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FORMATION OF UNNATURAL CYCLIC AMINO ACID EQUIVALENT FROM THE SIMPLE CYCLIC HYDRAZINE

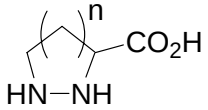
Duk Keun An,† Hye-Min Kim, Min Sung Kim,† Seung Kyu Kang, Jae Du Ha, Sung Soo Kim, Joong-Kwon Choi, and Jin Hee Ahn*

Medicinal Science Division, Korea Research Institute of Chemical Technology, Daejeon 305-600, Korea. E-mail: jhahn@krict.re.kr †Department of Chemistry, Kangwon National University, Chun-Chon 200-701, Korea

Abstract – An alternative method for the synthesis of unnatural cyclic amino acid equivalent from the simple cyclic hydrazine *via* oxidation and cyanation was developed.

INTRODUCTION

Unnatural amino acids are widely utilized as biological active compounds and synthetic intermediates. Among them, unnatural cyclic amino acid derivatives containing a cyclic hydrazine skeleton such as azaproline[1-3] and piperazic acid[4-6] are found in medicinal and organic chemistry area, many of which showed biological activity and used as useful building blocks in organic synthesis.



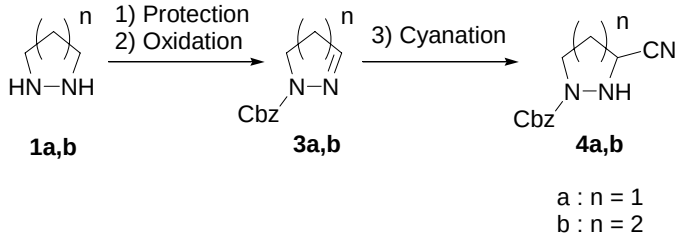
n = 1, Azaproline
n = 2, Piperazic aicd

Several approaches for the synthesis of these compounds have been reported. Of these, for the construction of cyclic hydrazine ring, intramolecular C-NN bond formation of acyclic hydrazine moiety with acid equivalent at α-position appear to be usual method for the synthesis of azaproline and piperazic acid;[2,7] however, yields were usually modest (38-63%). [2+3] Cycloaddition reactions of α,β-unsaturated carboxylic derivatives with diazomethane equivalents were reported,[8-10] but these methods used unstable diazomethane or could not provide six-membered hydrazine ring system. In view of the potential applications of unnatural cyclic amino acid, it is important to search for efficient synthetic methodologies for the preparation of these compounds. Recently, Boros[11] reported that simple unsubstituted pyrazolidine

(**1a**) could be effectively generated *via* alkylation from protected hydrazine. This prompted us to evaluate the synthesis of azaproline and piperazic acid from initially formed unsubstituted hydrazine. Now, we wish to report the synthesis of 5- and 6-membered unnatural amino acid equivalent applying an alternative route.

RESULTS AND DISCUSSION

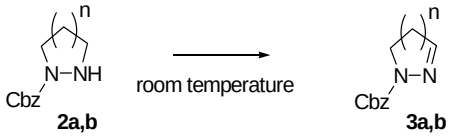
As a starting material, we chose a simple cyclic hydrazine, which could be efficiently oxidized to form cyclic hydrazone and cyanized. (**Scheme 1**) 5-Membered cyclic hydrazine (pyrazolidine, **1a**) was easily prepared from 1,3-dibromopropane and protected hydrazine by literature method,[11] also 6-membered hydrazine (hexahydropyridazine **1b**) was obtained with same procedure. These compounds were smoothly protected by CbzCl to furnish mono protected cyclic hydrazines in good yields. (**2a** and **2b**)



Scheme 1.

Recently, we have found that the mono-protected cyclic hydrazine (**2a**) was slightly oxidized in ambient condition (entry 1). We therefore examined reactions of cyclic hydrazine under several oxidation conditions at room temperature as shown in **Table 1**.

Table 1. Oxidation of cyclic hydrazine.[a]



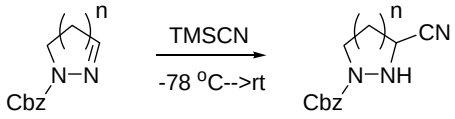
entry	Metal salt	O_2	time	solvent	yield[b]	
					3a (n=1)	**3b (n=2)**
1	none	air	24 h	isopropyl alcohol	~ 5%	~1%
2	none	O_2 balloon	24 h	isopropyl alcohol	~ 10%	not tested
3	CuI (1 eq.)	O_2 balloon	6 h	isopropyl alcohol	70%	not tested
4	$Cu(OAc)_2$ (1.1 eq.)	O_2 balloon	3 h	isopropyl alcohol	81%	81%[c]
5	$Cu(OAc)_2$ (0.01 eq.)	O_2 balloon	3 h	isopropyl alcohol	91%	~10%[c,d]
6	$Cu(OAc)_2$ (0.01 eq.)	O_2 balloon	3 h	THF	91%	not tested

[a] All reactions were carried out at room temperature. [b] Isolated yield. [c] 30h. [d] Starting material (~90%) was remained.

