1-(α-Boc-aminoacyl)benzotriazoles: stable chiral α-aminoacylation reagents

Alan R. Katritzky,* Mingyi Wang, Hongfang Yang, Suoming Zhang,§ and Novruz G. Akhmedov

Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, Florida 32611-7200
E-mail: katritzky@chem.ufl.edu

Submitted in honor of the 65th anniversary of Albert Padwa as a token of many years of friendship
(received 03 Aug 02; accepted 04 Sep 02; published on the web 12 Sep 02)

Abstract
The chiral α-N-(tert-butoxycarbonyl)aminoacylbenzotriazoles [(N-Boc-aminoacyl)-benzotriazoles] 3a–e are stable crystalline intermediates, easily prepared (61–88%) from N-Boc-α-amino acids 1a–e. Compounds 3a–e react with achiral or chiral amines at 0–20 °C to give α-(N-Boc-amino)amides with no detectable racemization.

Keywords: α-(N-Boc-aminoacyl)benzotriazoles, α-aminoacylation

Introduction

Amide bond formation between amino-acid components is a main goal in the synthesis of many organic compounds of biological interest such as peptides, peptoids, oligocarbamates, oligoamides, β-lactams, polynamides, benzodiazepines, diketopiperazines, and hydantoins. Contemporary protocols for the preparation of N-protected α-acylamino amides involve the formation of intermediate active esters. Many peptide coupling reagents¹ have essentially eliminated racemization of the amino acid component and the undesired side reactions² which can arise in direct synthesis of primary, secondary, and tertiary amides from acids or their classical activated derivatives (acyl halides, acid anhydrides, mixed anhydrides, or esters) with ammonia or amines. However, stable, crystalline chiral α-aminoacylation reagents have rarely been documented. Recent efforts to obtain easily isolated and stored active esters have linked modern activating groups (e.g., HOBt, HOAt, HOSu and PFP) to solid supports.³ Recently, stable N-hydroxysuccinimide (HOSu) - derived active esters have been obtained crystalline.⁴
$N$-Protected amino acid chlorides have long been known, their most successful application to peptide synthesis involved Fmoc-amino acids. Most $N$-protected amino acid chlorides proved not to be generally storable because of their high reactivity and sensitivity to cause degradation, decomposition and racemization on storage. $N$-Protected amino acid fluorides are more stable than the corresponding chlorides toward neutral oxygen nucleophiles such as water and methanol, yet are of high reactivity toward anionic nucleophiles and amines. Acid fluorides display considerable advantages in peptide synthesis; however, racemization was observed upon pretreatment of BOC-Phe-F with triethylamine in methylene chloride, low temperature is required for storage, especially in the t-BOC series and a large excess of acid fluorides was needed in the coupling step.

Acylbenzotriazoles have long been known as neutral acylating reagents. More recent work has included simple methods for their preparation and their application to prepare primary, secondary and tertiary amides and cinnamoyl hydrazides. We now extend the acylbenzotriazole chemistry to prepare stable $N$-Boc-$\alpha$-aminoacylbenzotriazoles derived from $N$-Boc-$\alpha$-amino acids and their utilization in the synthesis of chiral $\alpha$-($N$-protected amino)acid amides (Scheme 1).

![Scheme 1](image)

**Results and Discussion**

**Preparation of ($N$-Boc-$\alpha$-aminoacyl)benzotriazoles 3a–e**

As shown in Scheme 1, the ($N$-Boc-$\alpha$-aminoacyl)benzotriazoles 3a–e were prepared in 61–88% yields from commercially available $N$-protected $\alpha$-amino acids 1a–e and BtSO$_2$Me (2). Compounds 3a–e are colorless solids and crystallized from hexane–ethyl acetate; 3a–e showed no detectable change on storage at 20 °C for 6 months. The $^{13}$C NMR spectra of 3a–e displayed the expected signals characteristic of acylbenzotriazoles at $\delta$ ca. 131 (d), 127 (d), 120 (d), and 114 (d), and of the carbonyl carbons of the amide and carbamate groups at $\delta$ ca. 173 (s) and 155 (s), respectively.

