Oxygen Alkylation of Schiff Base Derivatives of Amino Acids

Martin J. O'Donnell,* Gwendolyn K. Cook, David B. Rusterholz
Department of Chemistry, Indiana University-Purdue University at Indianapolis, Indianapolis, IN 46205, USA

Higher imine esters 1a–h and 7a–b of amino acids and dipeptides are prepared in 68–91% yield by saponification of the benzophenone Schiff base methyl esters 3a–d and 6 using phase-transfer techniques followed by O-alkylation with an alkyl halide. The procedure occurs with retention of configuration at the α-carbon except with phenylglycine derivatives.

The introduction and removal of ester groups are important processes in organic chemistry since protection of carboxylic acids often involves use of the ester functionality. This is especially true in the area of amino acid and peptide chemistry where multifunctional molecules as well as chiral centers are often present.

Our research has focused on synthetic methodology in amino acid chemistry, especially in the utilization of benzophenone Schiff base esters 1 for the preparation of various types of amino acid derivatives. Thus, phase-transfer alkylations (carbon alkylation) of these and related Schiff base derivatives have provided ready access to a variety of amino acids via alkylative routes. Schiff base esters can also be exploited as cationic amino acid synths for reaction with nucleophilic reagents. Another application involves N-alkylation of either imino or amido esters with electrophiles which provides a convenient route to N-alkyl amino acids.

The Schiff base esters 1 are prepared either by condensation of the free amino ester with benzophenone in the presence of boron trifluoride etherate or more conveniently by transamination of the amino ester salt with benzophenone imine. This paper reports a new route to various Schiff base esters 1 which involves oxygen alkylation in conjunction with a two-step transesterification procedure.

A study of the preparation of Schiff base benzyl and isopropyl esters of several amino acids was undertaken to define the scope and limitations of the procedure. The two alkyl halides used are representative of active halides (benzyl bromide) and unreactive, sterically demanding halides (2-iodopropane). The resulting protected amino esters are of interest because the former represents a carboxyl protecting group which can be removed either by catalytic hydrogenation or hydrolysis, while the latter is a hindered ester available by O-alkylation which is more resistant to hydrolysis under basic conditions than either methyl or ethyl esters. Attempted preparation of tert-butyl esters by saponification of 3a followed by reaction with either tert-butyl chloride or bromide yielded only minor amounts of the tert-butyl ester (1, R¹ = H, R² = t-Bu) by comparison of HPLC retention times with an authentic sample. The major product of this reaction was benzophenone.

As expected, the rate of saponification is dependent on the steric bulk proximal to the carbonyl group of the methyl ester. Thus, the benzophenone Schiff base of glycine methyl ester (3a) is saponified in thirty minutes (Table 1) whereas substitution at the α-carbon by benzyl 3b, phenyl 3c or isopropyl 3d groups increases the time required for saponification. In the latter case, best results were obtained using acetonitrile and 20% aqueous sodium hydroxide. Attempts to increase the rate of saponification with the sterically hindered substrates by the use of ultrasound were unsuccessful; the reaction rate was the same both with and without sonication. The rate of alkylation also depends on the steric bulk at the α-carbon as well as the reactivity of the alkylating agent (Table 1).

With the less reactive (2-iodopropane); it was advantageous to use excess halide (5 equivalents), which could be readily removed during workup.

The effect of the transesterification procedure on imines derived from optically active amino acid methyl esters was studied by hydrolysis of the product Schiff bases 1e, 1f and 1g to the amino ester tosylates 4 as well as to the parent amino acids 5 (Table 2). With both phenylalanine and valine derivatives 1c and 1g, respectively, the resulting products showed no racemization within experimental error when compared with commercial samples.
Table 1. Compounds 1 and 7 Prepared

