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A simple method for preparation of *N*-mono- and *N*,*N*-di-alkylated α-amino acids

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Abstract

Reactions of α-amino acids with ketones under hydrogenation conditions using 20% $Pd(OH)_2/C$ as the catalyst gave *N*-mono-alkylated amino acids in high yields. Reductive methylation of *N*-mono-alkylated amino acids under the same hydrogenation conditions at 50°C afforded *N*,*N*-di-alkylated amino acids in excellent yields. This simple method has been used to synthesize *N*-mono- and *N*,*N*-di-alkylated amino acids on a scale of 200 g. © 2000 Elsevier Science Ltd. All rights reserved.

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N-alkylated amino acids are important synthetic building blocks in medicinal chemistry. The simplest way to synthesize *N*-alkylated amino acids is by reductive alkylation of protection-free α-amino acids. Bowman[1] and Quitt et al[2] have described a procedure where α-amino acids react with aldehydes under hydrogenation conditions to give *N*-alkylated amino acids. However, the scope of the reactions was limited to those amino acids with lipophilic side chains and aldehydes. Our recent literature search has shown that most reductive alkylation of amino acids with ketones were carried out using $NaBH_3CN$,[3] instead of using catalytic hydrogenation conditions. Furthermore, there are indications in the literature that histidine and tryptophan do not work well under hydrogenation conditions; only benzylation and dimethylation of histidine have been reported in the literature.[4] For example, Ebata et al have noted that histidine and tryptophan failed in their efforts to *N*-methylate α-amino acids using the method of Quitt et al, which involved two reductive alkylation steps under hydrogenation conditions.[5]

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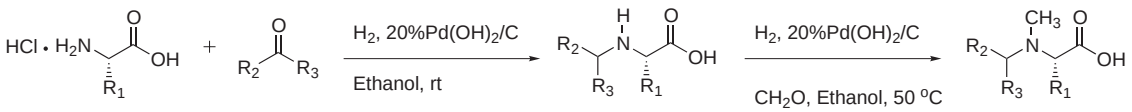
Our efforts on a calcium channel project called for preparation of *N*-alkylated amino acids on a relatively large scale. We found that in the presence of 20% $Pd(OH)_2/C$ and hydrogen, leucine and valine reacted readily with several ketones at ambient temperature to give the corresponding *N*-mono-alkylated amino acids in absolute ethanol; no dialkylated product was detected (Scheme 1). The *N*-mono-alkylated amino acids were sparingly soluble in most organic solvents. They precipitated out of the solution and mixed with the catalyst. The most convenient way to isolate and purify the final product was to treat the reaction mixture with concentrated HCl, to dissolve the *N*-mono-alkylated amino acids as their HCl salt, and remove the catalyst by filtration. Neutralization (pH 6.5) with aqueous NaOH solution generated the *N*-mono-alkylated amino acids. Trituration with water at 50°C gave the desired pure products. It is worth noting that the reaction of valine with 2-butanone at ambient temperature was sluggish, it could be due to steric reasons. However, when the reaction temperature was elevated to 45°C, the reaction proceeded readily to give compound **7** in a moderate yield, again no *N*,*N*-dialkylated product was observed.



Scheme 1.

The *N*-mono-alkylated amino acids can be further methylated by reaction with formaldehyde under the hydrogenation conditions at 50°C in good to excellent yields, even in the case of compound **9** where the nitrogen is quite sterically hindered, the reaction worked well.

It is noteworthy that this method is suitable for scale up. Compound **2** was made on a 200 g scale. Results are summarized in Table 1.

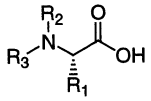
Evaluation of the reactions of a number of amino acids, including amino acids with hydrophilic side chains, with cyclohexanone revealed that this method works well for amino acids with lipophilic side chains; reactions of amino acids with hydrophilic side chains, in general, gave less satisfactory results, similar to the reactions of this type involving aldehydes as described in the literature. For example, when asparagine was reacted with cyclohexanone using this method, the desired product was isolated in a low yield and most of the starting amino acid was recovered. Similar results were obtained with glutamine, aspartic acid, and glutamic acid.