**Preparation of $N$-(acylamino)amides 4a,b, 5a–e, 6a–e**

Reactions of ($N$-Boc-$\alpha$-aminoacyl)benzotriazoles 3a and 3b with amines in THF at room temperature afforded amides 4a and 4b in 82–87% yields (Table 1, Scheme 2). These yields and
the procedure are comparable with those previously reported for the preparation of simple amides from RCOBt and amines (e.g., N-(4-methoxyphenyl)-2-pyridinecarboxamide, 83%).

The most reliable technique for the determination of enantiomer composition is by the NMR analysis of covalent diastereomer mixtures, as exemplified by the preparation of derivatives of chiral alcohols or amines from optically active acids. α-Methylbenzylamides of N-protected amino acids have frequently served as model compounds for studies of optical purity and stability towards racemization. With this in mind, (S)-(-)-α-methylbenzylamine 7 and its antipode (R)-(+)–α-methylbenzylamine 8 were converted into the corresponding diastereomeric modified amides 5a–e and 6a–e, respectively, in isolated yields of 85–99% (average 93%) by reactions with 3a–e at 0–20 °C.

![Diagram of reaction scheme](MBA = methylbenzylamine)

For designation of R in 5a–e and 6a–e, see Scheme 1 and Table 1

**Scheme 2**

The diastereomeric excess (de) values for compounds 5a–e and 6a–e were determined as 93–99% by 1H NMR analysis of the amides after column chromatographic purification (Table 1). For compounds 5a–d and 6a–d, the resonances for the terminal methyl of the amino acid portion of the molecules were separated by 0.01–0.05 ppm (Figure 1). For compounds 5e and 6e, the α-methyl proton resonances were separated enough to allow determination of the diastereomeric ratio (Figure 2). The de values of 5a–e and 6a–e are summarized in Table 1. This indicated that the α-aminoacylations occurred with complete retention of the chirality of both the precursors in the products. Optical rotations were also examined for compound 4a, which had a rotation of $[\alpha]_D^{20}$, -52°, that reported is -61.2°. The measured $[\alpha]_D^{20}$ of 4b is -5.5°, that reported is +9.2°. Problems with the measurement of the optical rotation for the determination of enantiomeric purity of optically active compounds have been discussed.

One-pot reaction has also been investigated for 4b, 5e and 6e. After the formation of the (N-Boc-α-aminoacyl)benzotriazoles 3a–e were completed, amines were added in situ to the reaction mixture at room temperature and stirred for an appropriate time to provide 4b, 5e and 6e in very
good one-pot yields. In cases 5e and 6e, one-pot reaction gave the same de values as the above method. This success in the one-pot procedure should encourage the application of (N-Boc-α-aminoacyl)benzotriazoles in the formation of the amide bond.

![Figure 1. 1H NMR spectra of compounds 5e and 6e in CDCl3 (aliphatic region).](image1)

![Figure 2. 1H NMR spectra of compounds 5d and 6d in CDCl3 (aliphatic region).](image2)

**Table 1. N-(Acylamino)amides 4a,b, 5a–e, 6a–e**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>[α]₂₀</th>
<th>Mp (°C)</th>
<th>De (%)</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>4a</td>
<td>CH₃</td>
<td>-52</td>
<td>174</td>
<td>-</td>
<td>82</td>
</tr>
<tr>
<td>4b</td>
<td>(CH₃)₂CH</td>
<td>-5.5</td>
<td>oil</td>
<td>-</td>
<td>87 (82ᵃ)</td>
</tr>
<tr>
<td>5a</td>
<td>CH₃</td>
<td>-</td>
<td>119.0–119.5</td>
<td>99</td>
<td>91</td>
</tr>
<tr>
<td>5b</td>
<td>(CH₃)₂CH</td>
<td>-</td>
<td>142–143</td>
<td>96</td>
<td>93</td>
</tr>
<tr>
<td>5c</td>
<td>CH₃CH₂</td>
<td>-</td>
<td>109–110</td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td>5d</td>
<td>(CH₃)₂CHCH₂</td>
<td>-</td>
<td>143–143.5</td>
<td>99</td>
<td>85</td>
</tr>
<tr>
<td>5e</td>
<td>PhCH₂</td>
<td>-</td>
<td>131–132</td>
<td>99</td>
<td>96 (80)</td>
</tr>
<tr>
<td>6a</td>
<td>CH₃</td>
<td>-</td>
<td>91.5–92.5</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>6b</td>
<td>(CH₃)₂CH</td>
<td>-</td>
<td>128–128</td>
<td>99</td>
<td>89</td>
</tr>
<tr>
<td>6c</td>
<td>CH₃CH₂</td>
<td>-</td>
<td>93–94</td>
<td>99</td>
<td>90</td>
</tr>
<tr>
<td>6d</td>
<td>(CH₃)₂CHCH₂</td>
<td>-</td>
<td>137–138</td>
<td>99</td>
<td>95</td>
</tr>
<tr>
<td>6e</td>
<td>PhCH₂</td>
<td>-</td>
<td>127–128</td>
<td>99</td>
<td>95 (77)</td>
</tr>
</tbody>
</table>

