Synthesis of 3-Substituted 2,3-Dehydroprolines: Oxidative Decarboxylation of Ethyl Hydrogen Acetoamidomalonate Derivatives

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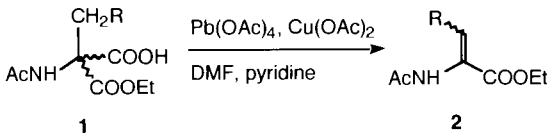
A new synthetic method for α,β-dehydroamino acid derivatives have been accomplished via lead(IV) tetraacetate oxidation of ethyl hydrogen acetoamidomalonate derivatives in the presence of copper(II) acetate. Four 3-substituted 2,3-dehydroprolines have been synthesized by this oxidative decarboxylation.

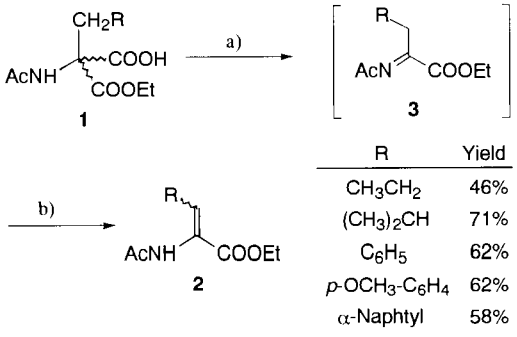
Proline is a well-known means of inducing conformational constraints into peptides.[1] In this view, many synthetic effort has been reinforced in the preparation of 3-substituted prolines, which have been viewed as conformationally constrained analogues of natural α-amino acids bridged by an ethylene group between α-nitrogen and the β-carbon.[2] Despite a growing interest in this type of α-amino acids, there are as yet very few practical methods for their preparation in optically pure form.[2c,3] A variety of optically active unnatural amino acids has been prepared by enantioselective hydrogenation of α,β-dehydroamino acids.[4] Therefore, we intended to synthesize 3-substituted 2,3-dehydroprolines as precursors for asymmetric synthesis of 3-substituted prolines.

In the course of the study, we found ethyl hydrogen acetoamidomalonates **1** can be oxidatively decarboxylated with lead(IV) tetraacetate in the presence of copper(II) acetate[5] to give α,β-dehydroamino acid derivatives **2** as depicted in the scheme below. Here we report the oxidative decarboxylation of acetoamidomalonate derivatives and novel synthesis of 3-substituted dehydroprolines by this method.



1 **2**

Ethyl hydrogen acetoamidomalonate derivatives **1** were synthesized by standard alkylation of diethyl acetoamidomalonate[6] followed by saponification with equimolar amount of sodium hydroxide. Heating a solution of the half-ester to 80 °C for 2 h, racemic *N*-acetyl amino acid ethyl ester was obtained in almost quantitative yield by spontaneous decarboxylation. However, the mono acid was treated with lead(IV) tetraacetate in the presence of copper(II) acetate, α,β-dehydroamino acid derivative was formed in 50–70% yield. When the R group is alkyl, a mixture of **1** and *N*-acetylimino compound **3** was obtained. Heating the reaction mixture at 90 °C for 12 h, the latter isomerized to the former to give sole product (Scheme 1).[7]



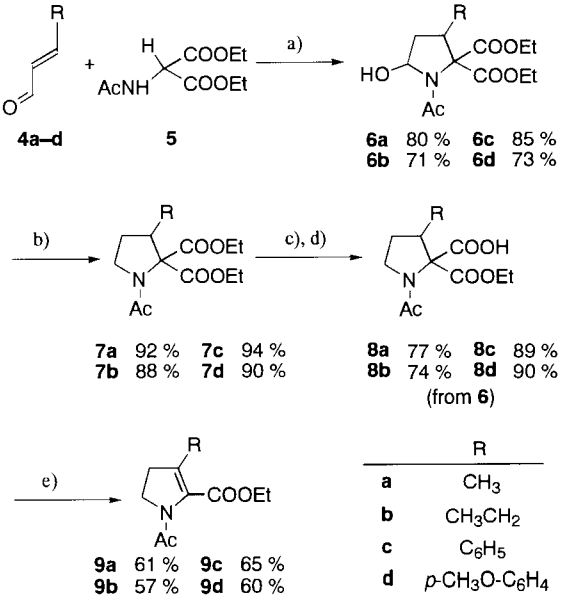
1 **3** **2**

R	Yield
CH_3CH_2	46%
$(CH_3)_2CH$	71%
C_6H_5	62%
p-OCH_3-C_6H_4	62%
α-Naphtyl	58%

