

## Research Article

# Synthesis of 1-([<sup>15</sup>N])amino-2-propanol hydrochloride

KATSUMI IIDA\*, KUNIAKI OHTAKA and MASAHIRO KAJIWARA\*

Department of Medicinal Chemistry, Meiji Pharmaceutical University, 2-522-1 Noshio, Kiyose-shi, Tokyo 204-8588, Japan

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**Abstract:** 1-[<sup>15</sup>N]Amino-2-propanol hydrochloride (**2**) was synthesized in three steps, i.e. Gabriel condensation of potassium [<sup>15</sup>N]phthalimide (**3**) with chloroacetone (**4**), reduction of the product ([<sup>15</sup>N]phthalimidoacetone (**5**)) with sodium borohydride, and hydrolysis in 33% total yield from the <sup>15</sup>N-source. Copyright © 2007 John Wiley & Sons, Ltd.

**Keywords:** <sup>15</sup>N-labeling synthesis; 1-[<sup>15</sup>N]amino-2-propanol; potassium [<sup>15</sup>N]phthalimide; vitamin B<sub>12</sub>; biosynthetic intermediate

## Introduction

We have investigated the biosynthesis of tetrapyrrole<sup>1,2</sup> by using a variety of stable-isotope-labeled δ-aminolevulinic acids (ALA, a biosynthetic intermediate of tetrapyrrole) that we have synthesized in various ways.<sup>3–5</sup> Studies on the sources of nitrogen in vitamin B<sub>12</sub> (**1**) have been done by means of feeding experiments with [<sup>15</sup>N]ALA<sup>2</sup>, [5-<sup>15</sup>N]riboflavin, potassium [<sup>15</sup>N]cyanide and L-[amide-<sup>15</sup>N]glutamine in *Propionibacterium shermanii*.<sup>6,7</sup> However, our D-[1-<sup>13</sup>C]glucose feeding experiment in *P. shermanii*<sup>8</sup> led us to postulate that the origin of amide (C-57) nitrogen was the nitrogen atom of 1-amino-2-propanol (**2**) derived from L-threonine via L-aspartic acid transformed from oxaloacetic acid, which itself is generated in the tricarboxylic acid (TCA) cycle via glycolysis (Figure 1.)

In order to test this hypothesis, we required 1-[<sup>15</sup>N]amino-2-propanol (**2**), and here we describe a convenient synthesis of **2** in three steps, in good yield.

## Results and discussion

The synthesis of 1-[<sup>15</sup>N]amino-2-propanol (**2**) by Kostyanovskii *et al.*<sup>9</sup> involved the addition to propylene oxide of <sup>15</sup>NH<sub>3</sub>, which was derived from (<sup>15</sup>NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>, in water in the presence of a basic catalyst. 1-[<sup>15</sup>N]Amino-2-propanol (**2**) was isolated from the residue of the

reaction mixture after distillation in 25% yield. This method is a very simple one-step reaction, but the yield from the <sup>15</sup>N-source ((<sup>15</sup>NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>) was only 4%. Therefore, we developed a synthetic method for 1-[<sup>15</sup>N]amino-2-propanol (**2**) with a higher labeling yield from potassium [<sup>15</sup>N]phthalimide (**3**) by modifying our previous ALA-labeling methods.<sup>3,4</sup>

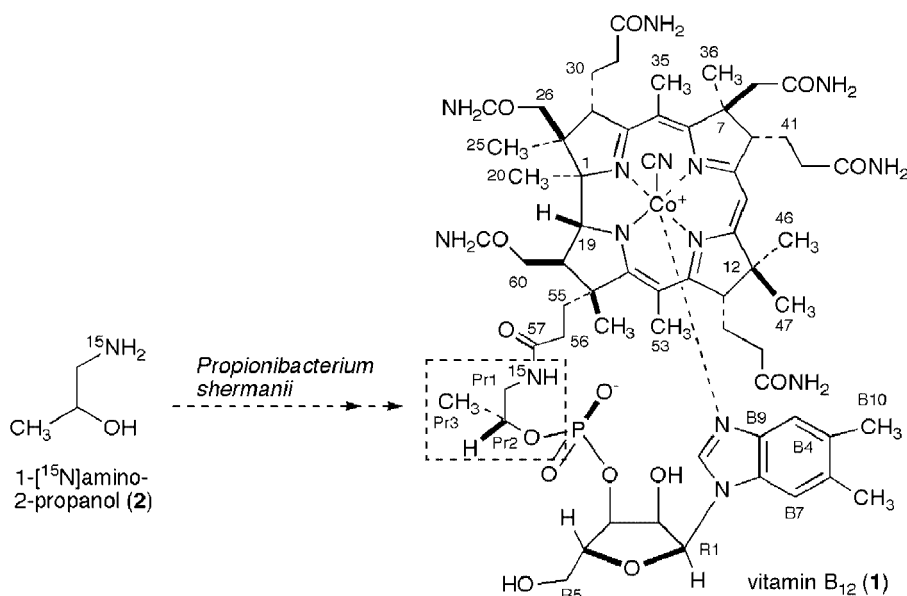
As shown in Scheme 1, Gabriel condensation of potassium [<sup>15</sup>N]phthalimide (**3**) with chloroacetone (**4**) in dry dimethylformamide by reflux under nitrogen gave [<sup>15</sup>N]phthalimidoacetone (**5**) in 83% yield. The reduction of the carbonyl group at C-2 of [<sup>15</sup>N]phthalimidoacetone (**5**) with sodium borohydride in dry ethanol at 0°C under nitrogen gave crude [<sup>15</sup>N]phthalimido-2-propanol (**6**). Finally, hydrolysis of non-isolated [<sup>15</sup>N]phthalimido-2-propanol (**6**) in 6 N hydrochloric acid under reflux gave 1-[<sup>15</sup>N]amino-2-propanol hydrochloride (**2**) in 40% yield for the two steps.