ᵃ Yields in parentheses are for the one-pot procedure.

In conclusion, we have described a methodology for the preparation and synthetic utilization of (N-Boc-α-aminoacyl)benzotriazoles 3a–e via N-methanesulfonylbenzotriazole 2. The excellent stability of the isolated (N-Boc-α-aminoacyl)benzotriazoles 3a–e may provide broad applicability. The simplicity, operational ease and lack of racemization offer advantages over
conventional coupling techniques and could make this methodology a method of choice for the preparation of amides and peptides using solid phase combinatorial techniques where crystalline, stable reagents have obvious advantages.

**Experimental Section**

**General Procedures.** Melting points were determined on a capillary melting point apparatus equipped with a digital thermometer. NMR spectra were recorded in CDCl₃ with tetramethylsilane as the internal standard for ¹H (300 MHz) and the solvent for ¹³C (75 MHz) NMR. THF was distilled from sodium/benzophenone under nitrogen immediately prior to use. All reactions with air-sensitive compounds were carried out under argon atmosphere. Column chromatography was conducted using silica gel (230–400 mesh) and ethyl acetate–hexane.

**General procedure for the preparation of 3a–e**

To a solution of N-protected amino acid (10 mmol) in THF (50 mL), BtMs (11 mmol) and Et₃N (11 mmol) were added at room temperature. The reaction mixture was heated and refluxed 6–12 h. The solvent was removed in vacuo to dryness. The residue was dissolved in ethyl acetate and washed sequentially with sat. citric acid, sat. Na₂CO₃ and H₂O, and dried over MgSO₄. Concentration under reduced pressure gave desired product, which can be recrystallized from hexane–ethyl acetate.

**L-tert-Butyl-N-[2-(1H-1,2,3-benzotriazol-1-yl)-1-methyl-2-oxoethyl]carbamate (3a).** Colorless prisms (61%), mp 68–69 °C, [α]D²⁰ = −17.7° (CHCl₃); ¹H NMR δ 8.27 (d, J = 8.1 Hz, 1H), 8.13 (d, J = 8.2 Hz, 1H), 7.67 (dd, J = 7.5, 7.6 Hz, 1H), 7.52 (dd, J = 7.5, 7.6 Hz, 1H), 5.74 (m, 1H), 5.32 (d, J = 5.9 Hz, 1H), 1.65 (d, J = 7.3 Hz, 3H), 1.45 (s, 9H); ¹³C NMR δ 173.2, 155.5, 146.4, 131.6, 131.1, 126.9, 120.7, 114.8, 80.8, 50.6, 28.7, 19.4. Anal. Calcd for C₁₄H₁₈N₄O₃: C, 57.92; H, 6.25; N, 19.30. Found: C, 58.06; H, 6.44; N, 19.30.

**L-tert-Butyl-N-[1-(1H-1,2,3-benzotriazol-1-ylcarbonyl)-2-methylpropyl]carbamate (3b).** Colorless needles (83%), mp 120–121 °C, [α]D²⁰ = −47.5° (CH₃OH); ¹H NMR δ 8.28 (d, J = 8.1 Hz, 1H), 8.14 (d, J = 8.2 Hz, 1H), 7.68 (dd, J = 7.4, 7.3 Hz, 1H), 7.54 (dd, J = 7.4, 7.5 Hz, 1H), 5.70–5.66 (m, 1H), 5.33 (d, J = 8.4 Hz, 1H), 2.47–2.17 (m, 1H), 1.46 (s, 9H), 1.11 (d, J = 6.7 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H); ¹³C NMR δ 171.9, 155.6, 145.9, 130.9, 130.5, 126.3, 120.2, 114.3, 80.1, 58.9, 31.4, 28.2, 19.6, 16.9. Anal. Calcd for C₁₆H₂₃N₄O₃: C, 60.36; H, 6.96; N, 17.60. Found: C, 60.56; H, 7.13; N, 17.72.