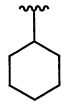
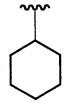
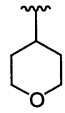
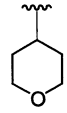
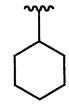
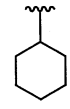
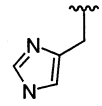
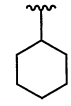
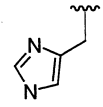
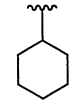
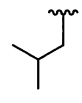
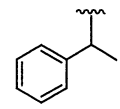
However, this method worked in the case of histidine. The reaction with aldehydes at ambient temperature did not stop at the monoalkylation stage, and some dialkylation also occurred, affording a mixture of mono- and di-alkylated product.[6] However, the reaction with cyclohexanone gave the corresponding *N*-mono-alkylated histidines in good yield. Compound **10** was also methylated at 50°C with formaldehyde to afford compound **11** in 70% yield (see Table 1).[7]

Reductive alkylation of amino acids with benzylaldehyde under hydrogenation conditions has been reported in the literature,[4] but the reaction of leucine with acetophenone did not afford the desired product (Table 1, entry 12).

Since the isolation and purification of final products involved an acid–base work up, racemization could occur. To address the possibility of racemization, racemate **12**, which was made from DL-leucine by this method, was coupled with (*S*)-1-phenyl-ethylamine to give a mixture of diastereomers **13**, and compound **3** was converted to amide **14** using the same coupling method. A HPLC analytical method has been developed with which the baseline separation of the two diastereomers **13** was achieved. Amide **14** was analyzed under the same

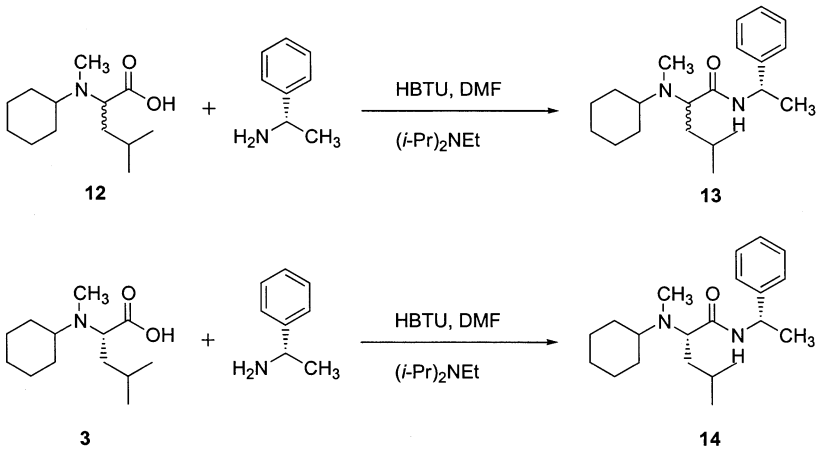
Table 1
Yields of *N*-mono- or *N*,*N*-di-alkylated amino acids



Compound #	R_1	R_2	R_3	Yield (%)[a]
1			H	51
2			H	93
3			Me	73
4			H	54
5			Me	92
6			H	92
7			H	54
8			H	70
9			Me	58
10			H	80
11			Me	70
12			H	0

[a] The yields were not optimized. Products were characterized by ^{1}H-NMR, IR, MS, and microanalysis.

HPLC conditions; only one stereoisomer was detected, indicating that the racemization was <5% during the two hydrogenation reactions and subsequent acid–base work up (Scheme 2).



Scheme 2.