## Experimental

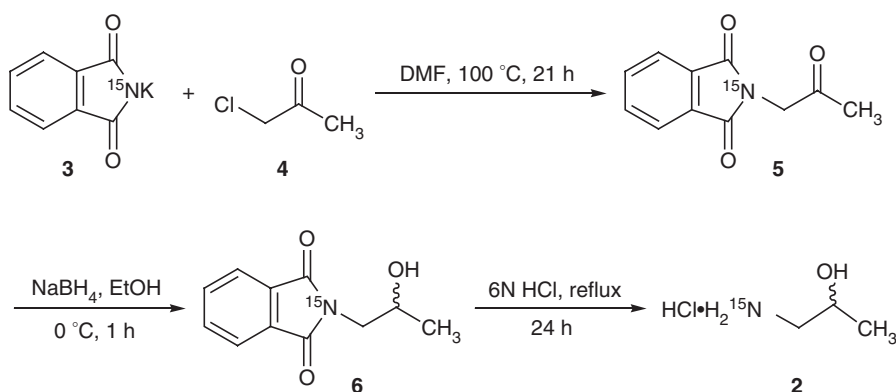
### Materials and instruments

Potassium [<sup>15</sup>N]phthalimide (**3**) (99.5 atom % <sup>15</sup>N) was purchased from Shoko Co., Ltd. All other chemicals were of analytical grade. Melting points were measured on a Yanako micro melting point apparatus and are uncorrected. All <sup>1</sup>H-NMR (300 MHz) and <sup>13</sup>C-NMR (75 MHz) spectra were recorded on a Varian Gemini-300 spectrometer. IR spectra were recorded on a Jasco VALORA-III FT-IR spectrometer. EI-MS spectrum was obtained with a JEOL JMS-DX-700 spectrometer.

\*Correspondence to: Katsumi Iida and Masahiro Kajiwara, Department of Medicinal Chemistry, Meiji Pharmaceutical University, 2-522-1 Noshio, Kiyose-shi, Tokyo 204-8588, Japan. E-mail: iida@my-pharm.ac.jp or Kajiwara@my-pharm.ac.jp



**Figure 1** The proposed source of amide (C-57) nitrogen of vitamin B<sub>12</sub> (**1**).



**Scheme 1** Synthesis of 1-[<sup>15</sup>N]amino-2-propanol hydrochloride (**2**).

### (<sup>15</sup>N)Phthalimidoacetone (**5**)

Chloroacetone (**4**) (5.3 ml, 66.6 mmol) was added dropwise to a suspension of potassium [<sup>15</sup>N]phthalimide (**3**) (10.4 g, 55.8 mmol) in dry dimethylformamide (100 ml) at room temperature under nitrogen, and the whole was heated under reflux for 21 h. The reaction was quenched with water (100 ml), and the mixture was extracted with ether (50 ml × 3). The combined extracts were washed with brine, dried over anhydrous magnesium sulfate and evaporated. Recrystallization of the crude product from 2-propanol/*n*-hexane gave [<sup>15</sup>N]phthalimidoacetone (**5**) (9.5 g, 83%), m.p. 121 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.27 (3H, s, C-3-CH<sub>3</sub>), 4.51 (2H, s,

