3-Amino-1-hydroxyacetone

Nisar Ullah, Clara Nanfe Fali, and Ian D. Spenser

Abstract: 3-Amino-1-hydroxypropan-2-one (3-amino-1-hydroxyacetone) was prepared in an overall yield of 52% in 6 steps starting with *N*-phthaloylglycine. This synthesis is readily adaptable for the preparation of bond-labeled samples, i.e., samples that are labeled intramolecularly at contiguous sites.

Key words: 3-amino-1-hydroxyacetone, 3-amino-1-hydroxypropan-2-one.

Résumé : On a préparé la 3-amino-1-hydroxypropan-2-one (3-amino-1-hydroxyacétone), avec un rendement global de 52 %, en six étapes à partir de la *N*-phtaloylglycine. La synthèse peut facilement être adaptée à la préparation d'échantillons portant des marqueurs intramoléculaires sur des sites voisins.

Mots clés : 3-amino-1-hydroxyacétone, 3-amino-1-hydroxypropan-2-one.

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Introduction

3-Amino-1-hydroxyacetone 1-O-phosphate (**2**), derived by oxidative decarboxylation of 4-hydroxy-L-threonine 4-O-phosphate (**1**), serves as a precursor of the C_3N unit, N-1,C-6,5,5′ of vitamin B_6 (**3**) in *Escherichia coli* (Scheme 1) (1).

In connection with our continuing investigations of the biosynthesis of vitamin B_6 in *E. coli* (2) and in yeast (3–5), we required a sample of aminohydroxyacetone that was intramolecularly contiguously $^{13}C,^{13}C$ or $^{15}N,^{13}C$ labeled, i.e., bond labeled. None of the reported syntheses of the compound (6–8) were readily adaptable to this purpose, since the starting materials employed in these synthetic sequences are not available in labeled form. The synthetic sequence here described starts from *N*-phthaloylglycine (**4**). Several syntheses of labeled samples of this compound, from commercially available labeled starting materials in almost quantitative yields, have been reported (see Scheme 2) in connection with the preparation of labeled samples of δ-aminolevulinic acid.

The preparation of the following singly and multiply labeled samples of *N*-phthaloylglycine (**4**) has been described: 1-^{14}C- (9–11), 1-^{13}C- (12–14), 2-^{13}C- (13–15), 1,2-$^{13}C_2$- (15), ^{15}N- (13, 14), 1-^{13}C,^{15}N- (16), 2-^{13}C,^{15}N- (16), and 1,2-$^{13}C_2$,^{15}N- (17). The corresponding acyl chloride (**5**), which was obtained quantitatively on treatment of the acid with thionyl chloride (9–17), was then converted into δ-aminolevulinic acid by several different routes.

In one of these routes, the labeled phthaloylglycyl chloride (**5**) was treated with diazomethane, an Arndt–Eistert reaction that was originally described by Balenović (18), yielding the correspondingly labeled 1-diazo-3-phthalimidopropan-2-one (**6**) (9, 10, 17), which was then used in the next step of the synthetic sequence, leading to labeled δ-aminolevulinic acid.

In the present preparation of aminohydroxyacetone, an acid-catalyzed decomposition of the diazo compound (**6**) (18) gave 1-hydroxy-3-phthalimidopropan-2-one (**7**), the *N*-phthaloyl derivative of the desired product. However, attempts to obtain (**10**) by hydrolytic removal of the phthaloyl group of (**7**) were unsuccessful.

The phthaloyl unit was removed by reaction with hydrazine. Before doing so, the keto group of (**7**) had to be protected. This was done by reaction with ethyleneglycol to yield 2-hydroxymethyl-2-phthalimidomethyl-1,3-dioxolane (**8**). This compound had been prepared previously by somewhat different reaction sequences (19, 20). Treatment of the ketal (**8**) with hydrazine, followed by dilute HCl, gave 2-hydroxymethyl-2-aminomethyl-1,3-dioxolane hydrochloride (**9**). For hydrolysis, the ketal was suspended in aqueous acetonitrile, and the mixture was refluxed in the presence of an ion-exchange resin, from which the product, 3-amino-1-hydroxyacetone hydrochloride (**10**), was eluted with 2 mol L^{-1} HCl and obtained in high yield.