In the case of 5-membered hydrazine (**2a**), under O_2 balloon, the desired product was only produced in ~10% yield. (entry 2) When CuI was added, the product (**3a**) yield was improved to 70% (entry 3). It is noteworthy that, when $Cu(OAc)_2$ was used as a catalyst (0.01 eq.), the reaction proceeded smoothly and the yield of **3a** reached to 91%. Use of THF as a solvent also gave satisfactory result (91%, entry 6). With 6-membered hydrazine (**2b**),[4,12] the desired oxidation product (**3b,** 81%) was obtained using 1.1 eq. of $Cu(OAc)_2$ in isopropyl alcohol under oxygen atmosphere. Both **3a** and **3b** were quite stable in the air.

Next stage was the adoption of CN group to C=N double bond via modified Strecker reaction[10] to produce cyclic amino acid equivalent. (**Table 2**) When the reaction of **3a** with TMSCN was performed without Lewis acid or $Ti(OiPr)_4$ as Lewis acid, no formation of cyanated cyclichydrazine (**4a**) was observed. (entries 1-2) On the other hand, treatment of **3a** with TMSCN in the presence of $TiCl_4$ in dichloromethane provided the corresponding CN addition product in 78% yield. (entry 3). The best result was obtained in THF (91%, entry 4). Also, Six membered **3a** was easily cyanated to afford the corresponding **4b** in 90% yield.

Table 2. Cyanation of the compound (**3**).



3a,b **4a,b**

entry	Lewis acid	solvent	time	yield[a] 4a (n=1)	yield[a] 4b (n=2)
1	none	CH_2Cl_2	12 h	NR[b]	not tested
2	$Ti(OiPr)_4$	CH_2Cl_2	12 h	NR	not tested
3	$TiCl_4$	CH_2Cl_2	1 h	78%	not tested
4	$TiCl_4$	THF	1 h	91%	90%

[a] Isolated yield. [b] No reaction.

In conclusion, synthesis of 5- and 6- membered cyclic unnatural amino acid equivalent (**4a** and **4b**) was developed *via* oxidation and cyanation from simple cyclic hydrazine. Enantioselective cyanation of compounds (**3a**) and **(3b**) with chiral Lewis acid is currently in progress.

EXPERIMENTAL

All reported yields are isolated yields after column chromatography. 1H-NMR spectra were recorede on FT-NMR Varian GEMINI-200FT in $CDCl_3$ with TMS as internal reference. MS spectra were run on a Shimadzu QP5050 spectrograph. Elemental analysis was performed by the ThermoFinnigan Flash 1112.

Pyrazolidine-1-carboxylic acid benzyl ester (**2a**): To a stirred solution of pyrazolidine·2HCl (1.02 g, 7.03 mmol) and triethylamine (2.85 g, 28.12 mmol) in CH_2Cl_2 (100 mL) was added CbzCl (0.84 mL, 5.86 mmol) dropwise at 0 ^oC, and the mixture was stirred overnight at rt. The reaction mixture was washed with brine. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by chromatography (eluent, ethyl acetate) to give 1.08 g (91%, oil) of pyrazolidine-1-carboxylic acid benzyl ester (**2a**): ^1H NMR ($CDCl_3$, 200 MHz) δ 7.41-7.29 (m, 5H), 5.19 (s, 2H), 3.52 (t, *J* = 7.4 Hz, 2H), 3.04 (t, *J* = 6.6 Hz, 2H), 2.13-1.98 (m, 2H).

Tetrahydropyridazine-1-carboxylic acid benzyl ester (**2b**): Oil, ^1H NMR ($CDCl_3$, 200 MHz) δ 7.32-7.39 (m, 5H), 5.18 (s, 2H), 3.59 (t, *J* = 5.4 Hz, 2H), 2.93 (t, *J* = 5.4 Hz, 2H), 1.68-1.50 (m, 4H).

4,5-Dihydr-pyrazole-1-carboxylic acid benzyl ester (**3a**): To a stirred solution of **2a** (0.5 g, 2.44 mmol) in THF (20 mL) was added $Cu(OAc)_2$ (4.4 mg, 0.024 mmol) at rt, and the mixture was stirred for 3 h under oxygen atmosphere. The reaction mixture was evaporated, and the residue was purified by chromatography (eluent, ethyl acetate) to give 1.08 g (91%, solid, mp 44-45 ^oC) of 4,5-dihydropyrazole-1-carboxylic acid benzyl ester (**3a**)**:** ^1H NMR ($CDCl_3$, 200 MHz) δ 7.44-7.30 (m, 5H), 6.92 (s, 1H), 5.27 (s, 2H), 3.82 (t, *J* = 10.3 Hz, 2H), 2.90 (t, *J* = 10.3 Hz, 2H); MS (relative intensity) 204 (M^+, 2), 91(100).