Representative procedure A for the preparation of *N*-mono-alkylated amino acids is as follows: A mixture of L-leucine (100 g, 0.76 mol) and cyclohexanone (149 g, 1.5 mol) was agitated in an atmosphere of hydrogen (pressure, 50 psi) at room temperature in absolute ethanol (1.6 L) in the presence of $Pd(OH)_2/C$ (20%, 8 g) until the absorption of hydrogen almost ceased and was then filtered. The filtrate was concentrated to afford a solid. The solid was combined with the solid from the filter funnel and treated with concentrated aqueous HCl (36.5%) until the desired product was dissolved in the acidic aqueous solution, the catalyst was then removed by filtration. The filtrate was treated with aqueous NaOH (50%) to adjust the pH to 6.5. White solid precipitated out, which was isolated via filtration. The white solid was triturated with a small amount of water at 50°C, then the mixture was filtered at 30–40°C. The resulting white solid was washed with acetone (3×500 mL) and dried under vacuum. The pure desired product **2** (151 g, 93%) was isolated as a white solid: mp >280°C; IR 3078, 2931, 1577, 1456, 1397, 1291, 837 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.939 (d, $J=6.27$ Hz, 3H, $HC(CH_3)_2$), 0.950 (d, $J=6.27$ Hz, 3H, $HC(CH_3)_2$), 1.05–1.19 (m, 1H, CH), 1.22–1.38 (m, 4H, 2×CH_2), 1.60–1.79 (m, 6H, 3×CH_2), 1.98–2.09 (m, 2H, CH_2), 2.98–3.05 (m, 1H, CH), 3.95 (dd, $J=5.55$, 7.96 Hz, 1H, $CHCO_2H$), 15.95 (bs, 2H, NH_2); MS(APCI$^+$): m/z 214.2 (MH^+). Anal. calcd for $C_{12}H_{23}N_1O_2 \cdot 0.06NaCl$: C, 66.47; H, 10.69; Cl, 0.98; N, 6.46. Found: C, 66.41; H, 10.69; Cl, 1.17; N, 6.37.

The following compounds were prepared in a manner similar to that described for compound **2**. Compound **1**: mp 293–296°C (dec.); IR 3070, 2955, 2871, 2418, 1573, 1380, 1358, 1292, 842, 565 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.938 (d, $J=6.03$ Hz, 3H, $HC(CH_3)_2$), 0.953 (d, $J=5.79$ Hz, 3H, $HC(CH_3)_2$), 1.26 (d, $J=6.51$ Hz, 6H, $HC(CH_3)_2$), 1.61–1.78 (m, 3H, CH and CH_2), 3.33 (septet, $J=6.51$ Hz, 1H, $HC(CH_3)_2$), 3.87 (dd, $J=8.20$, 5.30 Hz, 1H, $CHCO_2H$), 11.6 (bs, 2H, NH_2), MS(APCI$^+$): m/z 174.2 (MH^+). Anal. calcd for $C_9H_{19}N_1O_2$: C, 62.39; H, 11.05; N, 8.08. Found: C, 62.50; H, 10.86; N, 8.08. Compound **4**: mp >300°C; IR 3059, 2961, 2845, 1576, 1470, 1399, 1383, 1284, 1094, 1015, 843, 543 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.941 (d, $J=6.27$ Hz, 3H, $HC(CH_3)_2$), 0.950 (d, $J=6.27$ Hz, 3H, $HC(CH_3)_2$), 1.56–1.82 (m, 5H, CH and CH_2), 1.88–2.00 (m, 2H, CH_2), 3.29–3.36 (m, 3H, CH and CH_2), 3.89–3.99 (m, 3H, CH and CH_2), 11.9 (bs, 2H, NH_2, obscured by water peak); MS(APCI$^+$): m/z 216.2 (MH^+). Anal. calcd for $C_{11}H_{21}N_1O_3$: C,

61.37; H, 9.83; N, 6.51. Found: C, 61.39; H, 9.87; N, 6.40. The HCl salt of compound **10**[7]: mp 139–141°C; IR 3408, 2934, 2857, 2784, 1625, 1538, 1453, 1392, 832, 816, 622, 537 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.04–1.38 (m, 5H, CH and CH_2), 1.57–1.61 (m, 1H, CH), 1.73–1.76 (m, 2H, CH_2), 1.96–2.04 (m, 2H, CH_2), 3.02–3.23 (m, 3H, CH and CH_2), 4.01 (t, $J=6.99$ Hz, 1H, C*H*CO_2H), 7.34 (d, $J=1.21$ Hz, 1H, ArH), 8.56 (d, $J=0.965$ Hz, 1H, ArH); MS(APCI$^+$): m/z 238.2 (MH^+). Anal. calcd for $C_{12}H_{19}N_3O_2 \cdot 1.25HCl \cdot 0.45H_2O$: C, 49.53; H, 7.33; Cl, 15.23; N, 14.44. Found: C, 49.22; H, 7.45; Cl, 15.14; N, 14.59. Compound **8** has been reported previously.[8]

