A Facile Preparation of Enecarbamates

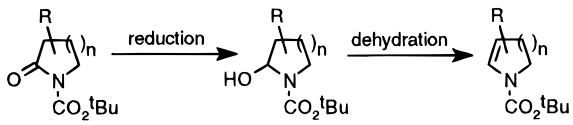
R. Karl Dieter* and Ram R. Sharma

Hunter Laboratory, Department of Chemistry, Clemson University, Clemson, South Carolina 29634-1905

Received January 23, 1996

Cyclic enecarbamates are versatile intermediates for the synthesis of alkaloids and nitrogen heterocycles.[1,2] In connection with our development of α-aminoalkylcuprate reagents,[3] we had need of a simple straight forward procedure for the preparation of enecarbamates. The principal synthetic route to these compounds has involved electrochemical oxidation[4,5] of carbamates or N-formyl derivatives in methanol to afford the corresponding N,O-mixed acetals. These N,O-mixed acetals can be converted into the enecarbamates either by elimination of methanol[5] upon heating with ammonium chloride or by conversion into an α-sulfonyl derivative[6] followed by base induced elimination of benzenesulfinic acid. Although several non-electrochemical methods are available for the preparation of enecarbamates they generally represent specialized systems and contain limitations with respect to substitution patterns.[7]

Reduction of the lactam carbonyl followed by dehydration (eq 1) provides a conceptually simple route to enecarbamates. Although the reduction of lactams and



eq. 1

cyclic imides to carbinol amines (lactamols) is well documented,[8] a literature report[9] suggested that enecarbamates could not be prepared by this route. The intermediate lactamols, under these reaction conditions, underwent ring opening and subsequent reduction to ω-hydroxycarbamates. In fact, literature reports suggest that reductions of simple lactams are sensitive to the reaction conditions also raising doubts about the feasibility of a reduction dehydration route to enecarbamates. Reduction of lactams with $NaBH_4$ in ethanol requires the addition of acid (e.g., HCl or H_2SO_4) to accelerate the reaction and prevent over-reduction via the ring opened aldehyde.[8c] Utilization of methanol, excess $NaBH_4$, and short reaction times at −4 °C chemoselectively reduces imides without the need for added acid.[10a] Although diisobutylaluminum hydride (DIBAL) has been successfully used for the chemoselective reduction of imides,[11] DIBAL reduction of 1-methylglutarimide proved problematic and the hydroxy lactam could only be obtained in modest yield with lithium triethylborohydride (Super Hydride).[10b]

In our initial study, 2-pyrrolidinone, protected as the N-*tert*-butoxycarbonyl (Boc) derivative, was reduced with DIBAL or superhydride to afford the 2-pyrrolidinol derivative in excellent yield (Table 1, 95%). Subsequent dehydration of the lactamol with a variety of reagents proved to be difficult. Reagents such as $MgBr_2$ etherate[12] (Et_3N, ultrasound), dicyclohexylcarbodimide (DCC)/CuCl,[13] methanesulfonyl chloride (MsCl)/(dimethylamino)pyridine (DMAP)/Et_3N/CH_2Cl_2[14] (Table 1, entry 2), and $MsCl/H_2O/DMAP/CH_2Cl_2$[15] (entry 3) all gave little to no enecarbamate while Ac_2O/DMAP/basic alumina/CH_2Cl_2[16] (entry 4) gave the enecarbamate in 40% yield. The latter three reaction conditions all converted the 2-hydroxypiperidine carbamate into the enecarbamate in 50-90% yields (entries 7−9). Consistent with these results, the 2-hydroxypiperidine derivative underwent facile dehydration upon attempted silica gel chromatography or upon standing in $CDCl_3$ (77%) as an NMR sample. Treatment of both the 2-hydroxypiperidine and 2-hydroxyhexahydroazepine derivatives with *p*-TsOH/toluene[10b] also afforded good yields of dehydration products (entries 10 and 14), although the procedure failed with the 2-hydroxypyrrolidine derivative (entry 5). Treatment of the latter compound with trifluoroacetic anhydride gave a nearly quantitative yield of N-(*tert*-butoxycarbonyl)-3-(trifluoroacetyl)-2-pyrroline resulting from initial dehydration and subsequent Friedel−Crafts acylation. After examination of a number of reagents, dehydration in hot HMPA[17] under essentially neutral conditions proved most promising for the pyrrolidine derivative. Under these conditions, Boc protected 2-hydroxypyrrolidine could be dehydrated to afford the enecarbamate in 70% yield (Table 1, entry 1).