<table>
<thead>
<tr>
<th>Product</th>
<th>Time (h)</th>
<th>Hydrolysis/Alkylation (%)</th>
<th>Yield* (Et₂O/hexanes)</th>
<th>Molecular Formula* or Lit. mp (°C)</th>
<th>δ, J (Hz)</th>
<th>[α]D, (temp °C), (c, solvent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>0.5/2</td>
<td>80</td>
<td>91–92</td>
<td>C₁₅H₁₃N₂O₄ (281.4)</td>
<td>4.2 (s, 2H), 5.2 (s, 2H), 7.0–7.8 (m, 15H)</td>
<td>–</td>
</tr>
<tr>
<td>1b</td>
<td>0.5/5</td>
<td>70</td>
<td>66–68</td>
<td>C₁₅H₁₃N₂O₄ (281.4)</td>
<td>1.2 (d, 6H, J = 6.9), 4.0 (s, 2H), 4.8–5.2 (m, 1H), 7.1–7.8 (m, 10H)</td>
<td>–</td>
</tr>
<tr>
<td>1c</td>
<td>1/4</td>
<td>81</td>
<td>oil</td>
<td>C₁₅H₁₃N₂O₄ (281.4)</td>
<td>3.1–3.5 (m, 2H), 4.2–4.4 (m, 1H), 5.1 (s, 2H), 6.5–7.7 (m, 20H)</td>
<td>–108.2 (20, 4, MeOH)</td>
</tr>
<tr>
<td>1d</td>
<td>1/16</td>
<td>68</td>
<td>oil</td>
<td>C₁₅H₁₃N₂O₄ (281.4)</td>
<td>1.2 (d, 3H, J = 7.0), 1.3 (d, 3H, J = 7.0), 3.1–3.3 (m, 2H), 4.1–4.3 (m, 1H), 4.9–5.2 (m, 1H), 6.5–7.9 (m, 15H)</td>
<td>+83.7 (20, 1, MeOH)</td>
</tr>
<tr>
<td>1e</td>
<td>1/4</td>
<td>75</td>
<td>82–85</td>
<td>C₁₅H₁₃N₂O₄ (281.4)</td>
<td>4.97 (s, 2H), 5.02 (s, 1H), 6.8–7.8 (m, 20H)</td>
<td>+28.4 (24, 1, EtOH)</td>
</tr>
<tr>
<td>1f</td>
<td>1/16</td>
<td>71</td>
<td>86–92</td>
<td>C₁₅H₁₃N₂O₄ (281.4)</td>
<td>1.1–1.3 (m, 6H), 4.8–5.1 (m, 2H), 7.0–7.9 (m, 15H)</td>
<td>+45.0 (20, 2, MeOH)</td>
</tr>
<tr>
<td>1g</td>
<td>16/6</td>
<td>86</td>
<td>oil</td>
<td>C₁₅H₁₃N₂O₄ (281.4)</td>
<td>0.8 (d, 3H, J = 6.8), 1.0 (d, 3H, J = 6.8), 2.2–2.5 (m, 1H), 2.85 (d, 1H, J = 4.5), 5.2 (d, 2H), 7.0–7.8 (m, 15H)</td>
<td>–143.5 (24, 2, MeOH)</td>
</tr>
<tr>
<td>1h</td>
<td>16/16</td>
<td>90</td>
<td>oil</td>
<td>C₁₅H₁₃N₂O₄ (281.4)</td>
<td>0.8 (m, 6H), 0.9 (m, 6H), 1.1–1.3 (m, 1H), 3.7 (d, 1H, J = 4.8), 4.8–5.2 (m, 1H), 7.0–7.8 (m, 10H)</td>
<td>–106.6 (20, 1, MeOH)</td>
</tr>
<tr>
<td>7a</td>
<td>16/16</td>
<td>85</td>
<td>oil</td>
<td>C₁₅H₁₃N₂O₄ (281.4)</td>
<td>0.7–1.1 (m, 12H), 2.0–2.5 (m, 2H), 3.8 (d, 1H, J = 4.4), 4.5–4.8 (m, 1H), 5.1 (s, 2H), 6.9–7.8 (m, 16H)</td>
<td>–33.85 (20, 1, MeOH)</td>
</tr>
<tr>
<td>7b</td>
<td>16/16</td>
<td>91</td>
<td>oil</td>
<td>C₁₅H₁₃N₂O₄ (281.4)</td>
<td>0.7–1.0 (m, 12H), 1.0–1.2 (m, 6H), 1.8–2.3 (m, 2H), 3.6 (d, 1H, J = 4.5), 4.3–4.5 (m, 1H), 4.7–5.1 (m, 1H), 6.75 (m, 1H), 7.0–7.8 (m, 10H)</td>
<td>–14.6 (20, 1, MeOH)</td>
</tr>
</tbody>
</table>

*a* Yields of isolated product.