Scheme 1. Oxidative decarboxylation of ethyl hydrogen acetoamidomalonates; a) $Pb(OAc)_4$, $Cu(OAc)_2$, pyridine, DMF; b) isomerization at 90 °C, 4 h.

This method is especially useful for the synthesis of 2,3-dehydroproline derivatives. Cyclic dehydroamino acids are difficult to prepare by other methods which utilize condensation strategy.[7,8] However, cyclic acetoamidomalonate compounds for this procedure can be easily prepared according to the schemes outlined by Chung et al., which entail condensation of an acetoamidomalonate to the appropriate α,β-unsaturated aldehyde, followed by a 5-deoxgenation reaction using triethylsilane. Thus, after saponification of the diesters with one equivalent of sodium hydroxide, half-esters oxidatively decarboxylated by this method in satisfactory yield (Scheme 2).[9] In this way, four 3-substituted 2,3-dehydroprolines have been prepared, which have substituent corresponding to phenylalanine, tyrosine, valine, and isoleusine residues, respectively.

Synthetic procedures for the preparation of **6d-9d** are as



R	
a	CH_3
b	CH_3CH_2
c	C_6H_5
d	*p*-CH_3O-C_6H_4

Scheme 2. Synthesis of 3-substituted 2,3-dehydroprolines; a) EtONa, EtOH; b) Et_3SiH, trifluoriacetic acid, CH_2Cl_2, 12h; c) 1 equiv. $NaOH/H_2O$; d) 1N HCl; e) $Pb(OAc)_4$, $Cu(OAc)_2$, pyridine, DMF.

follows : sodium (0.12 g, 5.22 mmol) was dissolved in a stirred solution of diethyl acetoamidomalonate (10.86 g, 50.00 mmol) in anhydrous ethanol (60 mL) at room temperature. The reaction mixture was cooled to 0 ℃, and a solution of **4d** (8.30 g, 51.2 mmol) dissolved in 20 mL of EtOH was then added dropwise. The resulting suspension was allowed to warm to room temperature. After stirring for 12 h at ambient temperature, the reaction was quenched with 1 mL of acetic acid. The solution was concentrated in vacuo, and the resulting residue was taken up in EtOAc and washed with water. The organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. The yellow residue was crystallized from *n*-hexane/ether to give 10.41 g of **6d** as colorless crystals. Chromatography of the filtrate over silicagel (EtOAc, R_f 0.55) afforded an additional product (3.49 g, total 73.3% yield).

To a chilled solution of **6d** (3.80 g, 10.01 mmol) and triethylsilane (2.0 mL, 12 mmol) in 15 mL of CH_2Cl_2 was added trifluoroacetic acid (2 mL) dropwise with stirring over 5 min. After stirring for 12 h at room temperature, the solution was washed with saturated aqueous $NaHCO_3$ solution until all the TFA was neutralized. The organic phase was dried over Na_2SO_4 and concentrated to give 5.36 g of pale yellow oil containing Et_3SiOH, which was sufficiently pure for the subsequent reaction. A pure sample was obtained as an colorless oil after flash chromatography (SiO_2, *n*-hexane-AcOEt, 3.29 g, 90.4%).

Crude diester **7d** (starting from 17.42 mmol of **6d**) was suspended in 10 mL of water, then added aqueous NaOH dropwise with external cooling, and the solution was stirred at room temperature overnight. The resultant solution was extracted once with benzene and then acidified to pH 2 with 1 N HCl. The aqueous solution was extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated under vacuum. The residue was crystallized from ether/petroleum ether to give **8d** as colorless granules (5.25 g, 89.9% from **6d**).

