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An Efficient Synthesis of δ-Aminolevulinic Acid (ALA) and Its Isotopomers

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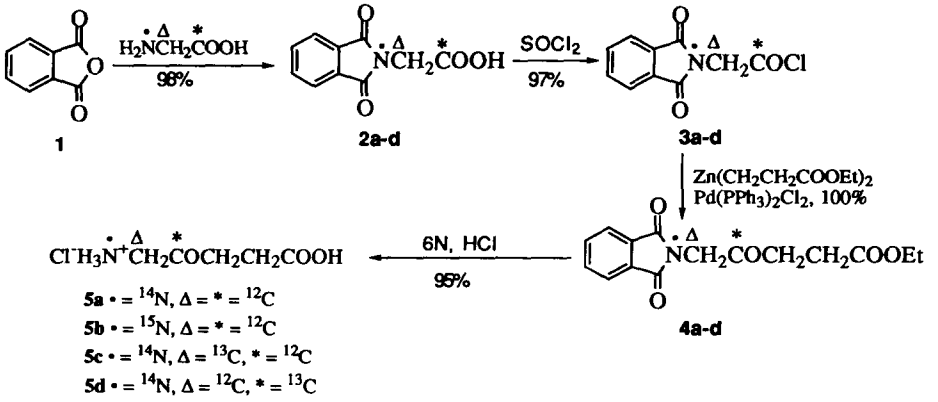
Abstract: A new and improved synthesis of ^{13}C-4-, ^{13}C-5- and ^{15}N-δ-aminolevulinic acid (ALA), with 90% overall yield in 4 steps from labelled glycine, is described.

δ-Aminolevulinic acid **5** (ALA) is the first common precursor in the tetrapyrrole biosynthetic pathway, leading to the hemes, chlorophylls, vitamin B_{12} and other tetrapyrroles. ALA is being developed as an insecticide and herbicide,[1] while its isotopomers regioselectively labelled with ^{13}C and ^{15}N have been widely used for the elucidation of the biosynthesis and metabolism of the tetrapyrrole family of natural products.[2] There have been several reports concerning the synthesis of ALA,[3a-h] but these methods suffer from the disadvantages of labour intensive multi-step routes, low yields and inconvenient purification, resulting in high costs for ALA in both labelled and unlabelled forms. Herein we report a new, efficient approach to the synthesis of ^{13}C-4-, ^{13}C-5- and ^{15}N-ALA, starting from labelled ^{13}C-1-, ^{13}C-2- or ^{15}N-glycine, respectively, which is also adaptable to the large scale preparation of the unlabelled amino acid.

As shown in Scheme 1, our synthetic strategy for the preparation of the target **5a-d** is based on the palladium-catalyzed coupling of the amino protected acyl chloride **3a-d** with zinc homoenolate of ethyl propionate, followed by deprotection of the phthalyl group. The synthesis of ^{13}C-4- ALA is given as an example. ^{13}C-1 labelled glycine was reacted with phthalic anhydride to give the amino protected acid **2d** in 98% yield. Treatment of compound **2d** with thionyl chloride afforded the acid chloride **3d** in 97% yield. The key step is the formation of δ-phthalimidolevulinic acid ethyl ester **4d**,[5] which was obtained in quantitative yield from the palladium-catalyzed coupling reaction of acid chloride **3d** with the zinc homoenolate prepared

Scheme 1



according to a published procedure.[4] Finally, the phthalyl protecting group, phthalyl, was removed by the hydrolysis of **4d** with 6 N HCl to give desired product **5d** in 96% yield. The spectral data (^{1}H, ^{13}C-NMR) for synthetic **5d** are in full agreement with those reported previously.[3c]

The above methology has been applied successfully to the syntheses of ^{13}C-5-(**5c**) and ^{15}N-ALA (**5b**), starting from ^{13}C-2- and ^{15}N-glycine respectively, with the same overall yields.

In summary, we have devised an efficient, reproducible, synthesis of ALA with overall 90% yield which is the most efficient preparation of this key amino acid so far recorded.

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5. Preparation of δ-phthalimidolevulinic acid ethyl ester **4d**: To a crude solution of the zinc homoenolate prepared from $ZnCl_2$ (1.32 g, 9 mmol) and ((1-ethoxylcyclopropyl)oxyl)-trimethylsilane (3.4 g, 19 mmol) were added at 0°C CH_3CONMe_2 (1.7 g, 2 mmol), $Pd(PPh_3)_2Cl_2$ (45 mg, 0.065 mmol) and ^{13}C-1-phthalimidoacetyl chloride **3d** (1.4 g, 6.5 mmol). After 1 h at 0°C, the reaction was continued for another 2 h at room temperature. Evaporation of the solvent in vacuo gave a residue which was dissolved in CH_2Cl_2 (100 ml). The resulting solution was washed with water (50 ml) and saturated NaCl (50 ml). The organic layer was separated, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was recrystallized from ethanol/n-hexane to give pure **4d** in 100 % yield. ^{1}H-NMR δ 7.80 (AA'BB', 4H, H-Ph), 4.56 (d, ^{2}J = 4.0, 2H, $NCH_2{}^{13}CO$), 4.14 (q, ^{3}J = 7.2, 2H, OCH_2CH_3), 2.84 (m, 2H, $^{13}COCH_2CH_2$), 2.65 (m, 2H, $^{13}COCH_2CH_2$), 1.26 (t, ^{3}J = 7.2, 3H, CH_2CH_3); ^{13}C-NMR δ 200.7 (^{13}CO), 172.2 (COO), 168.4 (COO), 134.2, 132.1, 123.6, 60.9 (OCH_2), 46.5 (d, J = 39.7, $NCH_2{}^{13}CO$), 34.5 (d, J = 40.8, $^{13}COCH_2$), 27.8 ($^{13}COCH_2CH_2$), 14.1 (CH_3). HRMS(FAB) Calcd for $C_{14}{}^{13}CH_{15}NO_5$ (M^++1) 291.1062, Found 291.1065.

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