A Facile Synthesis of Optically Pure Amines by Reduction of N-Acyl-α-methoxyalkylamines Derived from α-Amino Acids Using Triethylysilane

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Optically active amines have recently attracted much attention as versatile building blocks and chiral auxiliaries. Decarboxylation of α-amino acids having an asymmetric center in the side chain such as isoleucine and threonine and of peptides is a most straightforward method for the preparation of optically active amines. However, difficulty is frequently encountered in the decarboxylation of α-amino acids and peptides, for which drastic conditions are usually required. Recently, effective methods for the decarboxylation of α-amino acids and their derivatives have been reported based on the photochemical reductive decarboxylation of N-protected α-amino acid N-hydroxypyridine-2-thione esters and thermal decarboxylation of α-amino acids in the presence of cyclohexene.

Optically active amines were synthesized effectively by Lewis acid-catalyzed triethylysilane reduction of N-acyl-α-methoxyalkylamines which were readily obtained by anodic oxidation of N-acyl-α-amino acids. This method was also applied to the conversion of an N-acylpeptide into the corresponding optically pure amine derivative.

**Keywords** optically pure amine; triethylysilane; decarboxylation; α-amino acid; anodic oxidation; reduction; α-methoxyalkylamine

The results are shown in Table I. The electrolysis products 2a—f were obtained as mixtures of two diastereomers, and were used in the next step without further separation.

We next examined the Lewis acid-catalyzed Et₃SiH reduction of the N-acyl-α-methoxyalkylamines obtained above. As a result, BF₃·OEt₂ was found to be a good catalyst for the reduction. Thus, the reduction of the methylated compound 2a was carried out by use of Et₃SiH·BF₃·OEt₂ at 5°C (method A), affording (2R)-N-acyl-2-methylbutylylamine (3a) in 96% yield (Chart 1). Under similar conditions, 2b and 2f were converted to 3b and 3f in 84% and 89% yields, respectively. In the reduction of 2c, 2d, and 2e having acid-labile tert-butylidimethylsilyl (TBDMS) and tert-butoxyacarbonyl (Boc) protecting groups, the reactions were carried out below −40°C to give the desired products (method B). Trifluoroacetic acid (TFA)·Et₃SiH (method C) could also be employed for the reduction of 2b and 2f to afford 3b and 3f, respectively in satisfactory yields. However, in the case of 2c, desilylation occurred together with the formation of the desired reduction product 3c. These results are summarized in Table I.

The reduction of N-acyl-α-methoxyalkylamines described above presumably involves hydride transfer from silicon to the N-acyliminium ion and/or N-acylamine, which are formed under the Lewis acid-catalyzed conditions.

During the transformation, no epimerization took place at all at the asymmetric centers in the side chains; this was confirmed by the conversion of 3c and 3e into the known (2R)(−)-hydroxypropylamine and (3R)(−)-hydroxypropyridoline, respectively.

This method involving anodic oxidation and Et₃SiH reduction will provide a useful approach for the synthesis of optically pure amines from N-acyl-α-amino acids and peptides.

**Experimental**

All melting points are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu IR-420 infrared spectrophotometer. 1H-Nuclear magnetic resonance (1H-NMR) spectra were taken at 200 MHz on a Bruker AC-200 spectrometer with tetramethylsilane (TMS) as an internal reference. Mass spectra (MS) were obtained with a Hitachi M-60 instrument. Optical rotations were measured by the use of a Perkin-Elmer model 243 polarimeter with a 1 cm³ capacity (10 cm path length) quartz cell. The electrolyses were carried out by the use of a Hokuto Potentio-Galvanostat (10 A—100 V) coupled to Hokuto HA-108A coulamb meter.

**Starting Materials** Compounds 1a—e were obtained from the corresponding α-amino acids by the usual methods.

A Typical Electrolysis Procedure A solution of 1a (20 mmol) in MeOH...
TABLE I. Anodic Oxidation of 1b—f and Et₃SiH Reduction of 2b—f

<table>
<thead>
<tr>
<th>N-Acyl-z-aminoc acid</th>
<th>N-Acyl-z-methoxalkylamine</th>
<th>Yield (%)</th>
<th>N-Acylamine</th>
<th>Methoda</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZH₂NCOO⁻</td>
<td>ZHN COOH</td>
<td>98</td>
<td>A</td>
<td>C</td>
<td>84</td>
</tr>
<tr>
<td>ZH₂NCOO⁻</td>
<td>ZHN OMe</td>
<td>96</td>
<td>B</td>
<td>C</td>
<td>88</td>
</tr>
<tr>
<td>ZH₂NCOO⁻</td>
<td>ZHN Ph</td>
<td>92</td>
<td>3b (R = TBDM)</td>
<td>42 (3c)</td>
<td>51</td>
</tr>
<tr>
<td>ZH₂NCOO⁻</td>
<td>ZHN OMe</td>
<td>98</td>
<td>3c (R = H)</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>ZH₂NCOO⁻</td>
<td>ZHN Ph</td>
<td>96</td>
<td>3d</td>
<td>96</td>
<td></td>
</tr>
</tbody>
</table>