C-1-CH<sub>2</sub>), 7.75, 7.88 (4H, phenyl-H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ: 27.0 (C-3), 47.1 (d, *J*<sub>13C-15N</sub> = 12.2 Hz, C-1, this signal was shifted upfield by 0.55 Hz shift owing to the <sup>15</sup>N-nitrogen α-isotope effect), 123.5 (phenyl-C), 132.0 (d, *J*<sub>13C-15N</sub> = 8.3 Hz, phenyl-C, this signal was shifted upfield by 0.28 Hz shift owing to the <sup>15</sup>N-nitrogen α-isotope effect), 134.1 (phenyl-C), 167.5 (d, *J*<sub>13C-15N</sub> = 13.3 Hz, <sup>15</sup>N-C=O, this signal was shifted upfield by 0.55 Hz shift owing to the <sup>15</sup>N-nitrogen α-isotope effect), 199.5 (C-2); FT-IR (KBr) cm<sup>-1</sup>: 3468, 3430, 1770, 1717, 1611, 1467, 1408, 1385, 1370, 1301, 1188, 1116, 1088, 1017, 896, 792, 723, 709, 651; EI-MS *m/z* (rel. int. %): 204 (M<sup>+</sup>, 11), 162 (66), 161 (100), 133 (10), 104 (10), 77 (10), 76 (11).

## 1-[<sup>15</sup>N]Amino-2-propanol Hydrochloride (2)

Sodium borohydride (1.43 g, 37.8 mmol) was added to a solution of [<sup>15</sup>N]phthalimidoacetone (5) (7.77 g, 38.1 mmol) in dry ethanol (380 ml) at 0°C under nitrogen, and the reaction mixture was stirred for 1 h. The reaction was quenched with water (100 ml), and the whole was extracted with ether (50 ml × 3). The combined extracts were washed with brine, dried over anhydrous magnesium sulfate and evaporated to give crude [<sup>15</sup>N]phthalimido-2-propanol (6). A solution of the residue in 6 N hydrochloric acid (30 ml) was refluxed for 24 h. The reaction mixture was evaporated. The residue was dissolved in water (20 ml) and re-evaporated to remove the excess hydrogen chloride. The residue was re-dissolved in water (40 ml), and the solution was washed with ether (30 ml × 3) to remove phthalic acid. The water layer was concentrated to give 1-[<sup>15</sup>N]amino-2-propanol hydrochloride (2) (1.7 g, 40%), <sup>1</sup>H-NMR (D<sub>2</sub>O) δ: 1.15 (3H, d, *J* = 6.3 Hz, C-3-CH<sub>3</sub>), 2.79 (1H, dd, *J* = 9.2, 13.0 Hz, C-1-CH<sub>2</sub>), 3.01 (1H, dd, *J* = 2.6, 13.0 Hz, C-1-CH<sub>2</sub>), 3.95 (1H, m, C-2-CH<sub>2</sub>); <sup>13</sup>C-NMR (D<sub>2</sub>O) δ: 20.4 (C-3), 46.4 (d, *J*<sub>13C-15N</sub> = 5.53 Hz, C-1, this signal was shifted upfield by 0.02 Hz shift owing to the <sup>15</sup>N-nitrogen α-isotope effect), 64.7 (C-2).

## Conclusion

1-[<sup>15</sup>N]Amino-2-propanol hydrochloride (2) was synthesized by Gabriel condensation of potassium

[<sup>15</sup>N]phthalimide (3) with chloroacetone (4), followed by reduction with sodium borohydride and hydrolysis in 33% total yield from the <sup>15</sup>N-source in three steps.

## REFERENCES

1. Kurumaya K, Okazaki T, Kajiwara M. *Chem Pharm Bull* 1989; **37**: 1151–1154.
2. Okazaki T, Kurumaya K, Kajiwara M. *Chem Pharm Bull* 1990; **38**: 1727–1730.
3. Kurumaya K, Okazaki T, Seido N, Akasaka Y, Kawajiri Y, Kajiwara M, Kondo M. *J Label Compd Radiopharm* 1989; **27**: 217–235.
4. Iida K, Takao Y, Ogai T, Kajiwara M. *J Label Compd Radiopharm* 1997; **39**: 797–802.
5. Iida K, Kajiwara M. *J Label Compd Radiopharm* 2002; **45**: 139–143.
6. Kurumaya K, Okazaki T, Kajiwara M. *Chem Pharm Bull* 1990; **38**: 1058–1061.
7. Kurumaya K, Kajiwara M. *Chem Pharm Bull* 1990; **38**: 2589–2590.
8. Iida K, Kajiwara M. *Biochemistry* 2000; **39**: 3666–3670.
9. Kostyanovskii RG, Kadorkina GK, Chervin II, Romero Mal'donado IKA. *Khim Geterotsikl Soedin* 1988; **6**: 757–765.