When acetone, in place of acetonitrile, was employed as the solvent in the above procedure, the yield of product was less than 40%. Other methods used to carry out the deprotection of **9** were entirely unsuccessful. Attempted hydrolysis of **9** with HCl, with HCl in THF solution, or with CF_3CO_2H was unsuccessful, as was attempted hydrolysis with pyridinium *p*-toluenesulfonate (0.33, 0.66, 1.0, 1.5, and 2.0 g equiv.) and with *p*-toluenesulfonic acid in acetone at reflux temperature for 24 h. Hydrolysis with dilute sulfuric acid and cerium ammonium nitrate was successful, but the product could not be isolated since it could not be separated from the other water-soluble solids.

The unlabeled aminohydroxyacetone (**10**) was employed in two displacement experiments to test whether the compound serves as an intermediate in the biosynthesis of vitamin B_6 from glucose in yeast, as it does in *E. coli* (1).

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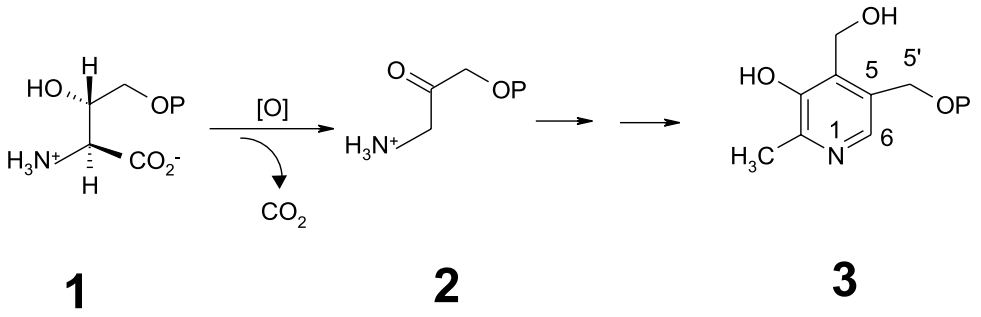
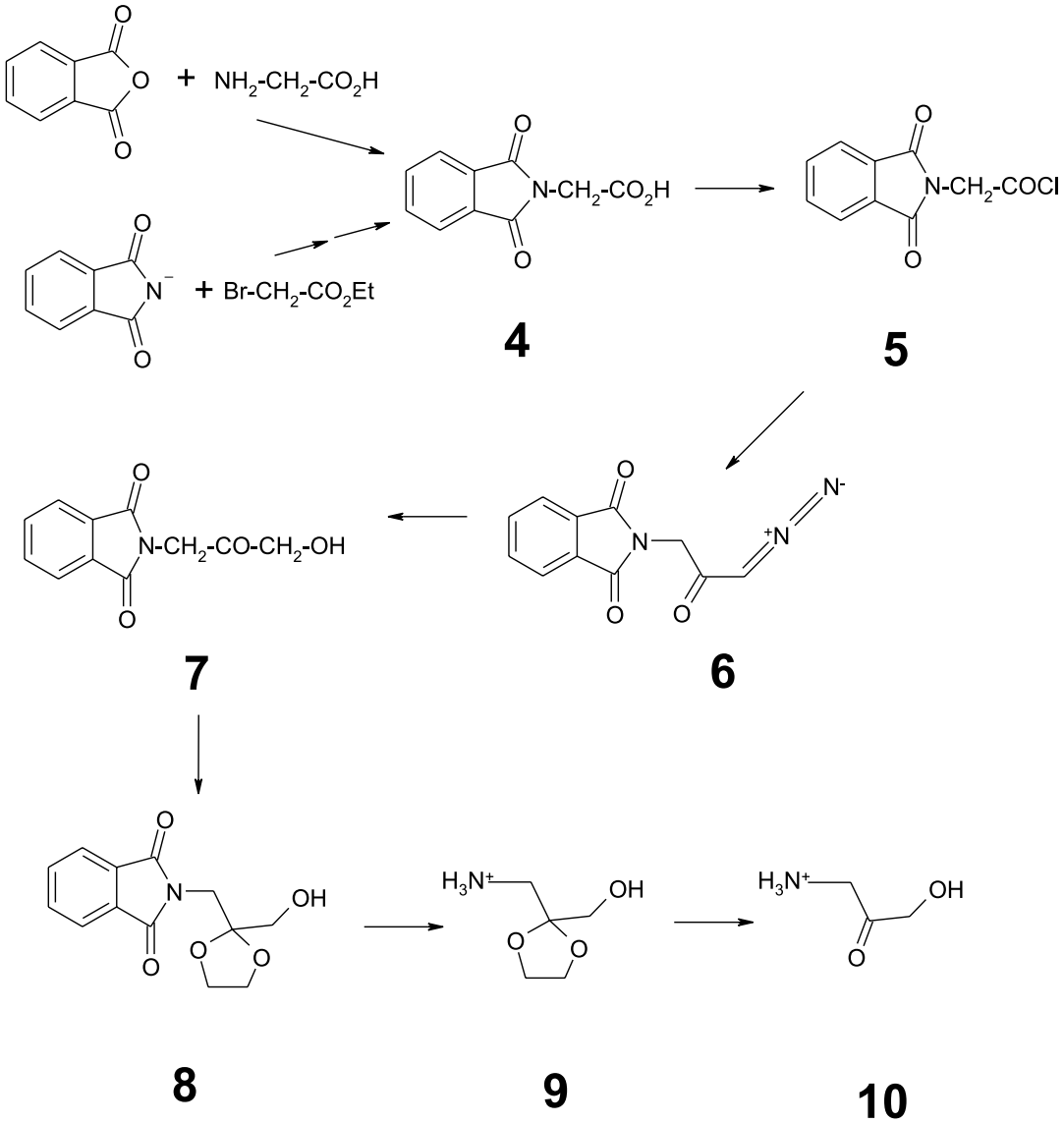
Scheme 1. Biosynthetic origin, in *E. coli*, of the C_3N unit N-1,C-6,5,5′ of pyridoxine phosphate.



