# THE ALKYLATION OF METHYL 2-(1-PYRROLYL)ACETATE. A NEW SYNTHETIC METHOD OF α-AMINO ACIDS

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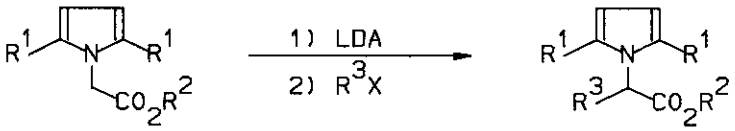
Abstract —— The alkylation of 2-(1-pyrrolyl)acetates was accomplished by the treatment with alkyl halides in the presence of LDA to give 2-(1-pyrrolyl)alkanoates, which were convertible into α-amino acids by ozonolysis.

Previously, we have reported the reaction products and the mechanism of the ozonolysis of various five membered heteroaromatics.[1] In the case of azoles having a nitrogen atom at the 1-position on the ring, the carboxamides were formed in a high yield. By this ring cleavage reaction, 2-(1-pyrrolyl)alkanoic acids were easily converted into α-amino acids, while pyrrole ring was comparably stable under the ordinary reaction conditions. These chemical behaviors of 2-(1-pyrrolyl)-alkanoic acids were utilized for the protecting group of N-terminals in the peptide synthesis.[2] On the other hand, 2-(1-pyrrolyl)alkanoic acids were accepted to be the convertible derivatives of α-amino acids. Therefore, the alkylation of 2-(1-pyrrolyl)acetic acid derivatives into 2-(1-pyrrolyl)alkanoic acid derivatives is of interest in the development of a new synthetic method of α-amino acids.

*The α-methylene group of 2-(1-pyrrolyl)acetic acid derivatives was expected to have* high acidity, since the α-methylene group was bonded to two electron withdrawing groups, a carbonyl group and an aromatic ring. Actually when methyl 2-[1-(2,5-dimethylpyrrolyl)]acetate (**1a**) was treated in deuteriomethanol in the presence of a trace amount of sodium methoxide, α-methylene protons on **1a** were exchanged 78 % with deuterium after 1 h. Further, the similar deuterium exchange of **1a** was observed by the treatment with lithium diisopropylamide (LDA) in tetrahydrofuran, followed by the treatment with deuteriophosphoric acid. From these results, the α-methylene group of 2-[1-(2,5-dimethylpyrrolyl)]acetates exhibited the acidity enough for the metallation by a strong base such as LDA.

In order to alkylate the α-methylene group of 2-[1-(2,5-dimethylpyrrolyl)]acetates,




**1**: $R^1$=Me, $R^2$=Me  **3**: $R^1$=H, $R^2$=Me
**2**: $R^1$=Me, $R^2$=Et  **4**: $R^1$=H, $R^2$=Et

**a**: $R^3$=H  **b**: $R^3$=D  **c**: $R^3$=Me
**d**: $R^3$=Et  **e**: $R^3$=$CH_2Ph$  **f**: $R^3$=$CH_2CO_2Me$

methyl 2-[1-(2,5-dimethylpyrrolyl)]acetate (**1a**) was treated with LDA in tetrahydrofuran, followed by the addition of methyl iodide, to give methyl 2-[1-(2,5-dimethylpyrrolyl)]propionate (**1c**) in a 71 % yield. Similarly, the alkylation reaction on α-methylene of **1a**, ethyl 2-[1-(2,5-dimethylpyrrolyl)]acetate (**2a**),

Table

The Alkylation of 2-(1-Pyrrolyl)acetates

| $R^1$ | $R^2$ | $R^3X$ | Base | Product (Yield %) |
|---|---|---|---|---|
| Me | Me | $D_3PO_4$ | LDA/THF | **1b** (50) |
| Me | Me | MeI | LDA/THF | **1c** (71) |
| Me | Et | MeI | LDA/THF | **2c** (36) |
| Me | Me | EtI | LDA/THF | **1d** (36) |
| Me | Me | i-PrBr | LDA/THF | (0) |
| Me | Me | $PhCH_2Br$ | LDA/THF | **1e** (28) |
| Me | Me | $MeO_2CCH_2Br$ | LDA/THF | **1f** (26) |
| H | Me | MeI | LDA/THF | **3c** (35) |
| H | Me | i-PrBr | LDA/THF | (0) |
| H | Me | $PhCH_2Br$ | LDA/THF | **3e** (6) |
| H | Et | MeI | NaOEt/EtOH | (0) |
| H | Et | MeI | NaH/DMF | **4c** (15) |
| H | Et | $PhCH_2Br$ | NaH/DMF | (0) |

methyl 2-(1-pyrrolyl)acetate (3a) and ethyl 2-(1-pyrrolyl)acetate (4a) with various alkyl halides afforded the corresponding 2-(1-pyrrolyl)alkanoates, as listed in the Table. From the Table, the steric effect of the alkyl halide influenced the yields, especially no product was detected in the case of isopropyl bromide. On the other hand, the alkylation of 4a using sodium hydride or sodium methoxide gave undesirable results.

After all, it was found that the alkylation reaction of the α-methylene group of 2-[1-(2,5-dimethylpyrrolyl)]acetates could take place using LDA as a base. Since the pyrrole ring could be cleaved by ozonolysis to convert into an amino group, this alkylation reaction was regarded as the new synthesis of α-amino acids, although the resulting compounds would be racemates.

## EXPERIMENTAL

### The Proton-Deuterium Exchange Reaction.

To a solution of methyl 2-[1-(2,5-dimethylpyrrolyl)]acetate (1a) in deuteriomethanol was added a trace amount of sodium hydride, and the solution was measured at appropriate intervals by $^1$H-nmr to evaluate the deuterium exchange rate of α-methylene protons of 1a.