*b* Satisfactory microanalyses obtained: C ± 0.4, H ± 0.3, N ± 0.2. Satisfactory HRMS were obtained for 1c, 1g and 1h.

Table 2. Comparison of Optical Rotations of Hydrolysis Products with Commercial Samples

<table>
<thead>
<tr>
<th>Schiff Base</th>
<th>Amino Ester Toseylate</th>
<th>[α]D, <em>c</em></th>
<th>Amino Acid*</th>
<th>[α]D, <em>b</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>t-1e</td>
<td>t-Phe-TsOH (t-4a)</td>
<td>–6.54 (−6.14)</td>
<td>t-Phe (t-5a)</td>
<td>−34.2 (−33.9)</td>
</tr>
<tr>
<td>d-1e</td>
<td>d-Phe-TsOH (d-4b)</td>
<td>–35.8 (−)</td>
<td>d-Phe (d-5b)</td>
<td>−85.5 (−157.9)</td>
</tr>
<tr>
<td>t-1g</td>
<td>t-Val-TosOH (t-4c)</td>
<td>−2.9 (−2.6)</td>
<td>t-Val (t-5c)</td>
<td>+26.7 (+27.0)</td>
</tr>
</tbody>
</table>

*a* Values in parentheses are for commercial samples (Sigma).

*b* c = 2, MeOH for all amino ester tosylate salts.

while phenylglycine derived from the Schiff base 1e was approximately 50% racemized. These results are consistent with the acidities of the parent imines and further illustrate the use of phenylglycine derivatives for a rigorous racemization test in such systems. Attempts to reduce racemization by decreasing the amount of base present in the system from 2.5 to 2.0 equivalents did give somewhat better results in terms of retention of configuration in the product amino acid (for 1e to 5b; optical rotation of −127.4° compared with −85.5°; rotation of an optically pure sample: −157.9°); however, the yield of Schiff base product was reduced as well (61% vs 75%).

Peptide esters can also be prepared by this method as illustrated by the synthesis of the benzyl and isopropyl ester derivatives of l-valyl-l-valine (Table 1). Conversion of the resulting products 7 into the known N-Boc peptide esters as well as independent preparation of compounds 8 by the titanium-mediated transesterification procedure reported by Steglich shows (Table 3) that our transesterification method occurs with retention of stereochemical integrity in the resulting dipeptide derivatives.

The saponification/O-alkylation method described here represents a complimentary alternative to our transamination procedure for the preparation of Schiff base esters.

Table 3. Optical Rotations of Boc-Dipeptide Esters Obtained from Schiff Base Dipeptide Esters

<table>
<thead>
<tr>
<th>Imine Product</th>
<th>[α]D, <em>c</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>This Work</td>
<td>Lit. 13</td>
</tr>
<tr>
<td>7a</td>
<td>−49.8</td>
</tr>
<tr>
<td>7b</td>
<td>−49.2</td>
</tr>
</tbody>
</table>

*a* See Experimental Section for details.

*b* c = 1, MeOH for all samples. This Work: results from hydrolysis of 7a or 7b; Repeat Lit.: repeat of the literature reported procedure in our laboratory.
of both amino acid and peptide derivatives with retention of chirality in the resulting products.