1 **2** **3**

Scheme 2. Synthesis of 3-amino-1-hydroxyacetone.



Incorporation of label from [$^{13}C_6$]glucose into pyridoxamine was not displaced by aminohydroxyacetone (**10**), either in *Saccharomyces cerevisiae* or in *Candida utilis* (5). This result made it unlikely that incorporation of a label from a sample of this compound into vitamin B_6 would be observed in these yeasts. The preparation of bond-labeled samples of aminohydroxyacetone was therefore not pursued.

Experimental

N-Phthaloylglycyl chloride (5) (18)

Phthaloylglycine (**4**) (15.4 g, 75 mmol) was suspended in thionyl chloride (21 mL, 40.2 g, 336 mmol), and the mixture was refluxed until a clear solution was obtained (ca. 35 min). Excess thionyl chloride was pumped off in vacuo,

and the residue solidified to yield the product (**5**) as a light yellow crystalline mass. mp 85 to 86 °C (lit. (18) value mp 84 to 85 °C). Yield 16.7 g, 99%. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.93–7.89 (m, 2H), 7.80–7.76 (m, 2H), 4.82 (s, 2H). ^{13}C NMR (75.5 MHz) δ: 169.0, 166.6, 134.6, 131.5, 123.9, 47.5.

1-Diazo-3-phthalimidopropan-2-one (6) (18)

Phthaloylglycyl chloride (**5**) (10.7 g, 48 mmol) in 500 mL dry ether was treated with excess diazomethane (generated from 49 g methylnitronitrosoguanidine in 500 mL dry ether, adding 112 mL 40% KOH). The product crystallized from the ether solution after being kept at room temperature overnight. It was recrystallized from ethyl acetate. mp 163–165 °C (with decomposition (decomp.)) after sintering from 158 °C (lit. (18) value mp 168 °C (decomp.)). Yield 11.0 g (98%). IR (KBr pellet) (cm^{-1}) ν: 2128, 1774, 1733, 1629. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.88–7.86 (m, 2H), 7.76–7.74 (m, 2H), 5.40 (s, 1H), 4.44 (s, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 186.5, 167.6, 134.2, 132.0, 123.6, 53.8, 44.1. MS (CI, NH_3) *m/z* (%): 247 (70, [M + NH_4^+]), 202 (100, [M – N_2 + H^+]). MS (DEI) *m/z* (%): 201 (43, [M – N_2^+], 160 (15, [M – $COCHN_2^+$]).