### The General Procedure of Alkylation of 2-(1-Pyrrolyl)acetates.

To a solution of lithium diisopropylamide (3 mmol) in tetrahydrofuran (10 ml) prepared by Einhorn's method,[3] a solution of 2-(1-pyrrolyl)acetate (2 mmol) in tetrahydrofuran (3 ml) was added at -20°C, and stirred for 30 minutes. To this solution was added deuteriophosphoric acid or a solution of alkyl halide (10 mmol) in tetrahydrofuran (3 ml), and stirred overnight at room temperature. The mixture was diluted with dilute hydrochloric acid, and extracted with dichloromethane. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and evaporated. The crude product was purified by chromatography on silica gel using benzene-ethyl acetate mixture to yield colorless liquids. The product was identified by the comparison with the authentic sample prepared by the method in the previous paper.[2]

### Methyl 2-[1-(2,5-Dimethylpyrrolyl)]butanoate (1d)

Mp : 46.0-47.0°C; $^1$H-nmr (δ, $CDCl_3$): 0.83 (3H, t, J=7.3 Hz), 1.84-2.51 (2H, m), 2.17 (6H, s), 3.72 (3H, s), 4.58 (1H, dd, J=5.9 and 9.8 Hz), and 5.78 ppm (2H, s); $^{13}$C-nmr (δ, $CDCl_3$): 10.7 (q), 13.3 (q), 24.5 (t), 52.4 (q), 58.5 (d), 106.4 (d), 128.2 (s), and 171.6 ppm (s); Anal. Calcd. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.77; N,

7.17 %. Found: C, 67.87; H, 8.85; N, 7.09 %.

Ethyl 2-[1-(2,5-Dimethylpyrrolyl)]acetate (2a)

$^1$H-Nmr (δ, $CDCl_3$): 1.26 (3H, t, J=7.3 Hz), 2.16 (6H, s), 4.21 (2H, q, J=7.3 Hz), 4.47 (2H, s), and 5.79 ppm (2H, s); $^{13}$C-nmr (δ, $CDCl_3$): 12.3 (q), 14.2 (q), 45.2 (t), 61.4 (t), 105.7 (d), 127.9 (s), and 168.9 ppm (s); Anal. Calcd. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.72 %. Found: C, 66.27; H, 8.24; N, 7.68 %.

Ethyl 2-[1-(2,5-Dimethylpyrrolyl)]propionate (2c)

$^1$H-Nmr (δ, $CDCl_3$): 1.25 (3H, t, J=6.8 Hz), 1.62 (3H, d, J=7.3 Hz), 2.19 (6H, s), 4.21 (2H, q, J=6.8 Hz), 4.82 (1H, q, J=7.3 Hz), and 5.77 ppm (2H, s); $^{13}$C-nmr (δ, $CDCl_3$): 13.2 (q), 14.1 (q), 17.3 (q), 52.7 (d), 61.5 (t), 106.3 (d), 127.8 (s), and 171.4 ppm (s); Anal. Calcd. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.77; N, 7.17 %. Found: C, 67.42; H, 9.02; N, 6.97 %.

Dimethyl 2-[1-(2,5-Dimethylpyrrolyl)]butanedioate (1f)

Ir ($CHCl_3$): 1740 $cm^{-1}$; $^1$H-nmr (δ, $CDCl_3$): 2.19 (6H, s), 3.07 (2H, ABX, J=5.9, 7.8, and 16.6 Hz), 3.69 (3H, s), 3.74 (3H, s), 5.34 (1H, dd, J=5.9 and 7.8 Hz), and 5.77 ppm (2H, s); $^{13}$C-nmr (δ, $CDCl_3$): 12.9 (q), 36.5 (t), 52.2 (q), 53.0 (q), 53.4 (d), 106.9 (d), 128.1 (s), 170.8 (s), and 171.0 ppm (s); Anal. Calcd. for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85 %. Found: C, 59.96; H, 7.11; N, 5.74 %.

Ethyl 2-(1-Pyrrolyl)acetate (4a)

$^1$H-Nmr (δ, $CDCl_3$): 1.27 (3H, t, J=7.3 Hz), 4.21 (2H, q, J=7.3 Hz), 4.60 (2H, s), 6.19, and 6.65 ppm (4H, $A_2X_2$); $^{13}$C-nmr (δ, $CDCl_3$): 14.1 (q), 50.8 (t), 61.5 (t), 109.0 (d), 121.7 (d), and 168.7 ppm (s); Anal. Calcd. for $C_8H_{11}NO_2$: C, 62.72; H, 7.23; N, 9.14 %. Found: C, 62.57; H, 7.32; N, 9.07 %.

Ethyl 2-(1-Pyrrolyl)propionate (4c)

$^1$H-Nmr (δ, $CDCl_3$): 1.24 (3H, t, J=6.8 Hz), 1.71 (3H, d, J=7.3 Hz), 4.17 (2H, q, J=6.8 Hz), 4.73 (1H, q, J=7.3 Hz), 6.17, and 6.75 ppm (4H, $A_2X_2$); $^{13}$C-nmr (δ, $CDCl_3$): 14.0 (q), 18.3 (q), 57.0 (d), 61.5 (t), 108.5 (d), 119.6 (d), and 171.2 ppm (s); Anal. Calcd. for $C_9H_{13}NO_2$: C, 64.64; H, 7.83; N, 8.37 %. Found: C, 64.45; H, 7.93; N, 8.30 %.

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