Nonprotein Amino Acids[1]: Preparation of 5-Substituted-2-Aminoadipic Acid Derivatives

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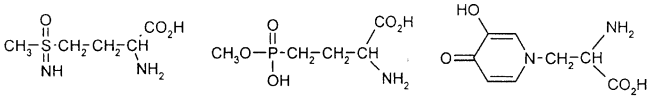
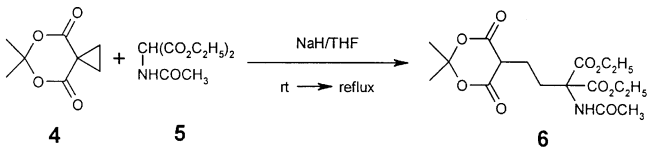
The number and structural types of nonprotein amino acids[2] have increased dramatically over the past few decades. Some of the synthetic amino acids and nonprotein amino acids found in several plants exhibit interesting biological activities. For instance, methionine sulfoxamine (**1**)[3] and phosphinothricin (**2**)[4] serve as herbicides, fluorine containing amino acids as suicide enzyme inhibitor, β-cyanoalanine as neurotoxicant,[5] mimosine (**3**) as rat liver crystathionine synthetase inhibitor,[6] selenium containing amino acids[7] and pipecolic acids as insect feeding deterrent, etc..



1 **2** **3**

In a course of our studies on insecticide with a new mode of action, and enzyme binding study for transglutaminase as well, we needed several derivatives of 5-substituted-2-aminoadipic acids. Here we present an efficient synthetic methodology of preparing 2-aminoadipic acid analogues, hitherto unknown unnatural amino acids.

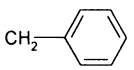
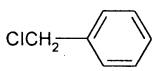
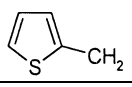
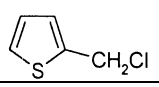
The main idea of this synthesis is to utilize cyclopropane dicarboxylate (**4**)[8] as ⊕ $CH_2CH_2CH_2CO_2H$ synthon and diethyl acetylaminomalonate (**5**)[9] as ⊖ $CH(CO_2H)NH_2$ synthon to prepare key intermediate **6** (Scheme 1).



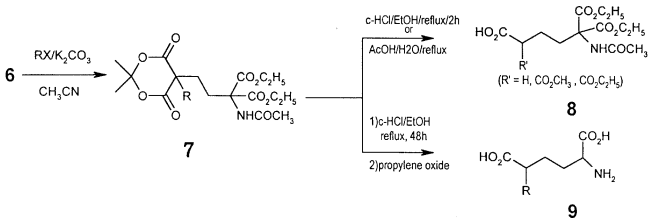
4 **5** **6**

Scheme 1

Table 1. Alkyl/Acylated products **7** from **6**

Entry	Compound	R	Reagent Used	Yield, %[a]
1	**7a**	CH_3	CH_3I	88
2	**7b**	C_2H_5	C_2H_5I	74
3	**7c**			63
4	**7d**	$CH_2CO_2CH_3$	$BrCH_2CO_2CH_3$	95
5	**7e**	$CH_3C{=}O$	CH_3COCl	60
6	**7f**			78

[a]Isolated yield with no optimization.



Scheme 2

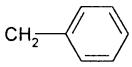
Compound **6** could easily be prepared in 50 g scale in 50-55% yield by treating **4** with **5** under basic condition. However, it is noteworthy that sodium hydride in DME (or THF) should be employed rather than sodium in ethanol for the success of this reaction. The latter and other conditions caused only decomposition of spiral compound **4** with no sign of product formation.

The key intermediate **6** was then alkyl and acylated with various alkyl and acyl halide under very mild condition to provide amino acid precursors **7** in excellent yield (Scheme 2). The results are summarized in Table 1.

With the key intermediate **6** in hand, we next examined the hydrolysis of compounds **7** to generate free amino acids **9** (Scheme 2).

