blodgett, R. H. Boutin, *J. Org. Chem.* **1984**, *49*, 4272–4276.