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A facile stereospecific synthesis of α-hydrazino esters

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Abstract—A convenient route to make α-hydrazino esters from their corresponding α-amino esters is reported. A key step is selective nitrosamine reduction using activated Zn, conc. HCl, and methanol at low temperatures giving nearly quantitative yields of the pure α-hydrazino esters

There has been significant interest in the design and synthesis of α-hydrazino carboxylic acids for incorporation into peptides due to the structural effects and biological activity of the derived peptidomimetics. The α-hydrazino carboxylic acids can be used as inhibitors for various amino acid metabolizing enzymes.[1] In addition, the α-hydrazino carboxylic acids are known to possess antibiotic activities.[2] Also, the α-hydrazino carboxylic acid containing peptidomimetics are metabolically stabilized compared to the natural peptides of similar structure.[3]

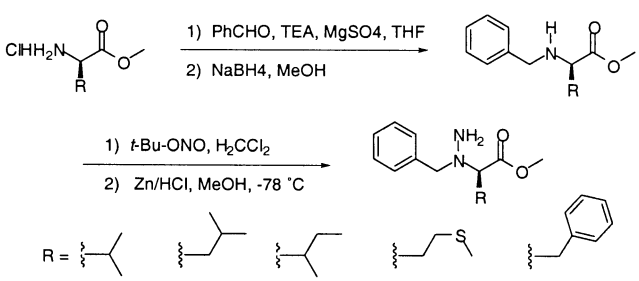
Several methods have been reported for the preparation of α-hydrazino carboxylic acids, most of which involve expensive reagents, laborious methods, or harsh reaction conditions. Previously reported methods for the syntheses of these compounds are; electrophilic aminations with oxaziridines,[4] rearrangement of hydantoic acids,[1c,5] nucleophilic substitution reactions of α-halo carboxylic acids[6] or 2-nosyloxy esters with hydrazine derivatives,[7] or electrophilic C-amination of chiral enolates by dialkyl azodicarboxylates.[8]

Our interest in the synthesis of constrained amino acids,[9] has led to the need L- α-hydrazino esters with a free N_{β}- and a benzyl-protected N_{α}-nitrogen. Herein, we report a very convenient, high yielding method to synthesize α-hydrazino esters from α-amino esters using inexpensive reagents.

Scheme 1 shows the sequence of steps for the preparation of α-hydrazino esters. Starting with the readily available HCl salt of the corresponding L-amino acid esters **1**, the α-amino group is protected by benzyl substitution via a two-step reductive amination procedure.[10–13] The benzyl protected amino acids **3** are then nitrosated with *tert*-butylnitrite in quantitative yields[14] and reduced using zinc/HCl at –78°C to generate the pure α-hydrazino esters **5**.[17]

The yield of the imines **2** increases when excess benzaldehyde is used and removal of excess benzaldehyde is not necessary since it does not affect the yield in the reduction step using excess sodium borohydride; the overall yield is 90–95%. The imines have a distinctive benzylidene proton signal, a singlet around 8 ppm in the ^{1}H NMR, which disappears after the reduction and gives a diastereotopic set of doublets around 3.6 and 3.8 ppm. The β-branched amino acids, Val- and Ile-, strongly favor the *trans* imine. Leu- and Phe- also favor *trans* imine, but Met- gives almost equal amounts of *cis* and *trans* isomers. Met- has a complex ^{1}H and ^{13}C NMR due to the overlap of chemical shifts of the two isomers of the imine, giving sets of multiplets. The methyl protons of -S–CH_3 stereoisomers appear at 2.08 and 2.02 ppm.

The nitrosated amino esters **4** form stereoisomers that give complex ^{1}H and ^{13}C NMR spectra. The isomers show similar multiplicity patterns with different chemi-



Scheme 1.

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cal shifts and intensities. For Met-, the ^{1}H NMR signals of -OCH_3 and -SCH_3 protons are 3.64, 3.50 and 1.95, 1.80 ppm, respectively, for the two isomers of **4d**. For Phe-, the chemical shifts of -OCH_3 protons of the two isomers of **4e** are 3.63 and 3.51 ppm. The purity of the nitrosamines was verified by elemental analysis.[14,15]

