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Efficient Synthesis of α-Substituted Amino Acid Ester: Alkylation and Hydrogenation Removal of Schiff's Base Protecting Group

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Abstract: A general and efficient synthetic route to α-amino acids by alkylation of the sodium salt of Schiff base ester **1** has been described previously. The α-substituted ethyl glycinates **4a–g** are prepared in excellent yield by a two-step sequence involving regioselective alkylation of the anionic glycine synthon **2** with various alkyl halides, followed by purification of the alkylated Schiff base on florisil and cleavage by catalytic hydrogenolysis. Reducible groups on the side chain may be reduced or preserved depending upon the deprotecting method utilized.

Keywords: Alkylation; Base; Ethyl; Glycinates; Schiff

INTRODUCTION

There is a great demand for an efficient method for the synthesis of natural and synthetic biologically active α-amino acids. Several approaches recently have been reported for highly stereospecific synthesis of amino acids from a bis-lactum.[1–4] Among the conventional methods for the preparation of α-amino acids, alkylation of glycine ester derivative has a particular advantage to prepare structurally diversified α-amino acids from a single starting material by the choice of alkylating agents. A number of higher homologs of amino acids have successfully been prepared by the alkylating route.[5–7] The standard condition employed in this technique involves generation of an anionic synthon either in the presence of a strong base or under various phase-transfer conditions.[8–12] The

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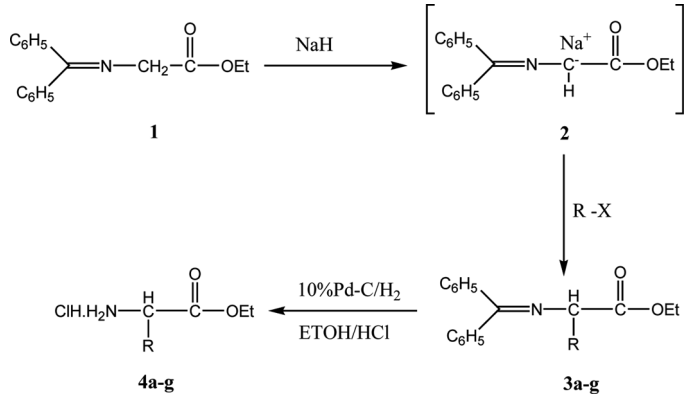


Scheme 1.

anion, thus generated, reacts with alkyl halides, giving α-substituted amino acids. The main limitation of this method is the instability of the ketimine or aldimine intermediate toward silica gel, making it necessary to hydrolyze the alkylated adduct immediately to the corresponding amino acids or esters without any purification.[8,13] Achqar et al.[14] used 2-hydroxypinane-3-one in which the OH group ortho to the carbonyl carbon prevented decomposition by chelating with the N-atom of the amine.

Our initial target was to find a synthetic route that would overcome these limitations and extend the scope and generality of the technique. This synthetic approach to α-substituted amino acids draws on the Stork et al.[7] procedure using NaH. Saturated and unsaturated amino acid esters were obtained in good to excellent yield by adding 0.98 equivalent alkyl halide derivative in benzene to a solution of anion in benzene. Because benzene is toxic, it should be properly disposed of. Alternatively, the reaction could be run in anhydrous dimethoxyethane. After gentle refluxing, the reaction mixture was cooled, quenched with ethanol, and worked up. The Schiff base was purified by flash chromatography over florisil, on which it was stable. Prior to our work, there was not a single example in the literature of cleavage of ketimine by catalytic hydrogenolysis. The C=N bond was conventionally hydrolyzed by refluxing with aqueous acid. In our hands, the ketimine was rapidly removed at room temperature by hydrogenolysis under neutral conditions using 10% palladium/charcoal. Addition of 2 mol excess of conc. HCl halved the reaction time. The esters (**4d–f**) were characterized as their stable oxalate salts, because the hydrochlorides were hygroscopic.

The use of florisil for purification of the alkylated Schiff base followed by catalytic hydrogenolysis under neutral or acidic condition is therefore an attractive approach to synthesis of a variety of amino acids.