**L-tert-Butyl-N-[1-(1H-1,2,3-benzotriazol-1-ylcarbonyl)propyl]carbamate (3c).** Colorless needles (78%), mp 85–86 °C, [α]D²⁰ = −45.0° (CHCl₃); ¹H NMR δ 8.29 (d, J = 8.1 Hz, 1H), 8.15 (d, J = 8.1 Hz, 1H), 7.68 (dd, J = 7.5, 7.8 Hz, 1H), 7.54 (dd, J = 7.5, 7.8 Hz, 1H), 5.75–5.61 (m, 1H), 5.31 (brd, J = 7.2 Hz, 1H), 2.25–2.06 (m, 1H), 1.98–1.82 (m, 1H), 1.46 (s, 9H), 1.08 (t, J = 7.5, 7.5 Hz, 3H); ¹³C NMR δ 172.1, 155.4, 145.8, 131.0, 130.5, 126.3, 120.1, 114.2, 80.1, 55.2,
28.2, 26.2, 9.9. Anal. Calcd for C\textsubscript{15}H\textsubscript{20}N\textsubscript{4}O\textsubscript{3}: C, 59.20; H, 6.62; N, 18.41. Found: C, 59.52; H, 7.08; N, 18.60.

\textit{L-tert-Butyl-N-[1-(1H-1,2,3-benzotriazol-1-ylcarbonyl)-3-methylbutyl]carbamate (3d).} Colorless needles (66%), mp 134–136 °C, \(\left[\alpha\right]_{D}^{20} = -4.0^\circ\) (CHCl\textsubscript{3}); \(^1\text{H NMR} \delta 8.27 (d, J = 8.1 \text{ Hz}, 1\text{H}), 8.13 \text{ (d, J = 8.1 Hz, 1H), 7.67 (dd, J = 7.8, 7.3 Hz, 1H), 7.53 (dd, J = 7.7, 7.6 Hz, 1H), 5.80–5.74 \text{ (m 1H), 5.23 (brs, 1H), 1.88–1.80 (m, 2H), 1.74–1.64 (m, 1H), 1.45 (s, 9H), 1.10 (d, J = 5.6 Hz, 3H), 0.98 (d, J = 6.0 Hz, 3H); } \text{\(^{13}\text{C NMR} \delta 172.9, 155.5, 146.0, 131.2, 130.6, 126.4, 120.3, 114.4, 80.3, 53.1, 41.9, 28.3, 25.3, 23.2, 21.3. Anal. Calcd for C}_{17}H_{24}N_{4}O_{3}: C, 61.43; H, 7.28; N, 16.85. Found: C, 61.74; H, 7.10; N, 17.00.}

\textit{L-tert-Butyl-N-[2-(1H-1,2,3-benzotriazol-1-yl)-1-benzyl-2-oxoethyl]carbamate (3e).} Colorless needles (81%), mp 144–145 °C; \(^1\text{H NMR} \delta 8.26 (d, J = 7.8 Hz, 1H), 8.17 (d, J = 8.1 Hz, 1H), 8.14 (dd, J = 5.9, 2.4 Hz, 1H), 7.68 (dd, J = 7.4, 7.7 Hz, 1H), 7.57–7.16 (m, 6H), 6.05–5.95 (m, 1H), 3.46 (dd, J = 4.5, 13.5 Hz, 1H), 3.19 (dd, J = 7.4, 13.9 Hz, 1H), 1.41 (s, 9H); \(^{13}\text{C NMR} \delta 171.3, 155.1, 146.0, 135.2, 131.0, 130.7, 129.2, 128.6, 127.2, 126.4, 120.3, 114.3, 80.3, 55.2, 38.8, 28.2. Anal. Calcd for C\textsubscript{20}H\textsubscript{22}N\textsubscript{4}O\textsubscript{3}: C, 65.56; H, 6.05; N, 15.29. Found: C, 65.68; H, 6.38; N, 14.90.}

**General procedure for the preparation of 4a,b, 5a–e, 6a–e**

To a solution of the \textit{N}- (\textit{N}-Boc-\alpha-aminoacyl)benzotriazole 3a–e (5 mmol) in dry THF (30 mL), a solution of the corresponding amines (5 mmol) in THF (2 mL) was added at 0 °C over 5 min. The reaction mixture was stirred at 0–20 °C overnight. The solvent was removed in vacuo and the residue was purified by column chromatography to give the desired products, which can be recrystallized from hexane–ethyl acetate.