(a) Method A, Et₃SiH·BF₃·OEt₂ at 5°C. method B, Et₃SiH·BF₃·OEt₂ at 
-40°C. method C, Et₃SiH·TFA at room temperature. b) Z = benzyloxy carbonyl; Boc = tert-butyl carbonyloxycarbonyl; TBDM = tert-butyldimethylsilyl. 

(30 ml) containing NaOMe (1 mmol) was electrolyzed at 5—10°C using a 6.4 cm² of graphite anode—graphite cathode system in a non-divided cell. The electrolysis current was maintained at 0.6 A during the electrolysis. After the theoretical amount of electricity had passed, the electrolyzed solution was evaporated to dryness in vacuo. The residue was dissolved in EtOAc. The solution was washed with saturated aqueous NaHCO₃ solution and brine, dried (MgSO₄) and evaporated to dryness in vacuo to afford compound 2a.

2(R)-N-Acetyl-1-methoxy-2-methylbutylamine (2a) mp 36—37°C. IR (Nujol): 3300 (NH), 1660 (CO), 1250 cm⁻¹. 1H-NMR (CDCl₃) δ: 0.91 (t, 3H, J = 6.0 Hz, CH₃), 0.93 (d, 3H, J = 6.0 Hz, CH₃), 1.03—1.29 (m, 1H, CH=H), 1.41—1.73 (m, 2H, CH₂, CH₃, CH₂), 2.10 (s, 3H, COCH₃), 3.32 (3H, OCH₃), 4.90—5.00 (m, 1H, CH=H), 6.05 (br s, NH). MS m/z: 128 (M⁺, CH₃O). 

Analyt Caled for C₃H₇NO₂: C, 60.34; H, 10.76; N, 8.80. Found: C, 60.46; H, 11.10; N, 8.69.

2(R)-N-Benzoylcarbonyl-1-methoxy-2-methylbutylamine (2b) Colorless syrup. IR (film): 3320 (NH), 1705 (CO), 1520 cm⁻¹. 1H-NMR (CDCl₃) δ: 0.88 (d, 3H, J = 6.6 Hz, CH₃), 0.90 (t, 3H, J = 6.6 Hz, CH₃), 1.00—1.30 (m, 1H, CH=H), 1.40—1.75 (m, 2H, CH₂, CH₃, CH₂), 3.34 (3H, OCH₃), 4.65—4.82 (m, 1H, CH=H), 4.99 (br s, NH), 5.13 (s, 2H, PhCH₂O), 7.34 (s, 5H, Ar-H). MS m/z: 219 (M⁺, CH₃O). Analyt Caled for C₁₀H₁₃NO₂: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.72; H, 8.51; N, 5.45.

2(R)-N-Benzoylcarbonyl-1-methoxy-2-methylbutylamino (2) Colorless syrup. IR (film): 3460 (NH), 3350 (NH), 1730 (CO), 1500 cm⁻¹. 1H-NMR (CDCl₃) δ: -0.06—0.05 (m, 6H, SiCH₃), 0.81—0.84 (m, 4H, tert-But), 1.04, 1.11 (each d, 3H, J = 6.4 Hz, CH₃), 2.93 (3H, OCH₃), 3.80—3.95 (m, 5H, Ar-H), 4.61, 4.71 (each dd, 1H, J = 14, 9.9 Hz, CH=H), 5.09 (s, 2H, PhCH₂O), 5.42 (d, 1H, J = 9.9 Hz, NH), 7.25—7.36 (m, 5H, Ar-H). MS m/z: 321 (M⁺, CH₃O). Analyt Caled for C₁₂H₁₄N₂O₂Se: C, 61.15; H, 8.84; N, 3.96; Se, 7.94. Found: C, 60.98; H, 9.27; N, 3.96; Se, 8.05.

2(R)-N-tert-Butylcarbonyl-1-methoxy-2-benzylamino (2d) Colorless syrup. IR (film): 3450 (NH), 3320, 1725 (CO), 1500 cm⁻¹. 1H-NMR (CDCl₃) δ: 1.14, 1.23 (each d, 3H, J = 6.5 Hz, CH₃), 1.44, 1.46 (each s, 3H, tert-But), 3.37, 3.38 (each s, 3H, OCH₃), 3.49—3.62, 3.65—3.82 (each s, 1H, CH=H), 4.40—4.85 (m, 3H, CH₂, OCH₃), 5.20, 5.35 (each br, 1H, NH), 7.25—7.35 (m, 5H, Ar-H). MS m/z: 263 (M⁺, CH₃O). Analyt Caled for C₁₅H₂₇NO₂Se: C, 65.06; H, 8.53; N, 4.74. Found: C, 64.81; H, 8.35; N, 4.41.