EXPERIMENTAL SECTION

Melting points (Pyrex® capillary) were determined on a Thomas Hoover capillary melting-point apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a GE,QE 300-MHz instrument and are reported in parts per million (ppm) relative to tetramethylsilane (TMS) (1%) as an internal standard. Fourier transform infrared (FTIR) spectra were recorded on a Nicolet 5DX spectrometer using KBr pellets unless otherwise specified. Elemental analyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley. All reactions were followed by thin-layer chromatography (TLC) carried out on Uniplate silica-gel GF (Analtech) plates. For purity tests of all compounds, a single spot (visualized by UV light and iodine vapor) was obtained. Florisil (200–300 mesh, Fluka) was used for flash chromatographic separation. Solutions were dried over Na_2SO_4 and concentrated using a Büchi rotary evaporator under water aspirator vacuum.

Alkylation of Schiff's Base Ester (1): General Procedure

A solution of **1** (1.0 g, 3.75 mmol) in dry benzene (5 mL) was added to a stirred suspension of NaH (0.098 g, 4.1 mmol; 60% oil dispersion) in dry benzene (1.5 mL) under argon. The mixture was refluxed gently at 90–95 °C for 1 h. The flask was removed from the heating bath, and a solution of alkyl halide (3.59 mmol) dissolved in a minimum quantity of benzene (~20 mL) was added through a dropping funnel. After the addition, the reaction mixture was gently refluxed with stirring until the starting material disappeared (checked by TLC analysis). The reaction mixture was cooled, and a small quantity of ethanol (~2 mL) was added to destroy unreacted NaH. The solution was concentrated, and the residue was partitioned between water and ether. The ether fraction was dried ($MgSO_4$), filtered, and concentrated to yield a gummy brown liquid. Flash chromatography on florisil gave monoalkylated Schiff base (**3a–g**).

Ethyl-N-(diphenylmethylene)phenylalaninate (3a)

Flash chromatography (5% ethyl acetate–benzene) gave an orange solid crystallized from benzene–pentane into pale yellow crystals, mp 65–67 °C (lit.[15] mp 68.5–69 °C).

Ethyl-N-(diphenylmethylene)-p-nitrophenylalaninate (3b)

Flash chromatography (4% ethyl acetate–benzene) gave an oil. It was then crystallized from ethanol into orange crystals, mp 104–105 °C, Rf = 0.48 (10% ethyl acetate–benzene). IR (KBr) 3071.9, 2987.5, 2959.4 (CH=CH, & CH_2-CH_2), 1743.0 (CO_2CH_2-), 1623.4 (N=C), 1595.3, 1567.2 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (t, 3H, CH_3), 3.4 (t, 2H, OCH_2), 4.5 (m, 1H, CH), 7.4–8.1 (m, 14H, aromatic). Anal. calcd. for $C_{24}H_{22}N_2O_4$: C, 71.62; H, 5.47; N, 6.96. Found: C, 71.41; H, 5.51; N, 6.73.

Ethyl-N-(diphenylmethylene) Cyclohexylalaninate (3c)

Flash chromatography (4% ethyl acetate–benzene) gave an oil. It was then crystallized from ethanol into orange crystals, mp 104–105 °C, Rf = 0.56 (20% ethyl acetate–benzene). IR (neat) 3057, 2924.2, 2851.2 (CH_2-CH_2), 1622.4 (N=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ1.2 (t, 3H, CH_3), 0.9–1 and 1.8–1.9 (m, 11H, alicyclic), 4.1–4.3 (m, 3H, CH, OCH_2-), 7.2–7.9 (m, 10H, aromatic); HRMS m/z (relative intensity) 363 (M^+, 41.0), 362 (51.1), 291 (23.0), 290 (100), 286 (12.7), 280 (17.5), 276 (99.4), 267 (13.8), 266 (20.1), 264 (6.0), 263 (32.0), 262 (73.7), 252 (8.1), 238 (31.4), 208 (43.2), 206 (22.5), 194 (28.6), 193 (65.0), 192 (12.8), 182 (64.5), 180 (20.4), 167 (29.3), 166 (22.7), 165 (56.2), 104 (21.9), 103 (18.9), 91 (16.5); HRMS calcd. for $C_{24}H_{29}NO_2$: (M^+) 363.1958, obsd. 363.2185, Anal. calcd for $C_{24}H_{29}NO_2$: C, 79.33; H, 8.04; N, 3.85, Found: C, 80.91; H, 7.70; N, 3.23.

