CONVENIENT SYNTHESIS OF L-PROLINE BENZYL ESTER

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Abstract: Mesylates or tosylates of δ-hydroxy-L-norvaline esters spontaneously afford L-proline esters upon exposure to aqueous buffer in near quantitative yield. This novel reaction has led to the development of a simple route to optically active proline esters. © 1999 Elsevier Science Ltd. All rights reserved.

Proline, first made in 1900 by Wilstätter[1] has been synthesized numerous times.[2,3] The simplest and most utilized routes toward synthetic proline involve formation of the N to C5 bond and use chiral starting materials from the readily available glutamic and pyroglutamic acid families.[4–7] The most common example of this bond formation is the 5-exo cyclization of nitrogen to displace a δ-leaving group in norvaline. First pioneered by Pravda and Rudinger in 1955,[8] improvements continue to appear in the literature.[9–17] Despite these efforts, the need still exists for a mild and convenient synthesis of proline esters and unnatural analogs.

We have found that mesylates and tosylates of δ-hydroxynorvaline esters **1a–c** in aqueous buffer spontaneously cyclize to proline esters **2a–c** in high yield[18,19] as shown in Scheme 1. To our knowledge, this cyclization in aqueous media to proline derivatives has not been previously reported. The high yield, rapid rate, and mild conditions of this novel reaction make it extremely attractive as a "green" alternative to existing procedures. Herein we report this general methodology to cyclic amino acids through the synthesis of L-proline benzyl ester (**2a**).


1a,	R = CH_3	R' = Bn
1b,	R = 4-$CH_3C_6H_4$	R' = Bn
1c,	R = 4-$CH_3C_6H_4$	R' = Ph

2a–c
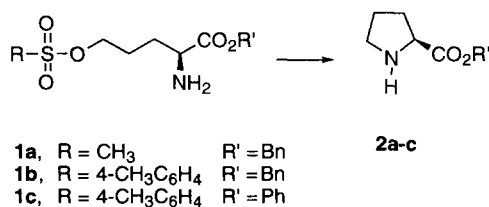
Scheme 1.

Currently, conversion of **3** to **4** (Scheme 2) typically requires treatment with strong base (NaH[10,11] or NaOEt/EtOH[12]) with yields ranging from 20–85%. Madou, et al.[13] have reported a mild variant with the terminal iodide under anhydrous conditions (Na$_2$CO$_3$, MeOH, 24 h, 90%) though due to transesterification these conditions are only suitable for preparation of methyl esters.[14] However, all these methods still require subsequent deprotection to afford the free proline ester.


X = Cl, Br, I, OMs, OTos
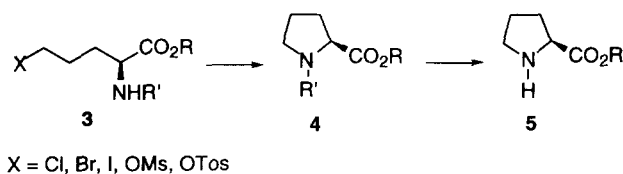
Scheme 2.

There have been only two reports of *N*-substituted-δ-halonorvaline cyclizations to the corresponding proline ester freebase, both of which were performed under anhydrous conditions. Joucla et al.[4,15] noted that the phenylmethyl imine of δ-chloronorvaline methyl ester cyclized to proline methyl ester (0.6 equiv NaI, THF, overnight reflux, 60%), albeit in low yield. More significant is the report in 1995 by Baldwin et al.[16] (Scheme 3) that upon removal of the Fmoc group, **6** subsequently underwent cyclization to **7**. Our report complements this research by allowing isolation of **1**.
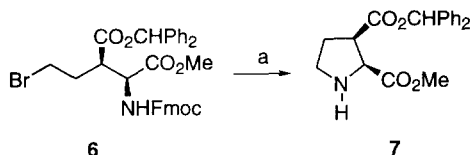
Scheme 3. *Reagents and Conditions*: (a) piperidine, DMF, 45 min, >90% (not isolated).

