Parallel Synthesis of New $\beta^2$-Amino Esters via Conjugate Nucleophilic Additions

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Abstract: The Michael addition of secondary cyclic aromatic and nonaromatic amines to methyl 2-[(tert-butoxycarbonylamino)methyl]acrylate afforded substituted $\beta^2$-amino esters in good to excellent yields.

Key words: addition reactions, eliminations, amines, heterocycles, esters

Naturally occurring $\beta$-amino acids are compounds with an interesting pharmacological profile.1 They are found as components in a wide variety of biologically active compounds,2 for instance in the anticancer agent taxol and peptides.3 The incorporation of $\beta$-amino acids has been successful in creating peptidomimetics4 that have potent biological activity. There are now many examples where $\beta$-amino acids have been used in the design of novel receptor-binding ligands such as adrenocorticotropic, angiotensin II, gastrin, oxytocin, inhibitors of platelet aggregation etc. The effect of incorporation of one additional carbon atom in the target molecule results in a powerful combination of peptide bond stabilisation and conformational manipulation; $\beta$-amino acids are also useful precursors in the synthesis of $\beta$-lactams.5 Moreover, recently Seebach’s6 and Gellman’s7 groups found that $\beta$-peptides (formed exclusively from $\beta$-amino acids) were able to adopt defined three dimensional structures (helical, turn and sheet structures) similar to those of natural peptides. The unnatural $\beta$-peptide backbone is resistant to protease degradation in contrast to $\alpha$-amino acid backbone. This new class of molecules constitutes a novel development in peptide and protein engineering.

Many approaches to the synthesis of $\beta$-amino acids have been published; both the racemic and enantioselective synthesis have been reviewed1,8 but to our knowledge $\beta^2$-amino acids with heterocycles in the side chain have not been described. We have recently explored9 a new efficient carbon–carbon bond forming reaction based on conjugate radical addition to the compound 1 easily obtained in high yield via reaction of HN(Boc)$_2$ with methyl 2-(bromomethyl)acrylate in the presence of potassium carbonate. We describe here the synthesis of new $\beta^2$-amino esters by conjugate nucleophilic addition of aromatic and nonaromatic heterocycles to the compound 2.

Reaction of morpholine (a) or imidazole (b) with the N-diprotected $\beta$-amino ester 1 in MeCN in the presence of K$_2$CO$_3$ at room temperature afforded only the starting material. At 80 °C the reaction did not give the addition compound but the addition-elimination product 3a and 3b (Scheme 1) due to the presence of the two acyl groups on the nitrogen. However, cleavage of one Boc group of 1 using TFA or better Scandium triflate [Sc(OTf)$_3$] afforded quantitively compound 2 which was reacted under the same experimental conditions with morpholine to give the addition compound 4a in 88% yield. A ‘one-pot’ reaction starting from 1, reaction with Sc(OTf)$_3$ and addition of N-benzyloxy carbonylpiperazine (selected because this heterocycle is often used in medicinal chemistry10) gave the addition product 4c in an overall yield of 46% (Scheme 2).

To generalize this methodology, parallel synthesis on the semi-automatic synthesiser ‘Quest 210’ of Argonaut Technologies was evaluated on a 0.5 mmole scale. Eight
secondary amines were selected, the reaction of morpholine was used as a reaction test to compare the result obtained with ‘Quest 210’ and in the standard conditions previously described.

The results gathered in Table 1 show that cyclic secondary amines gave good to excellent results. With noncyclic amines [diisopropylamine, dibenzylamine, R-(+)-N-benzyl-α-methylbenzylamine, 3-methylaminopropanol] no reaction was detected even with an excess (3 equiv) of nucleophile.

### Table 1 Reaction of Different Nucleophiles with 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>NuH</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>morpholine</td>
<td>MeCN</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>4d</td>
<td>piperidine</td>
<td>MeCN</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>4e</td>
<td>4-piperidone ethylene acetal</td>
<td>MeCN</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>4f</td>
<td>4-hydroxypiperidine</td>
<td>DMF</td>
<td>90</td>
</tr>
</tbody>
</table>

DMF was the solvent for the reaction of pyrrole (entry 3) because of the low reactivity of this molecule in MeCN. Indole (entry 4) can react with 2 at C-3 of indole or at the indole nitrogen; the presence in the 13C NMR spectrum of 4j of six CH signals between 102.3 and 128.7 ppm proved that the reaction took place at the indole nitrogen. For 7-azaindole (entry 5) the 13C NMR spectrum showed five CH signals (see experimental part).

