Convenient Syntheses of δ-Aminolevulinic Acid

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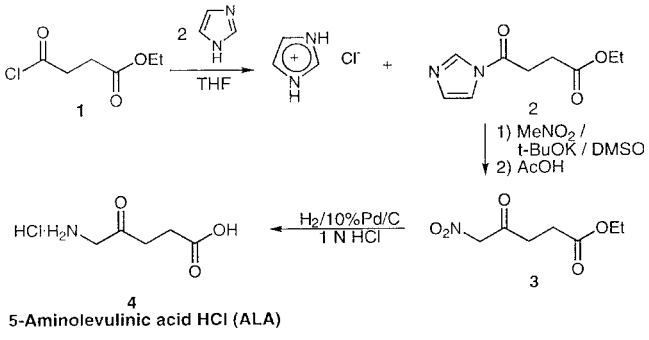
Abstract: Two convenient procedures for the synthesis of δ-aminolevulinic acid (5-ALA) are described.

Key words: oximation, hydrogenation, decarboxylation, hydrolysis

δ-Aminolevulinic acid (5-ALA) involved in heme biosynthesis, has been reported to be a precursor for protoporphyrin IX and is currently undergoing clinical trials as an agent for photodynamic therapy (PDT).[1–4]

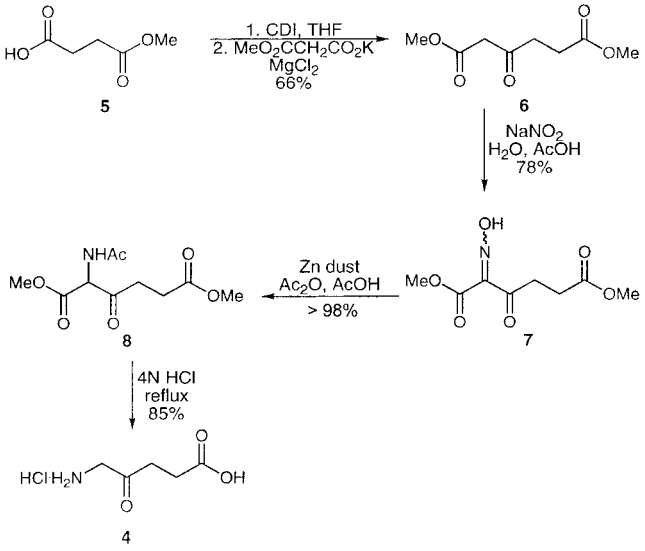
Although various synthetic procedures for 5-ALA have been described in the literature[5–21] as well as in patents, it still is a relatively expensive reagent (see Sigma Catalog). Based on analogous investigations to those dealing with the synthesis of the vitamers of biotin,[22] we developed the following two convenient synthetic procedures for 5-ALA, that neither require expensive reagents nor include difficult purification steps.

α-Nitro ketone ester **3** (Scheme 1) was prepared by an analogous procedure to that described earlier.[22,23] Selective reduction of aliphatic nitro groups, in particular in the presence of other sensitive functionalities, has been reported to be complicated.[24] Indeed, our attempts to reduce the nitro group by transfer-hydrogenation, using HCO_2NH_4/10%Pd-C failed.[25] However, **3** underwent facile reduction and concomitant hydrolysis under aqueous acidic catalytic hydrogenation conditions to give 5-ALA·HCl **4** in 94% yield.[26]



Scheme 1

In the second approach, oximation of the β-keto ester **6**, obtained from succinic acid mono-ester **5**, gave **7** as a mixture of *Z* and *E*-isomers. Reduction and in situ acetylation of **7** gave amide **8**[27] that underwent acid-catalyzed hydrolysis and decarboxylation yielding the desired 5-ALA.



Scheme 2

Ethyl 4-(Imidazol-1-yl)-4-oxobutyrate (2)

To a well-stirred solution of ethyl succinyl chloride **(1)** (98% purity, 1.04 g, 6 mmol) in anhyd THF (15 mL), imidazole (0.82 g, 12 mmol) was added. The solution was stirred at r.t. for 2 h. The precipitate was filtered and washed with Et_2O. The filtrate was evaporated to give the desired imidazole **2** as a white solid; yield: 1.19 g (quantitative).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.28 (t, 3H, *J* = 7.2 Hz, OCH_2*Me*), 2.83 (t, 2H, *J* = 6.5 Hz, CH_2), 3.20 (t, 2H, *J* = 6.5 Hz, CH_2), 4.18 (q, 2H, *J* = 7.1 Hz, O*CH*$_2$Me), 7.12 (s, 1H, CH), 7.51 (t, 1H, *J* = 1.5 Hz, CH), 8.22 (bs, 1H, CH).