Representative procedure B for the preparation of *N*-mono-alkylated amino acids, which have appreciable solubility in neutral aqueous media, is as follows: A mixture of L-valine (29.3 g, 0.25 mol) and acetone (18.4 mL, 0.25 mol) was agitated in an atmosphere of hydrogen (pressure, 50 psi) at room temperature in absolute ethanol (500 mL) in the presence of $Pd(OH)_2/C$ (20%, 4 g) until the absorption of hydrogen almost ceased, then filtered. The filtrate was concentrated to afford a solid. The solid was combined with the solid from the filter funnel and treated with concentrated aqueous HCl (36.5%) until the desired product was dissolved in the acidic aqueous solution, then the catalyst was removed by filtration. The filtrate was treated with aqueous NaOH (50%) to adjust the pH to 6.5. The solvent was stripped off azeotropically with added methanol affording a white solid. The solid was extracted twice with an excess amount of methanol. The combined methanol extract was concentrated in vacuo to give a white solid. Recrystallization from methanol gave 36.5 g (92%) of compound **6**[8] as white crystals: mp >250°C; MS(APCI$^-$): m/z 160.2 (MH^+). Anal. calcd for $C_{13}H_{25}N_1O_2$: C, 60.35; H, 10.76; N, 8.80. Found: C, 60.16; H, 10.8; N, 8.71. The HCl salt of compound **7** was prepared according to this procedure except that the reaction was run at 45°C and also the work-up was different. After removing the catalyst by filtration, the solvent of the acidic aqueous solution was stripped off azeotropically with added methanol affording a white solid. Trituration with acetone gave the HCl salt of compound **7** (a 1:4 mixture of diastereomers) as a white solid: mp (for the parent compound) 221–222°C; IR 2972, 2884, 1748, 1732, 1563, 1469, 1367, 1220, 1193, 1172, 842 cm^{-1}; ^1H NMR (for the major diastereomer, DMSO-d_6) δ 0.868 (t, $J=7.48$ Hz, 3H, CH_2CH_3), 0.978 (d, $J=6.99$ Hz, 3H, $HC(CH_3)_2$), 1.05 (d, $J=7.23$ Hz, 3H, $HC(CH_3)_2$), 1.24 (d, $J=6.51$ Hz, 3H, $CHCH_3$), 1.41–1.54 (m, 1H, CH), 1.78–1.88 (m, 1H, CH), 2.31–2.38 (m, 1H, CH), 3.01–3.09 (m, 1H, CH_2CHCH_3), 3.81 (d, $J=3.86$ Hz, 1H, C*H*CO_2H); MS(APCI$^+$): m/z 174.2 (MH^+). Anal. calcd for $C_9H_{19}N_1O_2 \cdot 0.95HCl \cdot 0.10H_2O$: C, 51.55; H, 9.69; Cl, 16.06; N, 6.68. Found: C, 51.25; H, 9.55; Cl, 15.76; N, 6.89.

A representative procedure for the preparation of *N*,*N*-di-alkylated amino acids is as follows: A mixture of (*S*)-2-cyclohexylamino-4-methyl-pentanoic acid (6.4 g, 30 mmol) and aqueous HCHO (7 mL of 37.2%, 2.6 g, 87 mmol) was agitated in an atmosphere of hydrogen (pressure, 50 psi) at 50°C in absolute ethanol (250 mL) in the presence of $Pd(OH)_2/C$ (20%, 1 g) until the absorption of hydrogen almost ceased. The catalyst was removed by filtration. The filtrate was concentrated in vacuo to dryness. Water (50 mL) was added and concentrated to dryness, this operation was repeated twice to remove most of the HCHO. The white solid collected was triturated with hot acetone, then cooled to 0°C for 10 minutes. Filtration and drying under vacuum gave 5.0 g (73%) of the desired product **3** as a white solid: mp 185–187°C (dec.); IR 2931, 2857, 1615, 1470, 1453, 1352, 1281, 1102, 844, 556 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.843 (d, $J=6.59$ Hz, 3H, $HC(CH_3)_2$), 0.872 (d, $J=6.59$ Hz, 3H, $HC(CH_3)_2$), 1.15–1.80 (m, 13H, CH and CH_2), 2.35 (s, 3H, NCH_3), 2.64–2.76 (m, 1H, NCH), 3.30 (dd, $J=8.06$, 6.78 Hz, 1H, C*H*CO_2H); MS(APCI$^-$): m/z 226.2 (M–H). Anal. calcd for $C_{13}H_{25}N_1O_2$: C, 68.68; H, 11.08; N, 6.16. Found: C, 68.69; H, 11.3; N, 6.10.