The hydrolysis step is turned out to be highly dependent upon reaction condition. At first, compound **6** (R=H of compound **7**) was utilized to find the optimum hydrolysis condition to obtain the amino acids **9**. When compound **6** was treated with conc.HCl in ethanol for 2h at reflux, only decomposition of the Meldrums acid moiety occurred to give compound **8** (R′= $CO_2C_2H_5$). However, when compound **6** was reacted with conc. HCl in ethanol, heated at reflux for 2 days, concentrated and treated with propylene oxide as an acid scavenger at 0 °C, 2-amino-adipic acid was obtained. This condition was then successfully extended for the preparation of amino acids **9a-9d** from the alkylated

Table 2. Amino Acids **9** derived from the hydrolysis of compounds **7**

Entry	Compound	R	Yield, %[a]
1	**9a**	CH_3	42
2	**9b**	C_2H_5	60
3	**9c**		50
4	**9d**	CH_2CO_2H	21

[a]Isolated yield with no optimization.

compound **7a-7d** in a moderate yield (Table 2). Unfortunately, the acylated compound **7e** and thiophene containing compound **7f** were transformed into 2-aminoadipic acid instead of the desired 5substituted-2-aminoadipic acid under the same reaction condition.

The acylated compound **7e** deserves some mention here. To avoid the deacetylation of compound **7e** during the hydroylsis, several different hydrolysis conditions were attempted with no success. Thus, when compound **7e** was treated with either acetic acid /water or acetic acid/methanol at reflux for various reaction time, compounds **8** (R′=H, CO_2CH_3, respectively) were obtained.

In summary, 5-substituted-2-aminoadipic acids, hitherto unknown 2-aminoadipic acid analogue, were prepared by utilizing readily available starting materials in three steps. It is envisioned that the extension of this synthetic methodology would have further synthetic potentials to prepare other unnatural amino acids containing heterocyclic compounds. The transglutaminase binding study for these synthetic amino acids is currently undergoing.

Experimental Section

^{1}H NMR spectra were recorded either on a JEOL (60 MHz) or on a Varian Gemini 200 (200 MHz) spectrometers. Chemical shifts were internally referenced to TMS and reported in part per million (δ) down field for most compounds. For amino acids, however, the chemical shifts were referenced to HOD (D_2O/NaOD, δ=4.90) and reported in δ value. Mass spectra were measured with Shimadzu QP-1000 Spectrometer. Melting point was determined on an electrically heated Thomas-Hoover capillary melting point apparatus and uncorrected. The progress of the reaction and the purity of all compounds were checked by TLC on precoated glass plate with silica gel 60 F-254 as absorbent. Most of the commercially available starting materials were purchased from Aldrich Chemical Company.

Synthesis of Compound 6. To a suspension of NaH (9 g, 0.3 mol) in THF (600 mL) was added diethyl acetylaminomalonate **5** (65.17 g, 0.3 mol) at 0 °C. After 50 min, compound **4** (17.01 g, 0.1 mol) was added and stirred at 0 °C for 30 min. The reaction mixture was warmed to r.t., and then heated at refluxed for 24 h. The reaction was cooled to r.t., and neutralized with c-HCl (*ca*. 30 mL). The resulting precipitate (NaCl) was removed and the filtrate was concentrated in vacuo to leave slurry which was filtered again to remove unreacted **5**. The final filtrate was filtered through a short celite bed and then concentrated to give the desired product (17.8 g, 46% yield): mp 107-108 °C; ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.30 (t, 6H), 1.80 (s, broad, 6H), 2.00-2.50 (m, 4H), 2.03 (s, 3H), 3.70 (t, 1H), 4.30 (q, 4H), 6.90 (1H).