1H-NMR spectra were obtained on a Varian 390 spectrophotometer using TMS as internal standard. Melting points were taken in open glass capillaries with a Thomas Hoover Uni-Melt apparatus and are uncorrected. HPLC was performed on a Waters Associates instrument equipped with an Alltech C-18 column, a Perkin-Elmer LC55 spectrophotometer and a Varian CDS-111 integrator. MeOH/water (80/20 or 90/10) with added NaHCO3 (0.1 g/L) was used as the eluent with a flow rate of 2.0 mL/min with detection at λ = 254 nm. Elemental analyses were performed by either Midwest Microlabs, Ltd. or Merrell-Dow Pharmaceuticals. Optical rotations were determined on a Perkin-Elmer 370 polarimeter. High resolution mass spectra were conducted at Eli Lilly and Company. Amino ester salts were purchased (Aldrich Chemical Co., Sigma Chemical Co. or United States Biochemical Corp.) or prepared from the corresponding amino acid or dipeptide.14

Schiff base methyl esters 3a–d and 6 were prepared by condensation of the corresponding aminoster hydrochlorides with diphenylethylene-imine according to the reported procedure.1 Analytical and spectral data of Schiff base methyl esters not reported in Ref. 7 are given below.

**Methyl N-(Diphenylmethylene)-1-phenylalaninate (3b):** yield: 78%; mp 56–58°C (Et2O/x-hexanes); [α]D20 = –308.3° (c = 2, MeOH).

C23H23NO3 calc. C 80.45 H 6.16 N 4.08 (343.4) found 80.54 6.16 4.34

1H-NMR (CDCl3): δ = 3.1–3.3 (m, 2H), 3.7 (3H), 4.1–4.3 (m, 1H), 6.5–7.7 (m, 15H).

**Methyl N-(Diphenylmethylene)-d-phenylglycinate (3c):** yield: 76%; mp 83–84°C (Et2O/x-hexanes); [α]D20 = +22.5° (c = 2, MeOH).

C23H23NO3 calc. C 80.22 H 5.81 N 4.25 (329.4) found 80.41 5.92 4.28

1H-NMR (CDCl3): δ = 3.6 (3H), 5.2 (s, 1H), 7.0–7.9 (m, 15H).

**Methyl N-(Diphenylmethylene)-l-valinate (3d):** yield: 87%; mp 48–53°C (Et2O/x-hexanes); [α]D20 = –199.8° (c = 2, EtOH).

C23H23NO3 calc. C 77.25 H 7.17 N 4.74 (295.4) found 77.24 7.10 4.64

**Methyl N-(N-(Diphenylmethylene)-l-valyl-l-valinate (6):** yield: 82%; waxy solid.

C24H31NO3S calc. C 73.07 H 7.67 N 7.01 (394.5) found 72.92 7.82 7.11

1H-NMR (CDCl3): δ = 0.8–1.1 (m, 12H), 2.0–2.4 (m, 2H), 3.7 (3H), 3.8 (d, 1H, J = 4.25 Hz), 4.5–4.7 (m, 1H), 7.0–7.8 (m, 11H).

**Schiff Base Benzyl or Isopropyl Esters of Amino Acids 1 and Dipeptides 7; General Procedure:**

Method A, for 1a–f: The benzophenone Schiff base methyl ester 3 (3.9 mmol) is dissolved in 2 mL of distilled CH2Cl2 and this solution is added in one portion to a rapidly stirred solution of 10% aq NaOH (3.9 g, 98 mmol) and Bu4NHSO4 (1.59 g, 4.7 mmol) under N2. The disappearance of starting imine, which is followed by HPLC, is complete after stirring 1 h at r.t. Water (5 mL) and CH2Cl2 (5 mL) are added to the mixture, the layers are separated and the organic layer is washed with water (3 mL). The water layers are washed with CH2Cl2 (2 mL) and the combined organic layers are returned to the reaction flask. Benzyl bromide (0.74 g, 4.3 mmol) or 2-iodopropane (3.32 g, 19.5 mmol) is dissolved in CH2Cl2 (2 mL) and this solution is added dropwise over 5 min to the rapidly stirred solution above. The reaction is complete (appearance of product by HPLC) after stirring 4 h at r.t. The mixture is filtered, evaporated and the residue is dissolved in Et2O (25 mL) and washed with 0.1% aq NaHCO3 (2×15 mL) and brine (1×15 mL). The solution is dried (MgSO4), filtered, evaporated and then purified by either crystallization (Et2O/x-hexanes) or by flash chromatography12 (EtOAc/petroleum ether, bp 30–60°C) to yield products 1 (Table 1).