Ethyl-N-(diphenylmethylene) Hexanoate (3d)

Flash chromatography (10% ethyl acetate–hexane) gave a pale yellow oil, Rf = 0.48 (20% ethyl acetate–hexane). IR (neat) 3057, 2957.4, 2924.2 (CH_2-CH_2-CH_3), 1735.5 (CO_2CH_2-), 1662.5, 1596.1 (N=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82–0.87 (t, 3H, CH_3), 1.12–1.27 (m, 5H, -CH_2-CH_3), 1.91 (m, 2H, -CH_2-), 4.10 (q, 2H, OCH_2), 4.22 (m, 1H, -CH), 7.15–7.82 (m, 10H, aromatic); HRMS m/z (relative intensity) 333 (M^+, 11.9), 322 (20.2), 266 (7.1), 251 (20.8), 250 (100), 238 (7.0), 223 (6.9), 222 (19.2), 208 (20.1), 206 (8.9), 194 (8.0), 193 (22.8), 183 (8.7), 182 (52.3), 108 (9.0), 166 (11.1), 165 (33.4), 105 (99.1), 104 (15.9), 91 (40.8), 84 (12.6), 77 (60.5); HRMS calcd. for $C_{21}H_{25}NO_2$ (M^+) 323.1678, obsd. 323.1885, Anal. calcd. for $C_{21}H_{25}NO_2$; C, 78.01; H, 7.79; N, 4.33, Found: C, 78.5; H, 7.57; N, 4.12.

Ethyl-N-(diphenylmethylene) Pentanoate (3e)

Flash chromatography (10% ethyl acetate–hexane) gave a yellow oil, Rf = 0.63 (20% ethyl acetate–hexane). IR (neat) 3057.8, 2952.3, 2868.0 (CH_2-CH_2-CH_3), 1735.9 (CO_2CH_2-), 1616.4, 1574 (N=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (t, 3H, CH_3), 1.22 (m, 5H), 1.89 (m, 2H), 4.05 (q, 2H, OCH_2-), 4.14 (m, 1H, -CH), 7.15–7.66 (m, 10H, aromatic); HRMS m/z (relative intensity) 309 (M^+, 7.2), 308 (3.8), 267 (4.0), 266 (5.3), 238 (5.0), 237 (19.0), 236 (100), 209 (4.3), 208 (8.9), 206 (3.8), 194 (6.8), 193 (15.5), 192 (4.5), 166 (6.8), 165 (22.7), 105 (7.9), 165 (33.4), 104 (10.6), 91 (41.7), 77 (10.5); HRMS calcd. for $C_{20}H_{23}NO_2$ (M^+) 309.1722, obsd 309.1730.

Ethyl-N-(diphenylmethylene) Pentynoate (3f)

Flash chromatography (15% benzene–hexane) gave an oil, Rf = 0.48 (5% ethyl acetate–benzene). IR (neat) 3096.9 (C≡CH), 3057, 2980.5 (CH_2-C≡CH), 1728.9 (CO_2CH_2-), 1658.6 (N=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23–1.28 (t, 3H, CH_3, J=7.0 Hz), 1.94–1.96 (t, 1H, C≡CH), 2.79–2.89 (m, 2H), 4.16–4.2 (q, 2H, OCH_2-), 4.26–4.31 (m, 1H, -CH), 7.25–7.82 (m, 10H, aromatic); HRMS m/z (relative intensity) 305 (M^+, 1.1), 304 (4.5), 266 (3.8), 238 (1.5), 233 (1.3), 232 (7.9), 194 (2.3), 193 (8.2), 192 (7.3), 191 (1.2), 184 (1.4), 183 (6.5), 165 (10.7), 164 (1.3), 163 (2.5), 154 (3.1), 152 (4.4), 144 (4.1), 128 (4.1), 127 (2.6), 115 (3.2), 106 (6.7), 105 (100); HRMS calcd. for $C_{20}H_{19}NO_2$ (M^+) 305.1258, obsd. 305.1342. Anal. calcd. for $C_{20}H_{19}NO_2$: C, 78.68; H, 6.27; N, 4.59. Found: C, 79.29; H, 6.22; N, 4.12.