1-Hydroxy-3-phthalimidopropan-2-one (7)

1-Diazo-3-phthalimidopropan-2-one (**6**) (10.9 g, 47.6 mmol) was suspended in dilute sulfuric acid (20% volume fraction) and stirred at 50 °C for 3 h until all the solid had gone into solution. The mixture was then extracted with ethyl acetate, and the solution was dried over $CaCl_2$. The solvent was removed, and the product was recrystallized from ethanol. Yield 9.3 g (82%). mp 119–121 °C (lit. (18) value mp 121 °C, rising to 142 °C on recrystallization). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.91–7.87 (m, 2H), 7.78–7.76 (m, 2H), 4.59 (s, 2H), 4.45 (s, 2H), 2.50 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 202.4, 167.5, 134.4, 131.9, 123.7, 66.8, 43.5.

2-Hydroxymethyl-2-phthalimidomethyl-1,3-dioxolane (8)

To a soluton of (**7**) (8.5 g, 39 mmol) in 500 mL toluene was added ethylene glycol (19.5 g, 310 mmol) and *p*-toluenesulfonic acid monohydrate (0.28 g, 2 mmol). The mixture was refluxed using a Dean–Stark trap to remove water. After 5 h, the mixture was allowed to cool to room temperature and was then concentrated. Purification by flash column (diethyl ether, 100%) gave the product (**8**). Yield 7.9 g, 77%. mp 98–100 °C (lit. (20) value mp 114–117 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.84–7.80 (m, 2H), 7.72–7.67 (m, 2H), 4.13–3.97 (m, 4H), 3.85 (s, 2H), 3.49 (s, 2H), 2.98 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 168.4, 134.1, 131.6, 123.4, 108.0, 65.3, 63.6, 38.8.

2-Hydroxymethyl-2-aminomethyl-1,3-dioxolane hydrochloride (9)

To a solution of the ketal (**8**) (7.5 g, 28.5 mmol) in 500 mL ethanol was added hydrazine monohydrate (3 mL) in ethanol (350 mL), and the mixture was allowed to stand at room temperature for 36 h. The mixture was then refluxed for 7 h, and the solvent was evaporated in vacuo to dryness. The residue was suspended in 1 mol L^{-1} HCl (300 mL), and the mixture was cooled to 0 °C, allowed to stand for 1 h, and filtered. The solid was washed with a little dilute HCl, and the filtrate was evaporated at 40 °C under reduced pressure to a thick syrup. Addition of methanol, followed by diethyl ether gave the product (**9**) as a crystalline solid. mp. 175–178 °C. Yield 4.2 g, 87%. ^{1}H NMR (200 MHz, D_2O) δ: 4.00 (s, 4H), 3.46 (s, 2H), 3.18 (s, 2H). ^{13}C NMR (75.5 MHz, D_2O) δ: 106.4, 65.8, 61.9, 41.5.

3-Amino-1-hydroxypropan-2-one (3-amino-1-hydroxyacetone) hydrochloride (10)

The ketal (**9**) (2.0 g, 12 mmol) (MW 169.5) was suspended in aqueous acetonitrile (5%, 100 mL). Dowex 50W-X8, 20–50 mesh (20 g) was added, and the mixture was refluxed for 5 h. The solvent was filtered off; the resin was applied to a column, and the column was eluted with 2 mol L^{-1} HCl. The eluate was evaporated in vacuo at 40 °C, and the residue was recrystallized from ethanol–ether to give the product. Yield 1.38 g, 93%. The procedure was repeated on a larger scale, when 3.3 g product (95%) was obtained from 4.85 g (29.1 mmol) ketal (**9**). mp 136 to 137 °C. (lit. (6) value mp 136 to 137 °C; lit. (8) value mp 134–136 °C; lit. (7) value mp 139 °C). ^{1}H NMR (200 MHz, D_2O) δ: 4.37 (s, 2H), 4.04 (s, 2H). ^{13}C NMR (75.5 MHz, D_2O) δ: 206.6, 65.7, 44.3.

Acknowledgments

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