Our short route, shown in Scheme 4, started either with reduction of the benzyl ester of *N*-Boc-pyroglutamic acid (**8**)[20] (Eq. 1, 92%)[10] or reduction of the δ-acid of *N*-Boc-L-glutamic acid-α-benzyl ester (**9**)[21] (Eq. 2, 77%), which afforded alcohol **10**.[22] The latter reaction was performed by esterification of **9** to *N*-hydroxysuccinimide ester **11**[23] followed by selective reduction with NaBH$_4$.[24] Importantly, the reductions were racemization-free and neither require anhydrous conditions. Preparation of the mesylate **12** according to standard procedures[25,26] and removal of the Boc group[27] afforded near quantitative yield of **1a** (>99%). The key step of our sequence involves brief exposure of **1a** to a TEACO$_3$ buffer,[28] lyophilization, and elution through silica to remove salts. Acidification (HCl in dioxane) and recrystallization from absolute ethanol provided **2a** as fine colorless crystals of the HCl salt (95%, [α]$_D$ −37.8° (*c* 1, ethanol).[29]
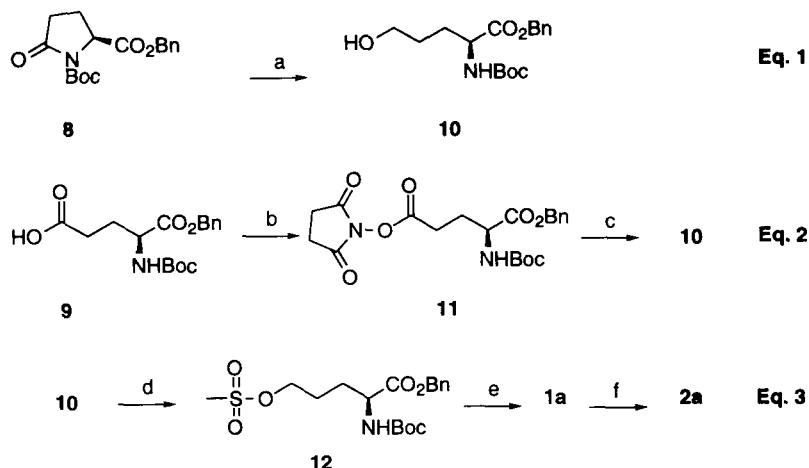
Scheme 4. *Reagents and Conditions*: (a) NaBH$_4$, 4:1-MeOH:H$_2$O, KH$_2$PO$_4$, 1.5 h, 0 °C, 92%; (b) SuOH, EDC, CH$_2$Cl$_2$, 92%; (c) NaBH$_4$, THF, 24 h, 4 °C, 84%; (d) MsCl, TEA, CH$_2$Cl$_2$, 3 h, –20 °C, 99%; (e) TFA, CH$_2$Cl$_2$, 3 h, room temperature, 99%; (f) TEACO$_3$ buffer (pH 8.4), 10% DMF, 5 min, room temperature, 96%.

In conclusion, an efficient method of obtaining proline esters has been developed. The methodology features inexpensive starting materials, a selective reduction and a mild cyclization reaction under aqueous conditions. Additionally, the prospect of using this methodology for solid-phase synthesis of imino acid terminated libraries is promising. Based on these features we believe this scheme will be applicable to the synthesis of a variety of natural and unnatural proline derivatives.

References and Notes

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18. We have observed this cyclization in buffers from pH 5–9 and the reaction reaches complete conversion immmediately at concentrations below 12.5 mM. In contrast, treatment of **1a** in water/DMF, 90:10 (no buffer) for 24 h proceeds to only 70% conversion.

19. The δ-iodo and bromo derivatives also cyclize under these conditions, though much slower and in lower yields.

20. Preparation of **8**: Li, M.; Sakamoto, T.; Kato, M.; Kikugawa, Y. *Synth. Commun.* **1995**, *25*, 4045 and references therein.

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22. Benzyl *N*-Boc-δ-hydroxy-*L*-α-aminovalerate **10**: $[\alpha]_D$ −4.8° (*c* 3, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.50–1.97 (m, 4H), 3.63 (t, 2H, *J* = 7.2 Hz), 4.39 (m, 1H), 5.17–5.26 (m, 3H), 7.36 (m, 5H); ^{13}C NMR (63 MHz) δ 172.9, 155.8, 135.6, 128.9, 128.7, 128.6, 80.3, 67.3, 62.3, 53.4, 29.7, 28.6, 28.5; HRMS *m/e* ($M+Na^+$) calcd: 346.1630, found: 346.1630.