\textit{[1-(\textit{N-tert-Butyloxy}carbonyl)amino-1-methyl]-\textit{N}-phenylacetamide (4a).} Colorless needles (82%), mp 174 °C (lit.\textsuperscript{14} 175 °C), \(\left[\alpha\right]_{D}^{20} = -52^\circ\) (lit.\textsuperscript{14} –61.2\(^\circ\)); \(^1\text{H NMR} \delta 8.44 (br s, 1H), 7.52 (d, J = 7.9 Hz, 2H), 7.31 (t, J = 7.6 Hz, 2H), 7.10 (t, J = 7.3 Hz, 1H), 5.06 (br s, 1H), 4.32 (m, 1H), 1.47 (s, 9H), 1.43 (d, J = 7.3 Hz, 3H); \(^{13}\text{C NMR} \delta 171.1, 156.1, 137.8, 128.9, 124.2, 119.8, 80.5, 50.7, 28.3, 17.8.}

\textit{[2-Methyl-1-(pyrrolidine-1-carbonyl)propyl]carbamic acid \textit{tert}-butyl ester (4b).} Colorless oil (87%), \(\left[\alpha\right]_{D}^{20} = -5.5^\circ\) (lit.\textsuperscript{15} +9.2 °C). \(^1\text{H NMR} \delta 5.31 (d, J = 9.0 Hz, 1H), 4.20–4.15 (m, 1H), 3.63–3.57 (m, 1H), 3.47–3.32 (m, 3H), 1.91–1.76 (m, 5H), 1.35 (s, 9H), 0.89 (d, J = 6.7 Hz, 3H), 0.85 (d, J = 6.7 Hz, 3H); \(^{13}\text{C NMR} \delta 170.2, 155.4, 78.7, 56.6, 46.2, 45.3, 30.9, 27.9, 25.6, 23.8, 19.1, 17.1.}

\textit{\textit{tert}-Butyl \textit{N}-(1S)-1-methyl-2-oxo-2-[(1S)-1-phenylethyl]amino}ethyl]carbamate (5a). Colorless needles (91%), mp 119–120 °C; \(^1\text{H NMR} \delta 7.35–7.22 \text{ (m, 5H), 6.62 (brs, 1H), 5.14–5.04 \text{ (m, 2H), 4.16 (brs, 1H), 1.47 (d, J = 7.0 Hz, 3H), 1.43 (s, 9H), 1.33 (d, J = 7.0 Hz, 3H); } \text{\(^{13}\text{C NMR} \delta 171.7, 155.6, 143.0, 128.6, 127.3, 126.0, 80.1, 50.1, 48.6, 28.2, 21.8, 18.0. Anal. Calcd for C}_{16}H_{24}N_{2}O_{3}: C, 65.73; H, 8.27; N, 9.58. Found: C, 65.66; H, 8.38; N, 9.60.}
**tert-Butyl N-[(1S)-2-methyl-1-{{[(1S)-1-phenylethyl]amino}carbonyl}propyl]carbamate (5b).** Colorless macrocrystals (93%), mp 142–143 °C; $^1$H NMR δ 7.41–7.28 (m, 5H), 6.34 (brd, $J = 7.4$ Hz, 1H), 5.25–5.10 (m, 2H), 3.93–3.88 (m, 1H), 2.20–2.05 (m, 1H), 1.53 (d, $J = 6.9$ Hz, 3H), 1.48 (s, 9H), 0.96–0.92 (m, 6H); $^{13}$C NMR δ 170.9, 156.0, 143.1, 128.5, 127.1, 126.0, 79.6, 60.0, 48.6, 30.8, 28.2, 21.7, 19.2, 17.9. Anal. Calcd for C$_{18}$H$_{28}$N$_2$O$_3$: C, 71.47; H, 8.81; N, 8.74. Found: C, 71.71; H, 9.10; N, 8.73.