Method B, for 1g–h and 7a–h: The benzophenone Schiff base methyl ester 3 or 6 (3.4 mmol) is dissolved in MeCN (2 mL) and this solution is added in one portion to a rapidly stirred solution of 20% aq NaOH (1.7 g, 8.5 mmol) and Bu4NHSO4 (1.39 g, 4.1 mmol). The disappearance of starting imine, which is followed by HPLC, is complete after stirring overnight at r.t. The layers are separated and CH2Cl2 (7 mL) is added to the MeCN layer and this organic solution is washed with water (3 mL). The combined aqueous layers are extracted with CH2Cl2 (2 mL) and the combined organic layers are returned to the reaction flask. Benzyl bromide (0.63 g, 3.7 mmol) or 2-iodopropane (2.9 g, 17.1 mmol) is dissolved in CH2Cl2 (2 mL) and added dropwise over 5 min to the rapidly stirred solution. The reaction is complete (appearance of product by HPLC) after stirring overnight at r.t. The solution is filtered, evaporated and the residue dissolved in Et2O (25 mL) and washed with 0.1% aq NaHCO3 (2×15 mL) and brine (15 mL). The organic phase is dried (MgSO4), filtered, evaporated and then purified by flash chromatography13 (EtOAc/ligroin or EtOAc/1,2-dichloroethane/petroleum ether, bp 30–60°C) to yield products 1 or 7 (Table 1).

**1-Phenylalanine Benzyl Esters p-Toluenesulfonate (4a); Typical Procedure:**

To a solution of Ie (2.0 g, 4.8 mmol) in MeCN (100 mL) is added a 0.6 N aq solution of TOSOH (1.8 g, 9.6 mmol) in one portion. The mixture is stirred at r.t. overnight and then the solvent is evaporated, Et2O (200 mL) is added and stirring is continued for 2 h. The resultant crystals are collected and recrystallized from MeOH/Et2O to yield: 1.85 g (93%); mp 159–162°C (Lit.16 mp 160–165°C).

1H-NMR (CDCl3): δ = 2.3 (s, 3H), 3.0–3.3 (m, 2H), 4.1–4.3 (m, 1H), 5.0 (s, 2H), 5.9–6.4 (m, 3H), 6.8–7.8 (m, 14H).

2-Phenylglycine Benzyl Esters p-Toluenesulfonate (4b); yield: 93%; mp 176–178°C.

C23H23NO3S calc. C 63.91 H 5.61 N 3.39 (413.49) found 64.19 5.76 3.33

1H-NMR (CDCl3): δ = 2.3 (s, 3H), 5.0 (s, 2H), 5.2 (s, 1H), 7.0–7.8 (m, 14H), 8.8–9.3 (m, 3H).

-Valine Benzyl Esters p-Toluenesulfonate (4c); yield: 99%; mp 158–161°C (Lit.17 mp 157–159°C).

1H-NMR (CDCl3): δ = 0.7–1.0 (m, 6H), 2.0–2.4 (m, 1H), 2.3 (s, 3H), 3.9 (d, 1H, J = 6.5 Hz), 5.1 (s, 2H), 7.0–8.5 (m, 12H).

**1-Phenylalanine (5a); Typical Procedure:**

1-Phenylalanine benzyl ester p-toluenesulfonate (4a; 1.0 g, 2.4 mmol) is refluxed in 6 N HCl (12 mL, 72 mmol) overnight. The solution is evaporated to dryness and the resulting white solid is stirred with Et2O, filtered and dried to give the crude amino acid hydrochloride. Ion exchange resin (Amberlite IR-120) and deionized water (50 mL/10 mmol of amino acid) are stirred with the amino acid hydrochloride overnight at r.t. The resin is filtered and washed with water, the filtrate is evaporated and the resulting white solid is stirred with Et2O, filtered and dried in a vacuum oven to afford 5a; yield: 0.25 g (63%); mp 280–283°C (Lit.18 mp 283°C).

2-Phenylglycine (5b); yield: 69%; mp 295°C (subl.) [Lit.19 mp 302°C (dec.)].

-Valine (5c); yield: 70%; mp 312–315°C (Lit.20 mp 315°C).

