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Expedient Syntheses of Racemic 2,3-Diaminopropanoic Acid Derivatives

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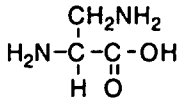
Abstract: *Functionalized 2,3-diaminopropanoic acid derivatives are readily prepared by conjugate addition of amines to dehydroalanine derivatives. The method readily permits differentiation of the two amine groups in substituted 2,3-diaminopropanoic acids and is suitable for the incorporation of substituted β-amino amino acid units within peptides.*

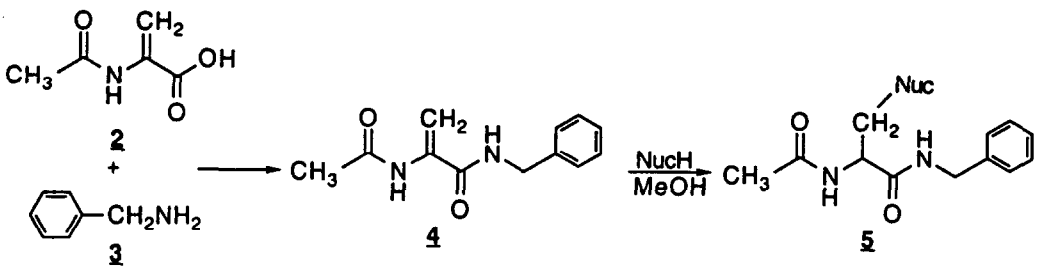
Vicinal diamines are important structural units found in many naturally occurring compounds and medicinal agents.[1] A diamine of particular interest is 2,3-diaminopropanoic acid (1).[1a] This β-amino amino acid is a structural component in bleomycin,[2] sulfazecin,[3] and capreomycin.[4] The biological significance of 2,3-diaminopropanoic acid derivatives has spurred the development of synthetic procedures for these compounds[5-9] and methodologies for differentiating the two amine groups within 1.[9,10] Elaborated routes include the Hofmann[5] and Curtius[6] rearrangements of asparagine derivatives, the Schmidt reaction with aspartic acid,[7] and the Mitsunobu displacement of the hydroxyl group in serine adducts with azides followed by reduction.[8,9] In this paper, we describe a simple procedure for the preparation of functionalized β-amino amino acids using readily available dehydroalanine derivatives.[11] Our report is prompted by a complementary study by Gani and coworkers on the regioselectivity of addition of propylamine to *N*-carbonyl protected dehydroalanines.[12]



1

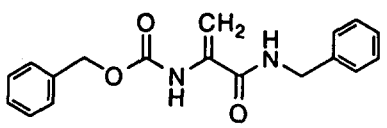
In connection with our development of new anticonvulsant agents,[13] we observed that ammonia, primary amines, and secondary amines readily underwent conjugate addition to *N*-acyldehydroalanine derivatives. When commercially available 2-acetamidoacrylic acid (2) was treated with benzylamine (3) under mixed anhydride coupling conditions[14] (isobutyl chloroformate, 4-methylmorpholine), *N*-acetyldehydroalanine-*N*-benzylamide[15] (4) resulted in a 72% yield (Scheme 1). Treatment of methanolic solutions of 4 with an excess of the amine at room temperature produced the desired functionalized 2,3-diaminopropanoic acid derivatives (i.e., 5a-e) in moderate to excellent isolated yields (22-93%).[16,17] Similarly, use of sodium methanethiolate in place of the amine provided the β-sulfur adduct 5 f (86% yield).

Scheme 1. Synthesis of Compound 5

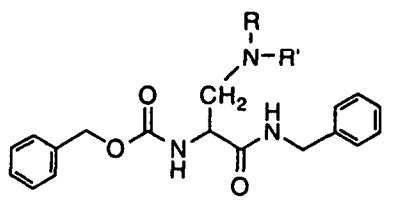


a Nuc = NH_2 (22%)
b Nuc = $N(H)CH_3$ (93%)
c Nuc = $N(H)CH_2CH_3$ (92%)
d Nuc = $N(CH_3)_2$ (92%)
e Nuc = N⌒O (72%)
f Nuc = SCH_3 (86%)

The facility of these conjugate-addition transformations led us to question whether this procedure was applicable for the preparation of functionalized β-amino amino acid derivatives suitable for peptide synthesis. The study of Gani and coworkers[12] indicated that Cbz-dehydroalanine derivatives do not react with amines to give the conjugate β-amino amino acid product. We found that treatment of Cbz-dehydroalanine-*N*-benzylamide (6) with methylamine and dimethylamine led to complex mixtures in which we were unable to isolate 7a and 7b, respectively.