The key to the overall synthesis is the reduction of the nitrosamines to the corresponding hydrazines. Previously reported literature procedures for related reactions gave very little to no yield of the desired hydrazine. In most cases, NMR and mass spectrometry results showed the formation of the parent amine, as a result of the cleavage of the N–N bond. We initially studied the reduction under the following conditions: Zn/AcOH/65°C, Zn/AcOH/rt, Zn/aq. HCl/rt, $TiCl_3$/rt, $TiCl_3$/NH_4OAc/rt,[16] Sn/aq. HCl, Zn/conc. HCl/MeOH/rt. The reduction with $TiCl_3$, and Sn did not give any hydrazine product. The reduction with Zn in aqueous HCl at rt gave useful yields of hydrazine product **5** along with the parent amino ester **1**. Attempted separation of these mixtures on flash column, enriched the sample in the amount of parent amino ester **1**. The β-*N* of **4** is apparently much more nucleophilic than the α-*N* of **1** causing much faster oligomer formation due to intermolecular attack on its ester carbon. Therefore, we carefully optimized the conditions to enable facile and rapid isolation of the pure hydrazines **5**.

The best results were obtained with Zn/conc. HCl/MeOH/−78°C.[17] There was a significant increase in the hydrazine **5**/amine **1** ratio with Zn/conc. HCl/MeOH in the order rt, 0°C, −78°C, giving 60/40, 82/18 and 100/0, respectively. For all the nitrosated amino esters tried, we obtained the respective hydrazines in high yield using Zn/conc. HCl/MeOH/−78°C. Reduction using more dilute HCl is not useful due to solidification of the reaction mixture. Reduction at low temperatures apparently increases the selectivity for reduction of the N=O bond over the N–N bond. It is important to perform FAB-MS, ^{1}H and ^{13}C NMR on the hydrazine immediately after the work-up due to the high reactivity of the hydrazine to undergo self-condensation. The hydrazines should be derivatized by acylation on the β-*N* or they can be stored as dilute solutions in H_2CCl_2 at –10°C for 24 h. The complex ^{1}H and ^{13}C NMR spectra of the nitrosamine stereoisomeric mixtures are greatly simplified in the analogous hydrazines.[17] We observed a broad singlet for the β-*N* protons around 3.2 ppm.

The scheme described here is analogous to the route first used by Enders and co-workers in their synthesis of RAMP and SAMP.[18] The difference being that they used LAH reduction of their nitrosamine intermediate, which is not useful in our synthesis since it would reduce the ester function as well.

In model studies, we have derivatized the β-*N* of **5a** and **5b** and the benzyl group was cleanly removed by hydrogenolysis in 95:5 EtOH–AcOH using 10% Pd/C and 50 psi H_2 in a Paar Hydrogenator. The N–N bond is completely inert to these conditions. This selectivity has precedent.[19]

To summarize, we report a convenient, high-yielding synthesis of α-hydrazino esters from the corresponding α-amino esters. The key step is chemoselective reduction of the N=O bond of the nitrosamine intermediates without any N–N bond cleavage using Zn/conc. HCl/MeOH/−78°C. The α-hydrazino esters are susceptible to self-condensation, so they must be prepared and used that same day or they maybe stored as dilute solutions at –10°C for 24 h. The N_α-benzyl-protecting group can be removed by hydrogenolysis without reducing the N–N bond of the hydrazine.

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12. **Typical experimental procedure for Schiff base formation (2)**. The HCl salt of the amino acid **1** (25.5 mmol) is dissolved in dry THF (25 mL) and brought to 0°C. Then $MgSO_4$ (5.1 g), benzaldehyde (51 mmol, 2 equiv.), TEA (25.5 mmol, 1 equiv.) are added and stirred at rt under argon for 5 h. The reaction mixture is filtered and solvent is evaporated under reduced pressure, giving imine **2** as yellow oil, along with excess benzaldehyde.
13. **Typical experimental procedure for reduction (3)**. The Schiff base **2** (25.5 mmol)/benzaldehyde from the previous step is dissolved in dry MeOH (75 mL) and $NaBH_4$ (51 mmol, 2 equiv.) is slowly added. The reaction mixture is stirred under argon for 30 min, quenched with 1N NaOH (20 mL), and extracted three times with ether. Combined ether layers are extracted with saturated NaCl solution, dried with Na_2SO_4, and evaporated under reduced pressure. The benzyl alcohol was removed under high vacuum at rt, giving amine **3** as colorless oil, yield 90–95%.
14. **Typical experimental procedure for nitrosoamine formation (4)**. The benzyl protected amine **3** (1.14 mmol) is dissolved in DCM (10 mL), brought to 0°C, and *tert*-butylnitrite (1.25 mmol, 1.1 equiv.) in DCM was added from an addition funnel. The mixture is brought to rt, refluxed for 3 h, and stirred overnight. The solvent is evaporated under reduced pressure, giving nitrosoamine **4** as yellow oil, yield 100%.
15. Most nitrosoamines and hydrazines are potent carcinogens and must be handled cautiously.
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17. **Typical experimental procedure for hydrazine formation (5)**. The nitrosoamine **4** (1.60 mmol) is dissolved in dry MeOH (15 mL) under argon and charged with conc. HCl (12.8 mmol, 8 equiv.). The reaction mixture is cooled to −78°C, and activated Zn (12.8 mmol, 8 equiv.) is slowly added to the stirred suspension from a solid addition funnel, and stirred under argon at −78°C for 3 h. The excess Zn is filtered cold, and the filtrate is treated with cold 6N KOH until strongly basic, pH 12–13, and extracted with three equal portions of cold ether. Ether layers are combined, dried with Na_2SO_4, and evaporated under reduced pressure from a rt water bath, yield 88%. The neat oil will oligomerize, so the hydrazines must be characterized quickly or stored at low temperature as dilute solutions.