**tert-Butyl N-[(1S)-1-{{[(1S)-1-phenylethyl]amino}carbonyl}propyl]carbamate (5c).** Colorless needles (93%), mp 109–110 °C (lit. no melting point given); $^1$H NMR δ 7.36–7.23 (m, 5H), 6.38 (brs, 1H), 5.16–5.00 (m, 2H), 4.02–3.92 (m, 1H), 1.91–1.76 (m, 1H), 1.66–1.56 (m, 1H) 1.48 (d, $J = 6.9$ Hz, 3H), 1.43 (s, 9H), 0.90 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (DMSO-$d_6$) δ 171.1, 155.3, 144.7, 128.2, 126.6, 125.8, 77.9, 55.6, 47.7, 28.2, 25.4, 22.5, 10.3.

**tert-Butyl N-[(1S)-3-methyl-1-{{[(1S)-1-phenylethyl]aminocarbonyl}butyl]carbamate (5d).** Colorless needles (85%), mp 142–143 °C; $^1$H NMR δ 7.37–7.22 (m, 5H), 6.45 (brd, $J = 7.1$ Hz, 1H), 5.12–5.05 (m, 1H), 4.89 (brs, 1H), 4.06 (brs, 1H), 1.67–1.53 (brs, 2H), 1.51–1.43 (m, 1H), 1.47 (d, $J = 6.9$ Hz, 3H), 1.43 (s, 9H), 0.91 (d, $J = 5.9$ Hz, 3H), 0.90 (d, $J = 6.0$ Hz, 3H); $^{13}$C NMR δ 171.7, 155.8, 143.2, 128.5, 127.2, 126.0, 79.9, 53.1, 48.6, 41.1, 28.3, 24.7, 22.9, 21.8. Anal. Calcd for C$_{19}$H$_{30}$N$_2$O$_3$: C, 68.23; H, 9.04; N, 8.38. Found: C, 68.38; H, 9.25; N, 8.41.

**tert-Butyl N-[(1S)-1-benzyl-2-oxo-2-{{[(1S)-1-phenylethyl]amino}ethyl}carbamate (5e).** Colorless needles (96%), mp 131–132 °C (lit. 138–139 °C); $^1$H NMR δ 7.30–7.08 (m, 10H), 6.07 (d, $J = 8.0$ Hz, 1H), 5.12 (brs, 1H), 5.07–5.00 (m, 1H), 4.32–4.22 (m, 1H), 3.07 (dd, $J = 6.4$, 13.6 Hz, 1H), 2.99 (dd, $J = 7.7$, 13.3 Hz, 1H), 1.41 (d, $J = 6.7$ Hz, 3H), 1.40 (s, 9H); $^{13}$C NMR δ 170.2, 155.4, 142.6, 136.6, 129.3, 128.6, 128.5, 127.2, 126.8, 126.0, 80.1, 55.9, 48.6, 38.5, 28.2, 21.5. Anal. Calcd for C$_{22}$H$_{28}$N$_2$O$_3$: C, 71.71; H, 7.66; N, 7.60. Found: C, 71.48; H, 7.88; N, 7.57.

**tert-Butyl N-[(1S)-1-methyl-2-oxo-2-{{[(1R)-1-phenylethyl]amino}ethyl}carbamate (6a).** Colorless needles (99%), mp 91.5–93.0 °C; $^1$H NMR δ 7.34–7.21 (m, 5H), 6.60 (brs, 1H), 5.12–5.03 (m, 1H), 4.94 (brs, 1H), 4.15–4.10 (m, 1H), 1.48 (d, $J = 6.9$ Hz, 3H), 1.42 (s, 9H), 1.34 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR δ 171.4, 155.6, 143.1, 128.6, 127.2, 125.9, 80.1, 49.9, 48.7, 28.2, 22.0, 17.6. Anal. Calcd for C$_{16}$H$_{24}$N$_2$O$_3$: C, 65.73; H, 8.27; N, 9.58. Found: C, 65.70; H, 8.61; N, 9.62.