In conclusion, we have described a short synthesis of new β2-amino esters in good yields. Methyl 2-[(tert-butoxycarbonyl)amino]methyl]acrylate (1) proved to be a good substrate for nucleophilic attack. This method could be applied to the synthesis of β2,3-amino esters starting from the analogues of 2 substituted in position 3. These precursors could be easily prepared by an aza Baylis–Hillman reaction, the aldehyde being replaced by an imine or by nucleophilic substitution displacing the alcohol functionality of the adducts arising from the Baylis–Hillman reaction with an amine or a carbamate.

Melting points were obtained using a Büchi 510 capillary apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer Fourier-transform spectrometer. 1H NMR spectra were recorded at 250 MHz using a Bruker AC250 instrument or at 400 MHz using a Bruker DRX–400 spectrometer. For 1H NMR spectra recorded in CDCl3, chemical shifts are quoted in parts per million and are referenced to the residual solvent peak. Coupling constants are reported in Hz. Low-resolution mass spectra were recorded on a micromass electrospray instrument with only molecular ion and other major peaks being reported. High-resolution mass spectra (HRMS) were recorded on a Jeol JMS SX 102A spectrometer. Flash chromatography was carried out using E. Merck silica gel (Kieselgel 60, 230–400 mesh) as a stationary phase. TLC was carried out on aluminum plates pre-coated with Merck silica gel 60F254 and were visualised by UV fluorescence or by staining with a 10% methanol-phosphomolybdic acid solution followed by heating. THF was distilled from sodium/benzophenone-ketyl. Reagents were supplied from commercial sources (Aldrich, Fluka).

### Table 2 Reaction of Heterocyclic Nucleophiles with 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>NuH</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4b</td>
<td>imidazole</td>
<td>MeCN</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>4h</td>
<td>2-methyl-5-nitroimidazole</td>
<td>MeCN</td>
<td>traces</td>
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<tr>
<td>3</td>
<td>4i</td>
<td>pyrrole</td>
<td>DMF</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>4j</td>
<td>indole</td>
<td>MeCN</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>4k</td>
<td>7-azaindole</td>
<td>MeCN</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>4l</td>
<td>gramine</td>
<td>MeCN</td>
<td>traces</td>
</tr>
<tr>
<td>7</td>
<td>4m</td>
<td>3-indoleacetic acid</td>
<td>MeCN</td>
<td>0</td>
</tr>
</tbody>
</table>

Methyl 2-[(tert-butoxycarbonyl)amino]methyl]acrylate (1) Method A: Trifluoroacetic acid (0.09 mL, 1.2 mmol) was slowly added to a solution of compound 1 (315 mg, 1 mmol) in CH2Cl2 (5 mL) at 0°C. The mixture was stirred for 18 h at r.t. and treated with sat. aq NaCl solution (20 mL). After neutralisation with aq NaOH solution (3 × 10 mL), the combined organic phases were washed with H2O, dried (MgSO4) and concentrated under reduced pressure to give a white solid (11.3 g, 95%); mp 62°C.

1H NMR (250 MHz, CDCl3); δ = 1.40 (s, 18 H), 3.65 (s, 3 H), 4.40 (s, 2 H), 5.50 (s, 1 H), 6.70 (s, 1 H).

13C NMR (400 MHz, CDCl3); δ = 166.7, 137.1, 125.6, 123.9, 83.1, 52.3, 46.6, 28.4.

MS (ESI): m/z = 316 (M + H)+, 328 (M + Na+), 653 (2 M + Na+). HRMS (FAB+); m/z calcd for C15H26NO6 (M + H+): 316.1760; found: 316.1745.