^{13}C NMR (300 MHz $CDCl_3$): δ = 14.14 (OCH_2*Me*), 28.06 (*C*H_2CO_2Et), 30.21 (*C*H_2CO), 61.16 (O*C*H_2Me), 116.05 (CH), 131.07 (CH), 136.18 (CH), 168.35 (CON), 171.73 (*C*O_2Et).

MS (CI, CH_4): *m/z* (%) = 197 (MH^+, 2), 129 ($MH^+ - C_3H_3N_2$, 100), 101 ($MH^+ - C_5H_8N_2$, 62).

HRMS (CI, CH_4): calcd for $C_9H_{13}N_2O_3$ (MH^+) 197.0926 found 197.0750.

Ethyl 5-Nitro-4-oxopentanoate (3)

To an ice-cold solution of $MeNO_2$ (0.75 g, 12 mmol) in DMSO (10 mL), under N_2, t-BuOK (1.13 g, 10 mmol) was added. After stirring the suspension at 0 °C for a few min, a solution of **2** (1.96 g, 10 mmol) in DMSO (10 mL) was added. The dark-orange mixture was stirred at r.t. for 48 h. The mixture was poured into water (20 mL) and was extracted with Et_2O (2 x 15 mL). The aqueous layer was

acidified with concd HCl to pH 4–5, and was extracted with EtOAc (5 x 25 mL). The organic layer was washed with brine (2 x 20 mL), dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography using hexane/EtOAc 2:1 as eluent (R_f = 0.41). The product **3** was obtained as a yellow oil; yield: 1.14 g (60%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.26 (t, 3H, *J* = 7.1 Hz, OCH_2*Me*), 2.72, 2.83 (AA'BB' system, 4H, CH_2CH_2), 4.15 (q, 2H, *J* = 7.2 Hz, O*C*H_2Me), 5.39 (s, 2H, CH_2NO_2).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 14.12 (OCH_2*Me*), 28.03 (*C*H_2CO_2Et), 34.92 (*C*H_2CO), 61.20 (O*C*H_2Me), 83.30 (CH_2NO_2), 171.94 (*C*O_2Et), 195.15 (CO).

MS (CI, CH_4): *m/z* (%) = 190 (MH^+, 19), 129 ($MH^+ - CH_3NO_2$, 100).

HRMS (CI, CH_4): calcd for $C_7H_{12}NO_5$ (MH^+) 190.0175 found 190.0750.

Dimethyl 3-Oxohexanedioate (6)[28]

To a solution of 5 (3.3 g, 25 mmol) in anhyd THF (35 mL) under N_2, CDI (4.86 g, 30 mmol) was added portionwise. After stirring the mixture at r.t. for 1 h, $MgCl_2$ (2.38 g, 25 mmol) and monomethyl malonate potassium salt (3.9 g, 25 mmol) were added at once. The mixture was stirred at 35 °C overnight. The resulting slurry was filtered and the filtrate was evaporated. The residue was dissolved in EtOAc (20 mL) and 1 N HCl (20 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL). The organic layers were washed with 5% $NaHCO_3$ (2 x 20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$) and evaporated. The product was purified by distillation 140 °C/0.5 Torr to give a colorless liquid; yield: 3.10 g (66%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.63 (t, 2H, *J* = 6.5 Hz, *C*H_2CO_2Me), 2.87 (t, 2H, *J* = 6.5 Hz, CH_2CO), 3.52 (s, 2H, $COCH_2CO$), 3.68 (s, 3H, OMe), 3.75 (s, 3H, OMe).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 27.70 (*C*H_2CO_2Me), 37.42 (*C*H_2CO), 49.04 (CO*C*H_2CO), 51.92 (OMe), 52.43 (OMe), 167.43 (*C*O_2Me), 172.85 (*C*O_2Me), 200.93 (CO).

MS (CI, NH_3): *m/z* (%) = 206 (MNH_4^+, 100), 189 (MH^+, 44)

HRMS (DCI, CH_4): calcd for $C_8H_{13}O_5$ (MH^+) 189.0763 found 189.0733.