23. *N*-hydroxysuccinimide ester **11**: mp 143–145 °C; $[\alpha]_D$ +6.5° (*c* 1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.08 (m 1H), 2.30 (m, 1H), 2.69 (m, 2H), 2.81 (s, 4H), 4.41 (m, 1H), 5.18 (s, 2H), 5.26 (m, 1H), 7.36 (m, 5H); ^{13}C NMR (100 MHz) δ 171.7, 169.3, 168.1, 155.6, 135.3, 128.8, 128.7, 128.5, 80.4, 67.6, 52.8, 28.5, 27.6, 27.5, 25.7; HRMS *m/e* ($M+Na^+$) calcd: 457.1587, found: 457.1570.

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26. Preparation of **12**: MsCl was added dropwise to a solution of 1.5 g (4.74 mmol) of **10** and 1.0 g (9.5 mmol) of TEA in 20 mL anhydrous CH_2Cl_2 at −20 °C. The reaction was completed after 3 h at −20 °C. Ethyl acetate was added and the organic phase washed with water and brine, dried ($MgSO_4$) and concentrated. Flash chromatography (Silica gel 60, 75:25-EtOAc:hexanes) afforded **12** as a white solid: 1.9 g (99%); mp 67–69 °C; $[\alpha]_D$ −0.8° (*c* 2, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.69–1.87 (m, 3H), 1.97 (m, 1H), 2.97 (s, 3H), 4.21 (t, 2H, *J* = 5.9 Hz), 4.38 (m, 1H), 5.09 (m, 1H), 5.18 (d, 2H, *J* = 3.7 Hz), 7.36 (m, 5H); ^{13}C NMR (100 MHz) δ 172.4, 155.6, 135.4, 128.9, 128.8, 128.6, 80.4, 69.3, 67.5, 53.0, 37.6, 29.2, 28.5, 25.4; HRMS *m/e* ($M+Na^+$) calcd: 424.1406, found: 424.1410.

27. Preparation of **1a**: TFA (2 mL) in anhydrous CH_2Cl_2 (10 mL) was slowly added to a solution of **12** (1.36 g, 3.4 mmol) in anhydrous CH_2Cl_2 (10 mL) at room temperature. The reaction mixture was stirred for 3 h and then concentrated under reduced pressure. The residue was evaporated twice with 10 mL of toluene to remove residual TFA and then dried under reduced pressure to afford **1a**: 0.90 g (>99%); ^1H NMR (250 MHz, $CDCl_3$) δ 1.66–2.22 (m, 4H), 2.95 (s, 3H), 4.08–4.27 (m 3H), 5.20 (d, 2H, *J* = 8.4 Hz) 7.35 (m, 5H); ^{13}C NMR (63 MHz) δ 169.5, 134.4, 129.2, 129.1, 128.8, 69.0, 68.9, 52.8, 37.3, 26.7, 24.8; HRMS *m/e* ($M+H^+$) calcd: 302.1062, found 302.1056.

28. Typical procedure for preparation of **2a**: **1a** (3.4 mmol) was dissolved in 271 mL of 10 mM triethyl ammonium carbonate ($TEACO_3$) buffer (pH 8.4, 10% DMF) at room temparature to obtain a concentration of 12.5 mM. The reaction mixture was stirred 10 min (HPLC showed that the reaction immediately reached completion) and then lyophilized. Flash chromatography (Silica gel 60, 95:5-EtOAc:MeOH) afforded **2a** as a clear oil: 0.7 g (96%); ^1H NMR (250 MHz, $CDCl_3$) δ 2.00–2.45 (m, 4H), 3.44 (t, 2H, *J* = 6.4 Hz), 4.47 (m, 1H), 5.22 (d, 2H, *J* = 3.7 Hz), 7.36 (m, 5H); ^{13}C NMR (63 MHz) δ 169.4, 129.4, 129.3, 129.1, 128.8, 69.0, 59.4, 46.3, 29.1, 24.1; HRMS *m/e* ($M+H^+$) calcd: 206.1181, found: 206.1179.

29. The purified HCl salt of **2a** (Aldrich Chem. Co.) had $[\alpha]_D$ −38.0° (*c* 1, ethanol).