Methyl 2-[(tert-Butoxycarbonyl)amino]methyl]acrylate (2) Method B: To compound 1 (315 mg, 1 mmol) dissolved in CH2Cl2 (5 mL) at 0°C, Trifluoroacetic acid (0.09 mL, 1.2 mmol) was slowly added to a solution of compound 1 (315 mg, 1 mmol) in MeCN (40 mL). The mixture was stirred for 72 h at r.t. and treated with sat. aq NaCl solution (50 mL). After extraction with EtOAc (3 × 30 mL), the combined organic phases were washed with H2O, dried (MgSO4) and concentrated under reduced pressure to give a white solid (11.3 g, 95%).

1H NMR (250 MHz, CDCl3); δ = 1.40 (s, 18 H), 3.65 (s, 3 H), 4.40 (s, 2 H), 5.50 (s, 1 H), 6.70 (s, 1 H).

13C NMR (400 MHz, CDCl3); δ = 166.7, 137.1, 125.6, 123.9, 83.1, 52.3, 46.6, 28.4.

MS (ESI): m/z = 316 (M + H)+, 328 (M + Na+), 653 (2 M + Na+). HRMS (FAB+); m/z calcd for C15H26NO6 (M + H+): 316.1760; found: 316.1745.
Methyl 3-[(tert-Butoxycarbonyl)amino]-2-(4-morpholinylmethy l)propionate (4a)

To a solution of compound 2 (103 mg, 0.47 mmol) in MeCN (4 mL) was added Cs₂CO₃ (0.46 g, 1.4 mmol) and morpholine (29 µL, 0.27 mmol). The mixture was refluxed for 24 h and treated with sat. aq NaCl solution. The mixture was extracted with EtOAc, the organic phase was dried (MgSO₄) and evaporated under reduced pressure to afford 4a as a pale yellow oil (125 mg, 88%).

1H NMR (250 MHz, CDCl₃): δ = 1.40 (s, 9 H), 2.32–2.38 (m, 4 H), 2.00–2.60 (2 m, 2 H), 2.50–3.00 (m, 1 H), 3.35 (t, J = 5.80 Hz), 3.60–3.63 (m, 4 H), 3.65 (s, 3 H), 5.20 (s, 1 H).

13C NMR (400 MHz, CDCl₃): δ = 28.8, 41.4, 43.6, 52.3, 54.1, 59.0, 67.4, 79.2, 156.2, 174.5.

HRMS (FAB⁺): m/z calcd for C₁₃H₁₆N₂O₄ (M + H⁺): 301.1896; found: 301.1892.

Methyl 3-[(tert-Butoxycarbonyl)amino]-2-[4-benzoyloxy carbonylpiperazin-1-yl)methyl]propionate (4c)

Compound 1 (945 mg, 3 mmol) and Sc(OTf)₃ (0.15 mmol, 73.8 mg) were dissolved in MeCN or DMF (3 mL) was refluxed for 6 h. After hydrolysis with aq sat. NaCl (10 mL), the product was extracted with EtOAc (3 × 10 mL). The organic layer was washed with H₂O, dried (MgSO₄) and evaporated. Purification by column chromatography on silica gel (EtOAc–hexane, 7:1) afforded 4c as a pale yellow oil (125 mg, 88%).

1H NMR (250 MHz, CDCl₃): δ = 1.27 (s, 9 H), 2.30–2.35 (m, 4 H), 2.35–2.37 (m, 1 H), 2.46–2.50 (m, 1 H), 2.69–2.72 (m, 1 H), 3.20–3.25 (m, 2 H), 3.30–3.35 (m, 4 H), 3.55 (s, 3 H), 4.98 (s, 2 H), 5.01 (s, 1 H).

13C NMR (400 MHz, CDCl₃): δ = 24.7, 26.5, 28.8, 41.2, 43.5, 52.2, 55.1, 60.2, 79.5, 128.3, 128.4, 128.9, 137.1, 155.6, 156.2, 174.5.

HRMS (FAB⁺): m/z calcd for C₂₃H₂₇N₂O₅ (M + H⁺): 436.2484; found: 436.2482.

Reaction of Amines with 2 on Quest 210; General Procedure

A mixture of compound 2 (0.5 mmol), the appropriate aromatic heterocycle (1 equiv, 0.5 mmol) and K₂CO₃ (0.345 g, 2.5 mmol) in MeCN or DMF (3 mL) was refluxed for 6 h. After hydrolysis with aq sat. NaCl (10 mL), the product was extracted with EtOAc (3 × 10 mL). The organic layer was washed with H₂O, dried (MgSO₄) and evaporated. Purification by column chromatography on silica gel (EtOAc–hexane, 1:1) provided the products as oils (Table 2).