Dimethyl 2-(Hydroxyimino)-3-oxohexanedioate (7)

To an ice-cold solution of **6** (1.88 g, 10 mmol) in glacial AcOH (5 mL), a solution of $NaNO_2$ (0.83 g, 12 mmol) in water (10 mL) was added dropwise over a period of 1 h, at such a rate that the temperature did not rise above 10 °C. Additional water (15 mL) was added and the mixture was allowed to reach r.t., and was stirred overnight. The solution was extracted with EtOAc (3 x 25 mL). The organic layer was washed with water (3 x 30 mL), 5% $NaHCO_3$ (3 ↔ 25 mL), and brine (3 x 25 mL), dried ($MgSO_4$), filtered and evaporated to give **7** as a yellowish solid; yield: 1.7 g (78%); mp 84–86 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.70 (t, 2H, *J* = 6.8 Hz, C*H*$_2$CO$_2$Me), 3.18 (t, 2H, *J* = 6.8 Hz, CH_2CO), 3.72 (s, 3H, OMe), 3.89 (s, 3H, OMe), 10.52 (bs, 1H, OH).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 27.33 (*C*H_2CO_2Me), 32.50 (*C*H_2CO), 52.30 (OMe), 52.75 (OMe), 150.13 (CN–OH), 161.08 (*C*O_2Me), 174.16 (*C*O_2Me), 193.66 (CO).

MS (CI, NH_3): *m/z* (%) = 235 (MNH_4^+, 100), 218 (MH^+, 11.3).

HRMS (DCI, CH_3): calcd for $C_8H_{12}NO_6$ (MH^+) 218.0664 found 218.0647.

Dimethyl 2-(Acetylamino)-3-oxohexanedioate (8)

To a solution of **7** (1.30 g, 6 mmol) and Ac_2O (3.67 g, 36 mmol) in glacial AcOH (20 mL), Zn dust (3.12 g, 48 mmol) was added over a period of 1 h. The mixture was stirred at r.t. and after 24 h, TLC indicated that the reaction was complete. The mixture was filtered and the cake was washed with EtOAc (40 mL). The filtrate was evaporated to give **8** as yellowish oil; yield: 1.47 g (~100%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.08 (s, 3H, COMe), 2.66 (m, 2H, C*H*$_2$CO$_2$Me), 2.94 (m, 1H, CH_2CO), 3.12 (m, 1H, CH_2CO), 3.67 (s, 3H, OMe), 3.84 (s, 3H, OMe), 5.33 (d, 1H, *J* = 6.6 Hz, CH), 6.77 (bd, 1H, *J* = 6.6 Hz, NH).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 22.69 (*Me*CONH), 27.69 (*C*H_2CO_2Me), 35.38 (*C*H_2CO), 51.97 (OMe), 53.42 (OMe), 62.51 (CH), 166.57 (MeCONH), 169.94 (*C*O_2Me), 172.55 (*C*O_2Me), 199.74 (CO).

MS (CI, NH_3): *m/z* (%) = 263 (MNH_4^+, 89), 246 (MH^+, 100).

HRMS (DCI, CH_4): calcd for $C_{10}H_{16}NO_6$ (MH^+) 246.0977 found 246.0980.

5-Amino-4-oxopentanoic Acid Hydrochloride (4)[8]

Method A: A suspension of **3** (0.37 g, 2 mmol) in 1 N HCl (10 mL), was hydrogenated at 22 psi over 10% Pd/C (0.19 g) overnight. The catalyst was filtered and washed with water (15 mL). The solvent was evaporated to give the desired product **4** as a yellowish solid; yield: 0.314 g (94%).

Method B: A suspension of **8** (0.49 g, 2 mmol) in 4 N HCl (6 mL) was refluxed for 4 h. To the resulting dark yellow solution active charcoal was added and the suspension was filtered. The filtrate was evaporated to give **4** as a white crystalline material; yield: 0.28 g (85%).

^{1}H NMR (300 MHz, D_2O): δ = 2.73 (m, 2H, C*H*$_2$CO$_2$H), 2.91 (t, 2H, *J* = 6 Hz, CH_2CO), 4.14 (s, 2H, C*H*$_2$NH$_3^+$).

^{13}C NMR (200 MHz, D_2O): δ = 27.97 (*C*H_2CO_2H), 34.92 (*C*H_2CO), 47.65 ($CH_2NH_3^+$), 177.33 (CO_2H), 204.68 (CO).

MS (CI, NH_3): *m/z* (%) = 132 (MH^+, 17).

HRMS (DCI, CH_4): calcd for $C_5H_{10}NO_3$ (MH^+) 132.0660 found 132.0649.

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