Facile New Method for Preparation of Optically Active Protected Proline

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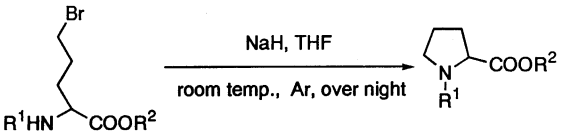
Treatment of L-*N*-protected 2-amino-5-bromopentanoic acid ester, which was prepared from protected L-glutamic acid, with sodium hydride in tetrahydrofuran (THF) proceeded to give the corresponding protected L-proline in high yield. On the other hand, the reaction of 2-aminobutyric acid derivative with sodium hydride gave the 1-aminocyclopropane-1-carboxylic acid derivative.

Among the common α-amino acids, proline is useful as a chiral source in asymmetric synthesis. Many methods including asymmetric synthesis of proline were reported.[1] However, development of a new and convenient method for preparation of optically active proline derivatives is still required. We now report that the cyclization of L- or D-*N*-protected 2-amino-5-bromopentanoic acid ester (**1**) gave the corresponding L- or D-proline derivative (**2**) under mild conditions in high yield, respectively (scheme 1).

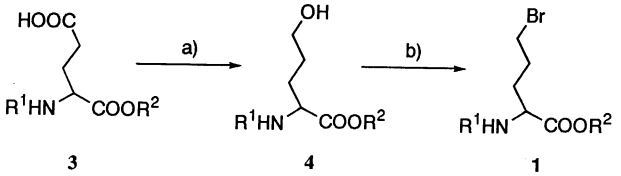


L-or D-1 L-or D-2

a; L-form, R^1=Z, R^2=*t*-Bu: **b**; L-form, R^1=Z, R^2=Me: **c**; L-form, R^1=Z, R^2=CH_2Ph: **d**; L-form, R^1=Boc, R^2=*t*-Bu: **e**; L-form, R^1=Fmoc, R^2=Me: **f**; D-form, R^1=Z, R^2=Me: **g**; D-form, R^1=Z, R^2=CH_2Ph: **h**; D-form, R^1=Boc, R^2=Pp.

Scheme 1.

As shown in scheme 2, various kinds of *N*-protected glutamic acid α-alkyl esters (**3**) were converted to the corresponding *N*-protected 2-amino-5-bromopentanoic acid esters (**1**). The mixed anhydrides prepared from **3** and isobutyl chloroformate in the presence of *N*-methylmorpholine (NMM) were reduced with sodium borohydride in THF to the corresponding alcohols (**4**) in 79-95% yields.[2] The following reactions of **4** with carbon tetrabromide and triphenylphosphine in dichloromethane at room temperature gave 2-amino-5-bromopentanoic acid derivatives (**1**) in 76-94% yield.[3]



3 4 1

a) i) Bu^tOCOCl, NMM, THF, -15 °C, 15 min, ii) $NaBH_4$, -30 °C, 5 min;
b) CBr_4, PPh_3, CH_2Cl_2, room temp., 3 min.

Scheme 2.

The reaction of **1a** with sodium hydride in THF at room temperature conveniently gave *N*-benzyloxycarbonyl (Z) proline *t*-butyl ester (**2a**) in high yield (Table 1, Run 1). The structure of **2a** was supported by ^1H NMR and mass spectra, melting point, and amino acid analysis after deprotection by HBr/AcOH. The cyclization of **1b** also proceeded to give **2b** in high yield (Run 2). In contrast no reaction proceeded when **1b** was treated with other reagents (triethylamine, 1,7-diazabicyclo-[5.4.0]-undec-7-ene (DBU), and potassium *t*-butoxide) instead of sodium hydride in THF under argon at room temperature. Since 9-fluorenylmethyloxycarbonyl (Fmoc) group was removed partially in treatment with sodium hydride, *N*-Fmoc-proline derivative (**2e**) was obtained in low yield (Run 5) On the other hand, D-proline derivatives (**2f**, **g** and **h**) were obtained in 90, 83, and 79% when D-glutamic acid derivatives were used as starting materials, respectively (Runs 6, 7 and 8).

Table 1. The transformation of protected 2-amino-5-bromopentanoic acid derivative (**1**) into the corresponding protected proline (**2**) with sodium hydride[a]

Run	Substrate	R^1	R^2	Product	Yield/%
1	**1a**	Z	*t*-Bu	**2a**	80[b]
2	**1b**	Z	Me	**2b**	80
3	**1c**	Z	CH_2Ph	**2c**	83
4	**1d**	Boc	*t*-Bu	**2d**	93
5	**1e**	Fmoc	Me	**2e**	26[c]
6[d]	**1f**	Z	Me	**2f**	90
7[d]	**1g**	Z	CH_2Ph	**2g**	83
8[d,e]	**1h**	Boc	Pp[f]	**2h**	79

[a] All the reactions were performed with the same procedure as described in the text, unless otherwise noted. [b] mp 43-45 °C (ref. mp 44-45 °C).[3] [c] The starting material was recovered in 21% yield. [d] D-Glutamic acid derivatives were used as starting materials. [e] The reaction was carried out for 3 days. [f] Phenylisopropyl ($C(CH_3)_2Ph$).

