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The Synthesis of Cyclic Amino Acids

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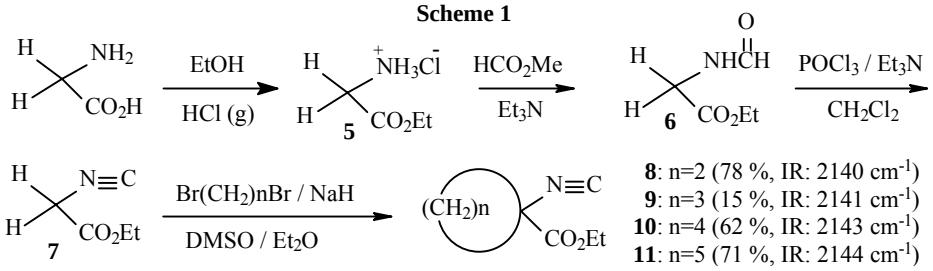
Abstract: Several cyclic amino acids (**1-4**) were synthesized from glycine. Isocyanate ester was prepared as the key intermediate and reacted with dibromoalkanes to afford the target compounds.

Keywords: Cyclic amino acid, isocyanate ester, dibromoalkane, ion exchange resin.

Cyclic amino acids, having no α-hydrogen and with ring tension, might express certain properties that differ from regular α-amino acids. It is of great significance to understand the related chemistry and the preparation of cyclic amino acids. Among the cyclic amino acids, 1-aminocyclopropanecarboxylic acid (ACC, **1**) is the most prominent one which was isolated from plant in 1957 and is known to convert to ethylene and ripen the fruits[1]. Several routes have been proposed for the synthesis of ACC[2]. In this paper, we report synthesis of several cyclic amino acids (**1-4**) using glycine as starting material.

As illustrated in **Scheme 1**, glycine was converted to the ethyl ester hydrochloride **5** and then converted to N-formyl ester **6** by refluxing 24 hours with methyl formate and triethylamine. The reaction was straightforward but required repeatedly removal of Et_3NHCl in purification process (yield 95 %, bp 180 °C / 1 mmHg). Dehydration of **6** to isocyanate ester **7** was performed by addition of $POCl_3$ (1.1 eq.) to the mixture of **6**, Et_3N and CH_2Cl_2 at low temperature (0-5 °C) and stirred 3 hours under the protection of argon. The product was obtained in satisfactory yield (88 %, 150 °C / 18 mmHg, light yellow oil) and was characterized by the pungent odor and strong CN band (2164 cm^{-1}) in IR. Cyclizations of **7** to **8-11** were the key reactions of this work which were

Scheme 1



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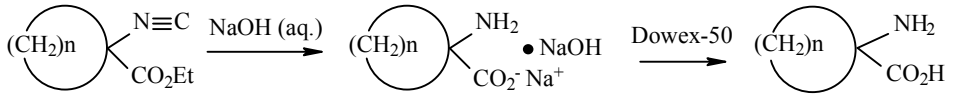
conducted by treating **7** with the corresponding dibromoalkanes using NaH as base and Et_2O-DMSO as solvent. Products **8-11** were obtained in fair yields (**Scheme 2**). The addition of DMSO (3 eq. relative to reactants) was noted to affect yields significantly.

Hydrolysis of cyclo isocyanate ester **8-11** to the corresponding cyclic amino acids **1-4** were carried out in aqueous NaOH. The occurring sodium salts of **8'–11'** were transformed to the neutral form (**1-4**) by cationic ion-exchange resin (Dowex 50). The structures of **1-4** were confirmed by spectral data.

Scheme 2



8: n=2; **9**: n=3
10: n=4 ; **11**: n=5

8': n=2; **9'**: n=3
10': n=4; **11'**: n=5

1: n=2 (93 %); **2**: n=3 (82 %)
3: n=4 (87 %); **4**: n=5 (90 %)

In summary, it was demonstrated that cyclic amino acids can be synthesized conveniently and effectively from glycine and various dibromoalkanes.

Acknowledgment

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References and Notes

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2. D. Kalvin, K. Ramalingam, R. W. Woodard, *Synth. Comm.*, **1985**, *15*, 267.
3. ^{1}H NMR (300 MHz, in D_2O if not specified, δppm) of 1: 1.27 (m, 2H, CH_2), 1.37 (m, 2H, CH_2). ^{1}H NMR of **2**: 1.40 (m, 2H, CH_3), 1.73 (t, 4H, J = 5.5 Hz, CH_2). ^{1}H NMR of **3**: 1.65 (t, 4H, J = 8.0 Hz, CH_2), 1.95 (t, 4H, J=7.5 Hz, CH_2); ^{1}H NMR of **4**: 1.25 (t, 2H, J = 8.5 Hz, CH_2), 1.60 (m, 4H, CH_2). 1.90 (t, 4H, J=10 Hz, 4H); ^{1}H NMR ($CDCl_3$) of **6**: 1.29 (t, 3H, J = 6.8Hz, CH_3), 4.07 (d, 2H, J = 5.4Hz, CH_2), 4.23 (q, 2H, J = 7.0Hz, CH_2), 6.85 (s, 1H, NH), 8.26 (s, 1H, CHO). ^{1}H NMR ($CDCl_3$) of **7**: 1.32 (t, 3H, J = 7.4 Hz, CH_3), 4.24 (s, 2H, CH_2), 4.29 (q, 2H, J = 7.4 Hz, CH_2). ^{1}H NMR ($CDCl_3$) of **8**: 1.30 (t, 3H, J = 7.2Hz, CH_3), 1.53-1.61 (m, 4H, CH_2CH_2), 4.23 (q, 2H, J = 7.0 Hz, CH_2). ^{1}H NMR ($CDCl_3$) of **9**:: 1.32 (t, 3H, J = 7.2Hz, CH_3), 1.90 (t, 2H, CH_2), 2.10 (t, 4H, J=10Hz, CH_2), 4.25 (q, 2H, J = 7.0 Hz, CH_2).

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