The following compounds were prepared in a manner similar to that described for compound **3**. Compound **5**: mp 185–190°C (dec.); IR 2959, 2867, 1628, 1464, 1337, 1253, 1094, 886.0, 567.3 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.834 (d, $J=6.59$ Hz, 3H, HC(CH_3)$_2$), 0.868 (d, $J=6.59$ Hz, 3H, HC(CH_3)$_2$), 1.31–1.46 (m, 4H, CH and CH_2), 1.57–1.76 (m, 3H, CH and CH_2), 2.26 (s, 3H, NCH_3), 2.68–2.77 (m, 1H, NCH), 3.18–3.29 (m, 2H, 2×CH), 3.35 (t, $J=7.51$, 1H, $CHCO_2H$), 3.82–3.86 (m, 2H, 2×CH); MS(APCI$^+$): m/z 230.2 (MH^+). Anal. calcd for $C_{12}H_{23}N_1O_3$: C, 62.85; H, 10.11; N, 6.11. Found: C, 62.81; H, 10.24; N, 6.05. Compound **9** (recrystallized from methanol instead of triturating with acetone): mp 175–177°C (dec.); IR 3053, 2932, 2859, 1631, 1617, 1473, 1314, 1108, 1086, 987, 772, 554 cm^{-1}; ^1H NMR (DMSO–d_6) δ 0.961 (d, $J=6.51$ Hz, 3H, HC(CH_3)$_2$), 1.09 (d, $J=6.51$ Hz, 3H, HC(CH_3)$_2$), 1.08–1.61 (m, 5H, CH and CH_2), 1.80–1.83 (m, 2H, CH_2), 1.83–2.20 (m, 2H, CH_2), 2.34–2.43 (m, 1H, NCH), 2.70 (s, 3H, NCH), 2.91–3.35 (m, 1H, CH), 4.03 (s, 1H, $CHCO_2H$), 13.4 (bs, 1H, CO_2H); MS(APCI$^+$): m/z 214.3 (MH^+). Anal. calcd for $C_{12}H_{23}N_1O_2$: C, 67.57; H, 10.87; N, 6.57. Found: C, 67.38; H, 10.85; N, 6.53. The HCl salt of compound **11**[7]: mp 199–200°C; IR 3445, 3142, 2983, 2670, 1620, 1457, 1427, 1395, 1264, 1006, 958, 856, 634 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.02–1.31 (m, 5H, CH and CH_2), 1.52–1.55 (m, 1H, CH), 1.68–1.70 (m, 2H, CH_2), 1.77–1.79 (m, 2H, CH_2), 2.46 (s, 3H, NCH_3), 2.75–2.81 (m, 1H, NCH), 3.00–3.10 (m, 2H, $ArCH_2$), 3.89 (t, $J=7.48$ Hz, 1H, $CHCO_2H$), 7.37 (d, $J=0.965$ Hz, 1H, ArH), 8.81 (d, $J=1.45$ Hz, 1H, ArH); MS(APCI$^-$): m/z 250.2 (M−H). Anal. calcd for $C_{13}H_{21}N_3O_2{\cdot}HCl{\cdot}H_2O$: C, 51.06; H, 7.91; N, 13.74. Found: C, 50.87; H, 8.11; N, 13.68.

Acknowledgements

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6. The aldehydes used in these experiments were cyclohexanecarboxaldehyde and 3-methyl-butyraldehyde, and similar results were obtained. The molar ratio of histidine and aldehydes was 1:2. The reactions using 1:1 molar ratio of histidine and aldehydes were not investigated.
7. The procedures for preparation of compound **10** and **11** were slightly different from those described in the representative procedures. Additional one equivalent of HCl in ethanol was added to the mixture of starting materials. Consequently, the HCl salts were isolated as the final product and the work-up procedures were also different. For compound **10**, after the absorption of hydrogen almost ceased, the catalyst was removed by filtration. The filtrate was concentrated in vacuo to give a pale amber semi-solid. Trituration with acetonitrile gave a white solid. Recrystallization from methanol and acetone gave the pure desired product. For compound **11**, the compound was purified by recrystallization from ethanol.
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