Table 2. Specific rotations of synthesized prolines (**2**)

Compound (**2**)	$[\alpha]_D$ (solvent)
2a	-48.8° (*c* 2.0, EtOH)[a]
2b	-38.3° (*c* 1.0, MeOH)
2c	-38.9° (*c* 2.4, MeOH)
2d	-50.2° (*c* 1.2, MeOH)
2e	-56.4° (*c* 0.8, MeOH)
2f	+36.0° (*c* 1.7, MeOH)
2g	+37.1° (*c* 2.5, MeOH)
2h	+68.7° (*c* 1.1, MeOH)

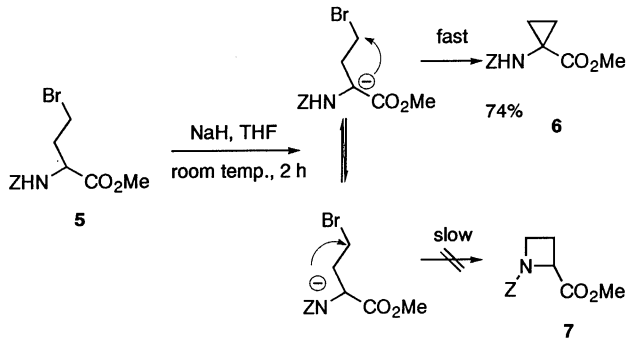
[a] $[\alpha]_D^{25}$-52.5° (*c* 2.2, EtOH)[3].

A typical experimental procedure is as follows: To a THF (2 ml) solution of *t*-butyl *N*-*t*-butoxycarbonyl (Boc)-2-amino-5-bromopentanoate (**1 d**, 109 mg, 0.308 mmol) was added a THF suspension of sodium hydride (50% in mineral oil, 16 mg, 0.33 mmol) at room temperature under argon, and the mixture was stirred over night. Then, the reaction was quenched by addition of water, and organic material was extracted with chloroform. The extract was dried (Na_2SO_4) and condensed under reduced pressure. The residue was purified by preparative TLC (*n*-hexane : EtOAc = 4 : 1) to give *N*-Boc-proline *t*-butyl ester (**2 d**, 78 mg, 93%).

Deprotection of **2 c** gave L-proline in 87% yield.[4] D-Proline was also obtained by deprotection of **2 g** in 82% yield.[5] Adamson *et al.* reported the use of 1-fluoro-2,4-dinitrophenyl-5-alanine amide (Marfey's reagent) to determine the DL ratio of some amino acids.[6] The coupling products of proline with Marfey's reagent gave diastereomers separable by reverse-phase HPLC. Peaks corresponding to Marfey's derivatives of L- and D-prolines were identified by comparison with DL-proline-Marfey's reagent standard run under identical conditions.[7] From these experiments, we found that little racemization (<3%) was detected in both cases.

On the analogy, it was assumed that treatment of 2-amino-4-bromobutyric acid derivative (**5**), which was easily prepared from aspartic acid, with sodium hydride would give the corresponding 4-membered ring compound (azetidine-2-carboxylic acid derivative, **7**). However, it was found that the reaction of **5** with 1.1 equivalents of sodium hydride at room temperature under argon proceeded to give methyl *N*-Z-1-aminocyclopropane-1-carboxylate (**6**) in 74% yield (Scheme 3). The structure of **6** was confirmed by ^1H NMR spectral data.[8] No formation of the azetizine-2-carboxylic acid derivative (**7**) was found. Rich and Tam reported that the reaction of *N*-Boc methionine methyl ester sulfonium salt with 2.2 equivalents of sodium hydride in *N*,*N*-dimethyformamide also gave the 1-aminocyclopropane-1-carboxylic acid derivative.[9]

It should be noted that the present reaction provides a convenient method for the preparation of L- and D-protected prolines, respectively. Further study including the application of this reaction to the cyclic transformation of various organic compounds is now in progress.



Scheme 3.

References and Notes

1 For example; R. Buyle, *Chem. Ind.*, **1966**, 380; P. J. Lawson, M. G. McCarthy, and A. M. Sargeson, *J. Am. Chem. Soc.*, **104**, 6710 (1982); M. Iwata and H. Kuzuhara, *Chem. Lett.*, **1985**, 1941; Y. N. Belokon', A. G. Bulychev, V. A. Pavlov, E. B. Fedorova, V. A. Tsyryapkin, V. A. Bakhmutov, and V. M. Belikov, *J. Chem. Soc., Perkin Trans. 1*, **1988**, 2075.

2 K. Ishizumi, K. Koga, and S. Yamada, *Chem. Pharm. Bull.*, **16**, 492 (1968).

3 G. W. Anderson and F. M. Callaham, *J. Am. Chem. Soc.*, **82**, 3359 (1960).

4 mp 219.5-220 °C (decomp.), $[\alpha]_D^{23}$ -74.7° (*c* 1.2, H_2O).

5 mp 218-219 °C (decomp.), $[\alpha]_D^{26}$ +76.8° (*c* 1.3, H_2O).

6 J. G. Adamson, T. Hoang, A. Crivici, and G. A. Lajoie, *Anal. Biochem.*, **202**, 210 (1992).

7 Conditions, 2ml/min of 10 to 25% acetonitrile (0.1% TFA) in 70 min. Retention time, L-proline derivative; 41.7 min; D-proline derivative, 45.6 min.

8 mp 60-62 °C. ^1H NMR(60MHz) TMS($CDCl_3$) δ=1.0-1.7 (m, 4H), 3.58 (s, 3H), 5.07 (s, 2H), 5.40 (brs, 1H, this signal disappeared by adding MeOH-*d*4), 7.25 (s, 5H).

9 D. H. Rich and J. P. Tam, *Synthesis*, **1978**, 46.