Ethyl-N-(diphenylmethylene) pentenoate[16] (3g)

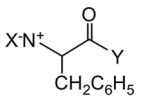
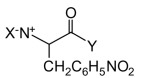
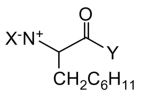
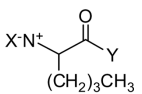
Flash chromatography (15% benzene–hexane) gave an oil, Rf = 0.45 (5% ethyl acetate–benzene). Yield 89%, IR (film) 3020, 1735, 1645, 1670, 1580, 1495, 1200, 1115, 995, 925, 75, 700 cm^{-1}; ^1H NMR($CDCl_3$) 1.2 (3H, CH_3), 2.5 (2H, CH_2), 4.00 (2H, OCH_2), 5.10 (2H, CH=CH_2), 5.60 (1H, CH=CH_2), 7.3–7.70 (5H, C_6H_5), 8.30 (1H, N=CH); m/z 230 (H^+) ($C_{14}H_{17}NO_2$ requires 231).

Hydrogenolysis: General Procedure

Method A

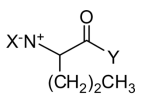
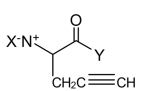
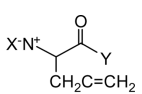
A mixture of **3a–g** (3.27 mmol) and 10% Pd-C (1.12 g) in ethanol (83 mL) was stirred under a balloon of H_2 gas at room temperature (see Table 1),

Table 1. Hydrogenolysis of Schiff base

		Compound 3		Compound 4		Amino acid esters
3	**R**	Reaction time	Yield (%)	Reaction time	Yield (%)	$X=H_3Cl^-$; $Y=OC_2H_5$
a	$-CH_2C_6H_5$	4 h	95	20 min 5 min	100 100[a]	 4a
b	$-CH_2C_6H_5NO_2$	7 h	85	20 min 5 min	100 100[a]	 4b
c	$-CH_2C_6H_{11}$	8 h	88	20 min 5 min	100 100[a]	 4c
d	$-(CH_2)_3CH_3$	5 h	77	20 min 5 min	100 100[a]	 4d

(*Continued*)

Table 1. Continued

3	R	Compound 3		Compound 4		Amino acid esters X=H_3Cl^-; Y=OC_2H_5
		Reaction time	Yield (%)	Reaction time	Yield (%)	
e	-$CH_2C_6H_5NO_2$	5.5 h	88	15 min 5 min	100 100[a]	 4e
f	-CH_2-C≡CH	4 h	88	15 min 5 min	100 100[a]	 4f
g	-CH_2C=CH_2	4 h	88	15 min 5 min	100 100[a]	 4g

[a]With addition of 2 mol equivalent of HCl.

purged with N_2 gas, and filtered through Celite®. The filtrate was concentrated, and free base was purified from diphenylmethane by flash chromatography (10% methanol–chloroform) over silica gel. Rf = 0.51 (12% methanol–chloroform). The pure amino acid esters were analyzed either as hydrochloride or oxalate salts.

Method B

The experiment was carried out in the same as described for method A with 2 mol equivalent of HCl. At the end of the reaction, the filtrate was concentrated and washed with dry ether, which removed diphenylmethane, leaving pure amino acid esters.

Phenylalanine Ethyl Ester Hydrochloride (4a)

Crystallized from ethanol ether into white crystals: mp 127 °C (lit.[17] mp 127 °C).

p-Nitro-DL-phenylalanine Ethyl Ester Hydrochloride (4b)

Crystallized from ethanol-ether into white crystals mp 176–179 °C (lit.[18] mp 179–180 °C).

p-Amino-DL-phenylalanine Ethyl Ester Hydrochloride (4b1)

HRMS m/z (relative intensity) 208 (M^+, 3.3), 135 (8.5), 118 (4.9), 107 (10.6), 106 (100.0), 77 (3.7); HRMS calcd. for $C_{11}H_{16}N_2O_2$ (M^+) 208.1206, obsd. 208.1216. The hydrochloride salt of p-amino-DL-phenylalanine ethyl ester[18] was crystallized from ethanol ether into pale yellow crystals: mp 232–233 °C. Anal. calcd. for $C_{11}H_{16}N_2O_2 \cdot 2HCl$: C, 46.97; H, 6.40; N, 9.96. Found: C, 45.81; H, 6.50; N, 9.66.