Methyl *N*-amino-*N*-benzyl-(*S*)-valinate (5a). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.33–7.26 (m, 5H), 3.78 (s, 2H), 3.74 (s, 3H), 3.16 (broad, 2H), 3.03 (d, $J=10.2$ Hz, 1H), 2.30–2.15 (m, 1H), 1.09 (d, $J=6.6$ Hz, 3H), 0.92 (d, $J=6.7$ Hz, 3H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 173.66, 138.87, 129.11, 128.83, 127.67, 74.41, 63.16, 51.26, 28.57, 20.16, 20.00; FAB-MS 237.2 $(M+H)^+$.

Methyl *N*-amino-*N*-benzyl-(*S*)-leucinate (5b). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35–7.28 (m, 5H), 3.97 (d, $J=13.3$ Hz, 1H), 3.87 (d, $J=13.3$ Hz, 1H), 3.73 (s, 3H), 3.56 (dd, $J=5.7$, 9.1 Hz, 1H), 3.22 (broad, 2H), 1.90–1.83 (m, 2H), 1.62–1.48 (m, 1H), 0.97 (d, $J=6.4$ Hz, 3H), 0.91 (d, $J=6.4$ Hz, 3H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 174.50, 138.95, 129.21, 128.88, 127.70, 65.68, 62.93, 51.56, 39.39, 25.07, 23.61, 22.01; FAB-MS 251.4 $(M+H)^+$.

Methyl *N*-amino-*N*-benzyl-(*S*)-isoleucinate (5c). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.36–7.26 (m, 5H), 3.77 (s, 2H), 3.76 (s, 3H), 3.16 (d, $J=10.2$ Hz, 1H), 3.09 (broad, 2H), 2.16–1.99 (m, 1H), 1.89–1.73 (m, 1H), 1.46–1.19 (m, 1H), 0.94–0.88 (m, 6H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 173.72, 138.82, 129.15, 128.82, 127.67, 72.50, 63.27, 51.24, 34.19, 25.75, 16.08, 10.75; FAB-MS 251.2 $(M+H)^+$.

Methyl *N*-amino-*N*-benzyl-(*S*)-methioninate (5d). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.34–7.27 (m, 5H), 3.96 (s, 2H), 3.76 (s, 3H), 3.68 (dd, $J=4.8$, 9.9 Hz, 1H), 3.13 (broad, 2H), 2.78–2.60 (m, 2H), 2.32–2.17 (m, 1H), 2.10–1.90 (m, 4H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 173.81, 138.74, 129.23, 128.94, 127.81, 66.04, 63.75, 51.77, 31.44, 29.73, 15.78; FAB-MS 269.2 $(M+H)^+$.

Methyl *N*-amino-*N*-benzyl-(*S*)-phenylalaninate (5e). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.32 (m, 10H); 3.97 (d, $J=13.4$ Hz, 1H), 3.89 (d, $J=13.4$ Hz, 1H), 3.77–3.66 (m, 1H), 3.73 (s, 3H), 3.22–3.18 (m, 2H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 173.35, 139.19, 138.55, 129.71, 129.16, 128.83, 128.62, 127.71, 126.69, 69.38, 63.69, 51.74, 36.35; FAB-MS 285.2 $(M+H)^+$.
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