Synthesis of Compound 7: General Procedure. A solution of compound **6** (1.2 g, 3 mmol), potassium carbonate (0.62 g, 4.5 mmol) and methyl iodide (0.28 mL, 4.5 mmol) in CH_3CN (30 mL) was refluxed for 1h. After cooling to room temperature, the reaction mixture was filtered to remove potassium carbonate. The filtrate was concentrated under reduced pressure, and then the residue was purified by flash column chromatography on silica gel (eluent: 50% ethyl acetate in hexane) to provide product **7a** (1.1 g, 88% yield) as a white solid: mp. 82-83 °C; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.30 (t, 6H), 1.60 (s, 3H), 1.73 (s, 6H), 1.90-2.50 (m, 4H), 2.00 (s, 3H), 4.30 (q, 4H), 6.90 (s, broad, 1H); MS (EI): m/z 401 (M^+). **7b**: mp. 65-66 °C; ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.95 (t, 3H), 1.30 (t, 6H), 1.70 (s, 3H), 1.73 (s, 3H), 2.00 (s, 3H), 1.8-2.3 (m, 4H), 4.30 (m, 6H), 6.80 (s, broad, 1H); MS (EI): m/z 415 (M^+). **7c**: mp. 163-164 °C; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.30 (t, 6H), 1.50 (s, 3H), 1.67 (s, 3H), 2.05 (s, 3H), 1.95-2.13 (m, 4H), 3.30 (s, 2H), 4.30 (q, 4H), 6.85 (s, broad, 1H), 7.15-7.30 (m, 5H); MS (EI): m/z 477 (M^+). **7d**: mp. 184-185 °C; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.25 (t, 6H), 1.90-2.35 (m, 4H), 1.85 (s, 3H), 1.88 (s, 3H), 2.00 (s, 3H), 3.15 (s, 2H), 3.65 (s, 3H), 4.20 (q, 4H), 6.80 (s, broad, 1H); MS: m/z 448 (M^+-18). **7e**: mp. 113-114 °C; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.30 (t, 6H), 1.70 (s, 3H), 1.76 (s, 3H), 2.05 (s, 3H), 2.30 (s, 3H), 2.10-2.35 (m, 4H), 4.30 (q, 4H), 6.85 (s, broad, 1H); MS: m/z 430 (M^+). **7f**: liquid; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.30 (t, 6H), 1.97 (s, 3H), 2.00 (s, 3H); 2.03 (s, 3H), 1.95-2.20 (m, 4H), 3.70 (s, 2H), 4.30 (q, 4H), 6.85-7.30 (m, 4H).

Synthesis of Compound 9: **General Procedure**. A solution of comound **7a** (0.92 g, 2.3 mmol) and c-HCl (6.27 mL, 69 mmol) in ethanol (3 mL) was refluxed for 2 days. The reaction mixture was concentrated *in vacuo*, diluted with ethanol (3 mL), and then propylene oxide (0.5 mL) was added at 0 °C. The resulting solution was stored in a refregerator (3-4 °C) overnight to get white solid, which was filtered and washed with cold ethanol to provide free amine acid **9a** (0.17 g, 42% yield) as a white solid: mp. 148-150 °C; ^{1}H NMR (200 MHz, D_2O/NaOD) δ 0.98 (d, 3H), 1.2-1.5 (m, 4H), 2.20 (m, 1H), 3.15 (m, 1H), 4.90 (HOD); MS: m/z 175 (M^+). **9b**: mp. 153-155 °C; ^{1}H NMR (200 MHz, D_2O/NaOD) δ 0.90 (t, 3H), 1.50-1.70 (m, 6H), 2.25 (m, 1H), 3.30 (m, 1H), 4.90 (HOD); MS: m/z 189 (M^+). **9c**: mp. 149-151 °C; ^{1}H NMR (200 MHz, D_2O/NaOD) δ 1.20-1.30 (m, 4H), 2.30 (s, broad, 1H), 2.58 (s, broad, 2H), 3.00 (s, broad, 1H), 4.90 (HOD), 7.05-7.20 (m, 5H); MS: m/z 233 (M^+-18). **9d**: mp. 133-136 °C; ^{1}H NMR (200 MHz, D_2O/NaOD) δ 1.00-1.30 (m, 4H), 1.85 (s, broad, 1H), 2.15 (broad, 2H), 2.55 (m, broad, 1H), 4.90 (HOD); MS: m/z 201 (M^+-18)

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