**Formation of Boc-L-Valim-L-Val-OBzI (8a) from the Benzophenone Schiff Base 7a; Typical Procedure:**

Benzyl L-L-Valim-L-Val-Hydrochloride: A solution of 7a (1.0 g, 2.2 mmol) in Et2O (1 mL) is added to 1 N HCl (1.0 mL, 63 mmol) and the resulting two-phase system is stirred for 4 h at r.t. The layers are separated, the aqueous layer is evaporated to dryness and the white crystals are recrystallized from EtOH/H2O; yield: 0.50 g (69%); mp 178–179°C.
Conversion of Benzyl t-Valyl-t-valinate Hydrochloride to 8a: The benzyl t-valyl-t-valinate hydrochloride formed above (0.10 g, 0.3 mmol) is suspended in DMF (1 mL) and Et₃N (0.04 g, 0.4 mmol) is added dropwise with stirring. The mixture is stirred for an additional 30 min and then di-i-tert-butyl dicarbonate (0.06 g, 0.29 mmol) in DMF (1 mL) is added dropwise over 30 min. The resulting solution is stirred overnight at r.t. and then water (5 mL) and EtOAc (5 mL) are added and the layers are separated. The organic layer is washed with 1 N HCl (2 x 2 mL), 5% aqueous NaCl (2 mL), 1 N aq KHC₂O₃ (3 x 2 mL) and 5% aq NaCl (2 mL). The organic layer is dried (MgSO₄), filtered, evaporated and the resulting crude product is recrystallized from EtOAc/ligroin to give 0.089 g 8a; yield: 0.089 g (73%); mp 56–59°C (Lit.13 55–58°C).

Preparation of Boc-i-Val-t-Val-OPr-i (8b) from the Benzophenone Schiff Base 7b:

The isopropyl ester hydrochloride of t-Val-t-Val is prepared from 7b using the procedure described above for 8a with the exception that all operations are carried out in a glove bag under nitrogen because of the hygroscopic nature of the product.

1H-NMR (CDCl₃): δ = 0.7–0.9 (m, 12 H), 1.1–1.2 (m, 6 H), 4.8 (q, 9 H), 1.8–2.2 (m, 2 H), 3.7–3.9 (m, 1 H), 4.3–4.5 (m, 1 H), 4.8–5.2 (m, 2 H), 6.2–6.4 (m, 2 H).

Preparation of Boc-t-Val-t-Val-OH (8a) by Titration Mediated Transesterification: Typical Procedure: Methyl N-t-butoxycarbonyl-t-valyl-t-valinate (0.25 g, 0.76 mmol) is dissolved in absolute THF (10 mL) containing benzyl alcohol (0.82 g, 76 mmol), 4 Å molecular sieves (1.6 g) and titanium isopropoxide (0.10 g, 0.38 mmol). The solution is refluxed under argon for 64 h, the mixture is cooled, filtered through Celite, evaporated in vacuo and excess benzyl alcohol is removed by vacuum pump. The residue is taken up in CH₂Cl₂ (50 mL), and the organic solution is washed with 2 N aq HCl (4×15 mL) and distilled water (15 mL). The solution is dried (MgSO₄), filtered, evaporated, and the residue is recrystallized from EtOAc/ligroin to give 8a; yield: 0.2 g (54%); mp 54–58°C (Lit.13 mp 55–58°C).

Boc-t-Val-t-Val-OPr-i (8b) Methyl N-t-butoxycarbonyl-t-valyl-t-valinate is converted to 8b by the same procedure used for the titrate-mediated transesterification to prepare 8a except that absolute isopropyl (0.46 g, 76 mmol) is used in place of benzyl alcohol. Workup and recrystallized from EtOAc/ligroin to give 8b; yield: 68%; mp 129–132°C (Lit.13 128–130°C).

H-NMR (CDCl₃): δ = 0.7–1.0 (m, 12 H), 1.1–1.2 (m, 6 H), 1.4 (s, 9 H), 1.8–2.2 (m, 2 H), 3.7–3.9 (m, 1 H), 4.3–4.5 (m, 11 H), 4.8–5.2 (m, 2 H), 6.2–6.4 (m, 1 H).

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