4b

1H NMR (250 MHz, CDCl₃): δ = 1.40 (s, 9 H), 2.90–3.05 (m, 1 H), 3.25–3.36 (m, 2 H), 3.65 (s, 3 H), 4.15–4.25 (m, 2 H), 4.80 (s, 1 H), 6.90 (s, 1 H), 7.00 (s, 1 H), 7.45 (s, 1 H).

13C NMR (400 MHz, CDCl₃): δ = 28.6, 39.6, 46.3, 48.1, 52.8, 80.3, 144.8, 152.6, 156.4, 172.3.

HRMS (FAB⁺): m/z calcd for C₁₅H₁₈N₂O₄ (M + H⁺): 284.1610; found: 284.1621.

4g

1H NMR (250 MHz, CDCl₃): δ = 1.37 (s, 9 H), 2.88–2.95 (m, 1 H), 3.20–3.31 (m, 2 H), 3.62 (s, 3 H), 4.10–4.18 (m, 2 H), 4.75 (s, 1 H), 6.05 (s, 2 H), 6.54 (s, 2 H).

13C NMR (400 MHz, CDCl₃): δ = 28.8, 40.3, 48.2, 49.0, 52.7, 80.1, 121.4, 126.9, 156.2, 173.3.


4i

1H NMR (250 MHz, CDCl₃): δ = 1.37 (s, 9 H), 2.88–2.95 (m, 1 H), 3.20–3.31 (m, 2 H), 3.62 (s, 3 H), 4.10–4.18 (m, 2 H), 4.75 (s, 1 H), 6.05 (s, 2 H), 6.54 (s, 2 H).

13C NMR (400 MHz, CDCl₃): δ = 28.8, 40.3, 48.2, 49.0, 52.7, 80.1, 121.4, 126.9, 156.2, 173.3.


4j

1H NMR (250 MHz, CDCl₃): δ = 1.45 (s, 9 H), 3.15–3.25 (m, 1 H), 3.35–3.42 (m, 2 H), 3.65 (s, 3 H), 4.20–4.31 (m, 1 H), 4.31–4.40 (m, 1 H), 4.90 (s, 1 H), 6.51–6.72 (m, 6 H).

13C NMR (400 MHz, CDCl₃): δ = 28.8 (CH₃), 40.3 (CH₂), 45.8 (CH₃), 47.0 (CH), 52.7 (CO₂Me), 80.2 (C), 102.3 (CH₃), 109.5 (CH), 120.0 (CH), 121.5 (CH₂), 122.2 (CH), 128.7 (CH), 129.2 (C), 136.3 (C), 156.3 (CeO), 173.5 (CeO).

MS (ESI): m/z = (M + H⁺) 333, (M + Na⁺) 355.

Anal. Calcd for C₁₅H₁₈N₂O₄ (332.4): C, 65.04; H, 7.27; N, 8.42.

Found: C, 64.38; H, 7.31; N, 8.38.
4k

$^1$H NMR (250 MHz, CDCl$_3$): $\delta$ = 1.40 (s, 9 H), 2.95–3.10 (m, 2 H), 3.20–3.35 (m, 1 H), 3.65 (s, 3 H), 4.41–4.62 (m, 2 H), 5.95 (s, 1 H), 6.41–8.20 (m, 5 H).

$^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ = 28.8 (CH$_3$), 39.2 (CH$_2$), 43.2 (CH$_2$), 46.7 (CH), 52.5 (CH), 79.7 (C), 100.6 (CH), 116.4 (CH), 121.0 (C), 129.2 (CH), 129.5 (CH), 143.2 (CH), 148.3 (C), 156.4 (C=O), 173.1 (C=O).

MS (ESI): $m/z$ = (M + H$^+$) 334.

Anal. Calcd for C$_{17}$H$_{23}$N$_3$O$_4$ (333.32): C, 61.25; H, 6.95; N, 12.60. Found: C, 61.18; H, 7.01; N, 12.65.

References