6

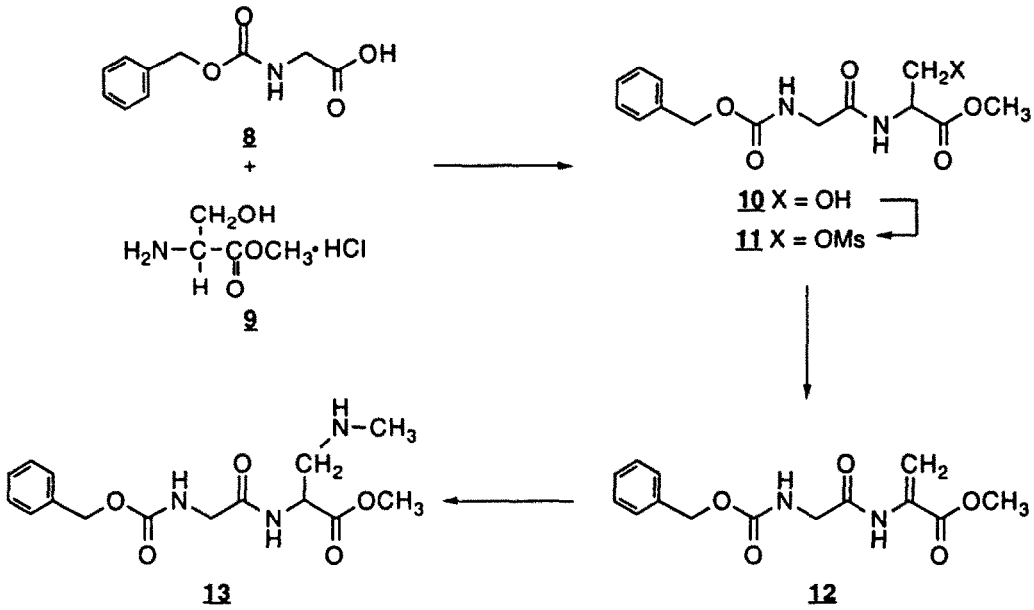


7a R = CH_3, R' = H
b R,R' = CH_3

This result prompted us to modify our strategy. The new approach required initial synthesis of a Cbz or other appropriately protected *N*-substituted *dipeptide* with serine as the second amino acid. Conversion of the serine to the *N*-acyldehydroalanine followed by conjugate addition of the nucleophile would provide a dipeptide unit suitable for oligopeptide synthesis. We tested this method by synthesizing 10 from commercially available Cbz-glycine (8) and DL-serine methyl ester hydrochloride (9), using the mixed anhydride coupling procedure[14] (80%) (Scheme 2). Treatment of 10 with methanesulfonyl chloride in pyridine followed by triethylamine led

to the installation of the dehydroalanine unit in a 60% overall yield. Dissolution of 12 in a methanolic methylamine solution produced 13 in a 30% yield.

Scheme 2. Synthesis of Compound 13



The ease and efficiency of conjugate addition of amines to *N*-acyldehydroalanine derivatives provide an attractive method to construct substituted 2,3-diaminopropanoic acid derivatives. The procedure readily differentiates the two amino residues in 1, is amenable to the incorporation of functionalized 2,3-diaminopropanoic acid units within peptides, and is suitable for the synthesis of β-thiosubstituted amino acid derivatives.