5,6-Dihydro-4H-pyridazine-1-carboxylic acid benzyl ester (**3b**): Semi solid, ^1H NMR ($CDCl_3$, 200 MHz) δ 7.44-7.31 (m, 5H), 6.97 (s, 1H), 5.28 (s, 2H), 3.76 (t, *J* = 5.8 Hz, 2H), 2.20-2.16 (m, 2H), 1.92-1.85 (m, 2H); MS (relative intensity) 218(M^+, 3), 91(100).

3-Cyanopyrazolidine-1-carboxylic acid benzyl ester (**4a**): To a stirred solution of **3a** (0.204 g, 1 mmol) in THF (20 mL) was added $TiCl_4$ (1.2 mL, 1.2 mmol) dropwise at -78 ^oC, and the cold bath was removed and the reaction is allowed to stir for a period of 15 min. The mixture was recooled to – 78 ^oC and TMSCN (0.54 mL, 4 mmol) was added and then the mixture was allowed to reach rt. After 1 h, the reaction mixture was washed with brine. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by chromatography (eluent, ethyl acetate: hexane 1:2) to give 0.21 g (91%, white solid, mp 48-50 ^oC) of 3-cyanopyrazolidine-1-carboxylic acid benzyl ester (**4a**) ^1H NMR ($CDCl_3$, 200 MHz) δ 7.41-7.33 (m, 5H), 5.19 (s, 2H), 4.51 (d, *J* = 6.3 Hz, 1H), 4.17-4.08 (m, 1H), 3.86-3.76 (m, 1H), 3.62-3.53 (m, 1H), 2.48-2.39 (m, 2H); MS (relative intensity) 231 (M+, 2), 140 (1), 91 (100); Anal. Calcd for $C_{12}H_{13}N_3O_2$: C 62.33, H 5.67, N 18.17. Found C 62.31, H 5.68, N 18.55.

3-Cyanotetrahydropyridazine-1-carboxylic acid benzyl ester (**4b**): Solid, mp 53-55 ^{o}C ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.40-7.34 (m, 5H), 5.19 (s, 2H), 4.06-3.93 (m, 2H), 3.38-3.26 (m, 1H), 2.02-1.59 (m, 4H); MS (relative intensity) 245 (M+, 2), 91 (100); Anal. Calcd for $C_{13}H_{15}N_3O_2$: C 63.66, H 6.16, N 17.13. Found C 63.41, H 6.21, N 17.44.

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REFERENCES

1. N. Fuchi, T. Doi, T. Harada, J. Urban, B. Cao, M. Kahn, and T. Takahashi, *Tetrahedron Lett*., 2001, **42**, 1305.
2. H. O. Kim, C. Lum, and M. S. Lee, *Tetrahedron Lett*., 1997, **38**, 4935.
3. M. R. Mish, F. M. Guerra, and E. M. Carreira, *J. Am. Chem. Soc*., 1997, **119**, 8379
4. C. J. Hobbs, R. A. Bit, A. D. Cansfield, B. Harris, C. H. Hill, K. L. Hilyard, I. R. Kilford, E. Kitas, A. Kroehn, P. Lovell, D. Pole, P. Rugman, B. S. Sherborne, I. E. D. Smith, D. R. Vesey, D. L. Walmsley, D. Whittaker, G. Williams, F. Wilson, D. Banner, A. Surgenor, and N. Borkakoti, *Bioorg. & Med. Chem. Lett*., 2002, **12**, 1365.
5. M. L. M. Cabrejas, S. Rohrbach, D. Wagner, J. Kallen, G. Zenke, and J. Wagner, *Angew. Chem., Int. Ed*., **1999**, *38*, 2443.
6. Y. Aoyagi, Y. Saitoh, T. Ueno, M. Horiguchi, K. Takeya, and R. M. Williams, *J. Org. Chem*., 2003, **68**, 6899.
7. K. J. Hale, J. Cai, V. Delisser, S. Manaviazar, S. A. Peak, G. S. Bhatia, T. C. Collins, and N. Jogiya, *Tetrahedron*, 1996, **52**, 1047.
8. G. Lawton, C. J. Moody, C. J. Pearson, and D. J. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1987, 885.
9. G. A. Whitlock, and E. M. Carreira, *Helv. Chim. Acta*, 2000, **83**, 2007.
10. F. M. Guerra, M. R. Mish, and E. M. Carreira, *Org. Lett*., 2000, **2**, 4265.
11. E. E. Boros, F. Bouvier, S. Randhawa, and M. H. Rabinowitz, *J. Heterocycl. Chem.*, 2001, **38**, 613.
12. C. Hemmerlin, M. T. Cung, and G. Boussard, *Tetrahedron Lett*., 2001, **42**, 5009.