2-Amino Cyclohexyl Ethyl Propionate (4c)

Yellow oil, Rf = 0.59 (20% ethyl acetate–hexane). IR (neat) 3388.3, 3310.9 (NH_2), 1728.9 (CO_2CH_2-) cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.9 (t, 3H, CH_3), 1.12–1.78 (m, 15H), 3.44–3.46 (m, 1H, -CH-), 4.14 (m, 2H, OCH_2). Hydrochloride salt crystallized from ethanol into white crystals: mp 170–171 °C. Anal. calcd. for $C_{11}H_{21}NO_2 \cdot HCl$: C, 55.98; H, 9.33; N, 5.93. Found: C, 56.1; H, 9.42; N, 5.87.

2-Amino Ethyl Hexanoate (4d)

Yellow oil, Rf = 0.62 (10% ethanol–chloroform). IR (neat) 3381.2, 3310.9 (NH_2), 1728.9 (CO_2CH_2-) cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.9 (t, 3H, CH_3), 1.12–2.08 [m, 11H, $CH_3(CH_2)_3$, NH_2], 4.04 (m, 1H, -CH-), 4.26 (m, 2H, OCH_2). HRMS m/z (relative intensity) 159 (M^+, 10.6), 102 (10.6), 87 (8.1), 86 (100.0), 84 (2.7), 74 (7.1); HRMS calcd. for $C_8H_{17}NO_2(M^+)$ 159.1254, obsd. 159.1260. Oxalate salt Crystallized from ethanol ether into white crystals, mp 119–120 °C. Anal. calcd. for $C_{10}H_{19}NO_6$: C, 48.18; H, 7.68; N, 5.62. Found: C, 48.02; H, 7.64; N, 5.40.

2-Amino Ethyl Pentanoate (4e)

Yellow oil, Rf = 0.62 (10% ethanol–chloroform). IR (neat) 3381.2, 3310.9 (NH_2), 1735.9 (CO_2CH_2-) cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.9 (t, 3H, CH_3), 1.25–1.69 [m, 11H, $CH_3(CH_2)_3$], 3.40 (m, 1H, -CH-), 4.22 (m, 2H, OCH_2). HRMS m/z (relative intensity) 146 (M^+, 0.5), 144 (1.0), 127 (2.6), 112 (0.5), 102 (0.8), 101 (1.2), 99(0.8), 98 (0.06), 83 (1.0), 74 (0.8), 73 (6.2), 72 (100.0), 71 (1.3), 70 (2.7); HRMS calcd. for $C_7H_{16}NO_2$ (M^+) 146.1048, obsd. 146.1181. Oxalate salt: White crystals: mp 115–116 °C. Anal. calcd. for $C_9H_{17}NO_6$: C, 45.95; H, 7.28; N, 5.96. Found: C, 45.97; H, 7.18; N, 5.83.

2-Amino Ethyl Pentynoate (4f)

Yellow liquid, Rf = 0.50 (5% ethanol–ethyl acetate). IR (neat) 3381.2 (C≡C), 3289.8, 3219.5 (NH_2), 1728.9 (CO_2CH_2-) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.26 (t, 3H, CH_3), 1.77 (s, 2H, NH_2), 2.08 (m, 1H, C≡CH), 2.61 (m, 2H, CH_2), 3.60 (t, 1H, CH), 4.19 (m, 2H, OCH_2). Oxalate salt: Crystallized from ethanol ether into white crystals: mp 146 °C. Anal. calcd. for $C_9H_{13}NO_6$: C, 45.18; H, 5.62; N, 5.85. Found: C, 45.03; H, 5.33; N, 5.59.

2-Amino Ethyl Pentenoate (4g)

Liquid, Rf = 0.43 (5% ethanol–ethyl acetate). IR (neat) 3381.2, 3310.9 (NH_2), 1728.9 (CO_2CH_2-), 913.28 C=C) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, CH_3), 1.65 (s, 2H, CH_2), 2.3 (m, 2H, CH_2), 3.49–3.53 (t, 1H, CH), 4.10–4.21 (m, 2H, OCH_2), 5.68 (m, 1H, CH=C). HRMS m/z (relative intensity) 143 (M^+, 0.2), 142 (0.6), 102 (100.0), 74 (77.7), 73 (6.2), 71 (16.1), 70 (20.1); HRMS calcd. for $C_7H_{13}NO_2(M^+)$

143.0808, obsd. 143.094. Oxalate salt: Crystallized from ethanol ether into white crystals, mp 111–112°C. Anal. calcd. for $C_9H_{15}NO_6$; C, 43.02; H, 6.77; N, 5.57. Found: C, 42.86; H, 7.40; N, 5.32.

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