**tert-Butyl N-[(1S)-2-methyl-1-{{[(1R)-1-phenylethyl]amino}carbonyl}propyl]carbamate (6b).** Colorless macrocrystals (89%), mp 127–128 °C; $^1$H NMR δ 7.34–7.22 (m, 5H), 6.28 (brd, $J = 6.7$ Hz, 1H), 5.13–5.06 (m, 2H), 3.88–3.82 (m, 1H), 2.19–2.08 (m, 1H), 1.48 (d, $J = 7.0$ Hz, 3H), 1.43 (s, 9H), 0.96 (d, $J = 6.7$ Hz, 3H), 0.91 (d, $J = 6.3$ Hz, 3H); $^{13}$C NMR δ 170.7, 155.9, 142.9, 128.5, 127.2, 126.0, 79.7, 60.2, 48.7, 30.5, 28.2, 21.9, 19.3, 18.0. Anal. Calcd for C$_{18}$H$_{28}$N$_2$O$_3$: C, 67.47; H, 8.81; N, 8.74. Found: C, 67.67; H, 9.04; N, 8.61.

**tert-Butyl N-[(1R)-1-{{[(1R)-1-phenylethyl]amino}carbonyl}propyl]carbamate (6c).** Colorless needles (90%), mp 93–94 °C (lit. no melting point given); $^1$H NMR δ 7.34–7.23 (m, 5H), 6.40 (m, 1H), 5.15–5.05 (m, 1H), 4.96 (brs, 1H), 4.05–3.85 (m, 1H), 1.95–1.80 (m, 1H), 1.81–1.54 (m, 1H), 1.48 (d, $J = 7.0$ Hz, 3H), 1.43 (s, 9H), 0.95 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (DMSO-$d_6$) δ 171.1, 155.3, 144.4, 128.1, 126.5, 126.0, 77.9, 55.6, 47.7, 28.2, 25.2, 22.5, 10.4.
tert-Butyl N-[(1S)-3-methyl-1-[(1R)-1-phenylethyl]aminocarbonyl]butyl]carbamate (6d). Colorless needles (95%), mp 137–138 °C; $^1$H NMR δ 7.35–7.23 (m, 5H), 6.56 (brs, 1H), 5.11–5.06 (m, 1H), 4.86 (d, $J = 8.2$ Hz, 1H), 4.88–4.08 (m, 1H), 1.72–1.64 (m, 2H), 1.49–1.43 (m, 1H), 1.48 (d, $J = 6.9$ Hz, 3H), 1.43 (s, 9H), 0.95 (d, $J = 6.4$ Hz, 3H), 0.94 (d, $J = 6.2$ Hz, 3H); $^{13}$C NMR δ 171.4, 155.8, 143.1, 135.5, 128.3, 127.1, 125.9, 80.1, 52.9, 48.6, 40.6, 28.2, 24.7, 22.8, 22.1, 22.0. Anal. Calcd for C$_{19}$H$_{30}$N$_2$O$_3$: C, 68.23; H, 9.04; N, 8.38. Found: C, 68.40; H, 9.42; N, 8.40.

tert-Butyl N-((1S)-1-benzyl-2-oxo-2-[(1R)-1-phenylethyl]amino)ethyl)carbamate (6e). Colorless needles (95%), mp 127–128 °C (lit. 17 no melting point given); $^1$H NMR δ 7.32–7.15 (m, 10H), 5.91 (brs, 1H), 5.10 (brs, 1H), 5.02–4.90 (m, 1H), 4.31–4.25 (m, 1H), 3.12 (dd, $J = 6.0$, 13.6 Hz, 1H), 2.99 (dd, $J = 13.5$, 8.0 Hz, 1H), 1.41 (s, 9H), 1.29 (d, $J = 6.7$ Hz, 3H); $^{13}$C NMR δ 170.3, 152.6, 142.8, 129.6, 129.5, 128.9, 128.8, 127.5, 127.1, 126.2, 68.0, 56.2, 49.0, 38.9, 28.5, 21.9. Anal. Calcd for C$_{22}$H$_{28}$N$_2$O$_3$: C, 71.71; H, 7.66; N, 7.60. Found: C, 71.36; H, 7.87; N, 7.96.

References

§ Current address: Neurogen Corporation, 35 Northeast Industrial Road, Branford, CT 06405.