To stirred solution of **8d** (1353.0 mg, 4.03 mmol), copper(II) acetate (0.5 mmol), dry pyridine (0.2 mL) and anhydrous DMF (15 mL) at 0 ℃ was added lead(IV) tetraacetate (2290.0 mg, 5.15 mmol). The reaction mixture was stirred at room temperature under nitrogen atmosphere. As the color of the solution turns green, the mixture was gradually heated up to 90 ℃ for 4 h. The solution was cooled to room temperature, poured onto 20 mL of 1 N HCl, then extracted with 50 mL of dichloromethane. The organic layer was successively washed with 0.5 N sodium bicarbonate, water, and brine. After drying over Na_2SO_4, evaporation of the solvent and chromatographic separation gave **9d** (703.4 mg, 60.3%). Recrystallization from AcOEt-ether gave colorless needles

In conclusion, this oxidative decarboxylation allows novel synthesis of dehydroamino acid, especially cyclic dehydroamino acids, by utilizing classical diethyl acetoamidomalonate procedure. Further studies for enantioselective hydrogenation of 3-substituted dehydroprolines are now in progress and will be reported in elsewhere.

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9 Satisfactory analytical and spectroscopic data have been obtained for the new dehydroproline derivatives. **9a**: colorless oil, ^{1}H-NMR ($CDCl_3$) δ 4.31 (q, *J* = 6.8 Hz, 2 H, Et), 3.91 (br t, *J* = 8.6 Hz, 2 H, 5-H), 2.65 (br t, *J* = 8.6 Hz, 2 H, 4-H), 2.08 (s, 3 H, Ac), 1.91 (s, 3 H, Me), 1.31 (t, *J* = 6.8 Hz, 3 H, Et). HR-MS, *m/e* calcd for $C_{10}H_{16}NO_3$ (M^++H) 198.1130, found 198.1128. **9b**: colorless oil, ^{1}H-NMR ($CDCl_3$) δ 4.31 (q, *J* = 6.8 Hz, 2 H, Et), 3.91 (br t, *J* = 8.6 Hz, 2 H, 5-H), 2.68 (br t, *J* = 8.6 Hz, 2 H, 4-H), 2.30 (br q, *J* = 7.3 Hz, 2 H, Et), 2.05 (s, 3 H, Ac), 1.33 (t, *J* = 6.8 Hz, 3 H, Et), 1.05 (t, *J* = 7.3 Hz, 3 H, Et). HR-MS, *m/e* calcd for $C_{11}H_{18}NO_3$ (M^++H) 212.1287, found 212.1326. **9c**: colorless needles (AcOEt-ether), ^{1}H-NMR ($CDCl_3$) δ 7.35-7.25 (m, 5 H, ArH), 4.32 (q, *J* = 6.8 Hz, 2 H, Et), 4.02 (br t, *J* = 8.7 Hz, 2 H, 5-H), 3.14 (br t, *J* = 8.7 Hz, 2 H, 4-H), 2.11 (s, 3 H, Ac), 1.30 (t, *J* = 6.8 Hz, 3 H, Et). HR-MS, *m/e* calcd for $C_{15}H_{18}NO_3$ (M^++H) 260.1287, found 260.1247. **9d**: colorless needles (AcOEt-ether), ^{1}H-NMR ($CDCl_3$) δ 7.28 (d, *J* = 8.8 Hz, 2 H, ArH), 6.85 (d, *J* = 8.8 Hz, 2 H, ArH), 4.32 (q, *J* = 6.8 Hz, 2 H, Et), 4.00 (br t, *J* = 8.7 Hz, 2 H, 5-H), 3.83 (s, 3 H, OMe), 3.10 (br t, *J* = 8.7 Hz, 2 H, 4-H), 2.11 (s, 3 H, Ac), 1.30 (t, *J* = 6.8 Hz, 3 H, Et). HR-MS, *m/e* calcd for $C_{16}H_{20}NO_4$ (M^++H) 290.1392, found 290.1405.