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16. General Procedure: The amine (15-22 equiv) was added to a stirred methanolic solution of 4 (~7 mL methanol/mmol of 4) at room temperature. The solution was maintained at room temperature (1-4 d) and the solvent was removed *in vacuo*. The residue was either triturated with diethyl ether or purified using column chromatography to provide the desired functionalized 2,3-diaminopropanoic acid 5.
17. Satisfactory spectral (IR, ^{1}H and ^{13}C NMR, low and high resolution mass) data were obtained for all compounds reported in this study. Select data: Compound 5a: mp 119-120 °C; ^{1}H NMR ($CDCl_3$) δ 2.04 (s, C(O)CH_3), 2.70 (dd, *J* = 8.1, 12.0 Hz, CHH'NH_2), 3.36 (dd, *J* = 2.4, 12.0 Hz, CHH'NH_2), 4.28-4.34 (m, CH), 4.45 (d, *J* = 6.0 Hz, $NHCH_2$), 6.85 (br d, *J* = 5.1 Hz, NH), 7.25-7.36 (m, 5 PhH), 7.91 (br s, NH). Compound 5b: mp 107-108 °C; ^{1}H NMR ($CDCl_3$) δ 2.01 (s, C(O)CH_3), 2.40 (s, $NHCH_3$), 2.53 (dd, *J* = 8.4, 11.7 Hz, CHH'N(H)CH_3), 3.14 (dd, *J* = 3.3, 11.7 Hz, CHH'N(H)CH_3), 4.30-4.34 (m, CH), 4.33-4.51 (m, $NHCH_2$), 6.87 (br d, *J* = 3.9 Hz, NH), 7.24-7.35 (m, 5 PhH), 8.25 (br s, NH). Compound 5c: mp 90-91 °C; ^{1}H NMR ($CDCl_3$) δ 1.03 (t, *J* = 7.2 Hz, $NHCH_2CH_3$), 2.01 (s, C(O)CH_3), 2.50 - 2.61 (m, CHH'N(H)CH_2CH_3), 2.50 - 2.72 (m, $NHCH_2CH_3$), 3.16 - 3.21 (m, CHH'N(H)CH_2CH_3), 4.31 - 4.37 (m, CH), 4.35 - 4.51 (m, $NHCH_2$), 6.94 (br d, *J* = 5.4 Hz, NH), 7.24 - 7.35 (m, PhH), 8.43 (br s, NH). Compound 5d: mp 125-126 °C; ^{1}H NMR (DMSO-d_6) δ 1.83 (s, C(O)CH_3), 2.15 (s, $N(CH_3)_2$), 2.32-2.49 (m, $CH_2N(CH_3)_2$), 4.25-4.28 (m, $NHCH_2$), 4.36-4.44 (m, CH), 7.20-7.37 (m, 5 PhH), 7.99 (br d, *J* = 7.8 Hz, NH), 8.55 (br t, *J* = 5.4 Hz, NH). Compound 5e: mp 147-148 °C; ^{1}H NMR ($CDCl_3$) δ 2.03 (s, C(O)CH_3), 2.29-2.42 (m, CHH'N(CHH'$CH_2)_2$O), 2.71-2.79 (m, CHH'N(CHH'$CH_2)_2$O), 3.45-3.56 (m, N($CH_2CH_2)_2$O), 4.31 (dd, *J* = 4.2, 14.4 Hz, NHCHH'), 4.34-4.39 (m, CH), 4.58 (dd, *J* = 6.3, 14.4 Hz, NHCHH'), 6.58 (br d, *J* = 3.3 Hz, NH), 7.26-7.37 (m, 5 PhH), 8.33 (br s, NH). Compound 5f: mp 142-143 °C; ^{1}H NMR ($CDCl_3$) δ 2.02 (s, C(O)CH_3), 2.15 (s, SCH_3), 2.78 (dd, *J* = 7.8, 13.8 Hz, CHH'SCH_3), 2.90 (dd, *J* = 5.4, 13.8 Hz, CHH'SCH_3), 4.46 (d, *J* = 5.7 Hz, $NHCH_2$), 4.52-4.57 (m, CH), 6.56 (br d, *J* = 6.6 Hz, NH), 6.93 (br s, NH), 7.26-7.36 (m, 5 PhH). Compound 13: syrup; ^{1}H NMR ($CDCl_3$) δ 2.37 (s, $NHCH_3$), 2.90 (dd, *J* = 5.0, 12.5 Hz, CHH'N(H)CH_3), 3.00 (dd, *J* = 3.6, 12.5 Hz, CHH'N(H)CH_3), 3.73 (OCH_3), 3.91 (d, *J* = 5.4 Hz, $NHCH_2$), 4.60-4.66 (m, CH), 5.11 (s, $PhCH_2$), 5.49 (br s, NH), 6.89 (br d, *J* = 7.2 Hz, NH), 7.33 (s, 5 PhH).

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