Typical Procedures for Et₃SiH Reduction Method A: A solution of 2a (2mmol) and Et₃SiH (2.4mmol) in dry CH₂Cl₂ (3ml) was treated with BF₃·OEt₂ (2.4mmol) at 5°C. After being stirred at 5°C for 2h, the reaction mixture was diluted with CHCl₃. The solution was washed with saturated aqueous NaHCO₃ solution and brine. The organic layer was dried (MgSO₄) and concentrated to dryness in vacuo, and the resulting syrup was subjected to silica gel chromatography (CHCl₃—acetone, 5:1) to afford compound 3a.

Method B: A solution of 2b (2mmol) and Et₃SiH (4mmol) in dry CH₂Cl₂ (3ml) was treated with BF₃·OEt₂ (4mmol) at -40°C. The reaction mixture was diluted with CHCl₃. The solution was washed with saturated aqueous NaHCO₃ solution and brine. The organic layer was dried (MgSO₄) and evaporated to dryness in vacuo. Purification of the
residue by silica gel chromatography (n-hexane-EtOAc, 10:1) gave compound 3c.

Method C: A solution of 2h (2 mmol) and Et_3SiH (2.4 mmol) in dry CH_2Cl_2 (3 mL) was treated with TFA (6 mmol) at 5°C. The reaction mixture was stirred at room temperature for 2 h, then quenched by addition of saturated aqueous NaHCO_3 solution. The mixture was extracted with CHCl_3. The organic layer was separated, dried (MgSO_4) and then evaporated to dryness in vacuo to give a syrup, which was purified by silica gel chromatography (n-hexane-EtOAc, 10:1) to afford compound 3b.

(2R)-N-Acetyl-2-methylbutylamine (3a) This compound was prepared by method A. Colorless syrup, [α]_D^21_2.5 = +23.2 (c = 1.11, CHCl_3), IR (film): 3300 (NH), 1655 (CO) cm⁻¹; 1H-NMR (CDCl_3): δ = 0.87-0.94 (m, 6H, C_6H_2, C_6H_2, C_6H_2, C_6H_2, C_6H_2, C_6H_2, C_6H_2), 1.04-1.26 (m, 1H, C_6H_2), 1.39-1.67 (m, 2H, C_6H_2, C_6H_2, C_6H_2), 1.99 (s, 3H, COCH_3), 2.99-3.26 (m, 2H, C_6H_2, C_6H_2, 5.61 (br, 1H, NH), MS m/z: 129 (M^+). Anal. Calc. for C_13H_25NO: 70.65; C, 70.14; H, 9.07; N, 36.3.

Conversion of 3c to (3R)-(-)-Hydroxypropirolidine Hydrochloride A mixture of compound 3c (1.26 g, 5.18 mmol) and 6N HCl (5 mL) was refluxed for 6 h. After cooling, the reaction mixture was diluted with H_2O (5 mL), and the solution was washed with EtOAc. The aqueous layer was concentrated to dryness in vacuo. The crystalline residue was triturated with ether to give pale brown needles (559 mg, 88%). An analytical sample was prepared by recrystallization from EtOH–ether (1:1), mp 101–107°C (lit. 109°C), [α]_D^21_2 = -9.20 (c = 1.74, MeOH) (lit. [α]_D^21_2 = -7.60 (c = 3.45, MeOH)). IR (Nujol): 3400 (NH), 1620, 1450 cm⁻¹; 1H-NMR (CD_3OD): δ = 2.02–2.25 (m, 2H, C_6H_2, 3.26–3.55 (m, 4H, C_6H_2, C_6H_2, C_6H_2), 4.61–4.68 (m, 1H, C_6H_2). MS m/z: 87 (M^+).

Acknowledgment We are grateful to Dr. I. Chibata, President, and Dr. S. Saito, Research and Development Executive, for their encouragement and interest. Thanks are also due to Drs. T. Tosa and K. Matsumoto for their valuable comments during this study.

References and Notes
12) In any case, the ratio of the diastereomers was observed to be approximately 2:1 from the NMR spectra.
14) The conversion of N-acetylxylthihydrylamines to the corresponding N-acetylxylthihydrines using Et_3SiH-TFA has been claimed by Weinreb et al. see, J. Auerbach, M. Zamore, S. M. Weinreb, J. Org. Chem., 42, 725 (1976).