Application of this dehydration protocol to a variety of lactamols, generated by DIBAL or superhydride reduction of Boc-protected lactams, afforded good to excellent yields of the desired enecarbamates (Table 1). The ease of the dehydration proved quite sensitive to the substrate structure. The highest yields were obtained with the piperidine derivative (entry 6) and generally lower yields were obtained with pyrrolidine (entries 1, 15) and hexahydroazepine (entry 11) derivatives.

(1) (a) Plehiers, M.; Hootele', C. *Tetrahedron Lett.* **1993**, *34*, 7569. (b) Durant, A.; Hootele', C. *Can. J. Chem.* **1992**, *70*, 2722. (c) Driessens, F.; Hootele', C. *Can. J. Chem.* **1991**, *69*, 211.

(2) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172.

(3) (a) Dieter, R. K.; Alexander, C. W. *Tetrahedron Lett.* **1992**, *33*, 5693. (b) Dieter, R. K.; Alexander, C. W. *Synlett* **1993**, 407. (c) Alexander, C. W.; Lin, S.-Y. *J. Organomet. Chem.* **1995**, *503*, 213.

(4) Shono, T. *Tetrahedron* **1984**, *40*, 811.

(5) Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S.; Kanazawa, T.; Aoki, T. *J. Am. Chem. Soc.* **1982**, *104*, 6697.

(6) Brown, D. S.; Charreau, P.; Hansson, T.; Ley, S. V. *Tetrahedron* **1991**, *47*, 1311.

(7) (a) Martin, S. F.; Rein, T.; Liao, Y. *Tetrahedron Lett.* **1991**, *32*, 6481. (b) Hanson, G. J.; Russell, M. A. *Tetrahedron Lett.* **1989**, *30*, 5751. (c) Brettle, R.; Mosedale, A. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2185. (d) Kraus, G. A.; Neuenschwander, K. *J. Org. Chem.* **1981**, *46*, 4791.

(8) For a review see: (a) Hiemstra, H.; Speckmp, W. N. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Vol. 2, p. 1047, 1991. (b) Guzman, A.; Romero, M.; Muchowski, J. M. *Can. J. Chem.* **1990**, *68*, 791. (c) Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437.

(9) Nagasaka, T.; Tamano, H.; Maekawa, T.; Hamaguchi, F. *Heterocycles* **1987**, *26*, 617.

(10) (a) Chamberlin, A. R.; Nguyen, H. D.; Chung, J. Y. L. *J. Org. Chem.* **1984**, *49*, 1682. (b) Thomas, E. W.; Rynbrandt, R. H.; Zimmermann, D. C.; Bell, L. T.; Munchmore, C. R.; Yankee, E. W. *J. Org. Chem.* **1989**, *54*, 4535.

(11) Winterfeldt, E. *Synthesis* **1975**, 617. (b) Hart, D. J.; Tsai, Y. *J. Org. Chem.* **1982**, *47*, 4403. (c) Kim, M. Y.; Weinreb, S. M. *Tetrahedron Lett.* **1979**, 579. (d) Oostveen, A. R. C.; de Boer, J. J. J.; Speckamp, W. N. *Heterocycles* **1977**, *7*, 171.

(12) Brown, D. S.; Charreau, P.; Hansson, T.; Ley, S. U.; Ley, S. V. *Tetrahedron* **1991**, *47*, 1311.

(13) Elmar, S.; Carsten, H.; Dieter, S. *Synlett* **1991**, 916.

(14) Yadav, J. S.; Mysorekar, S. V. *Synth. Commun.* **1989**, *19*, 1057.

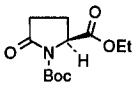
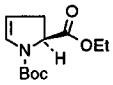
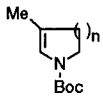
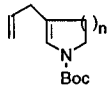
(15) Jun, F.; Naoka, M.; Hisayoshi, K.; Shigeo, I.; Shigeo, N.; Shigenobu, O. *Chem. Pharm. Bull.* **1985**, *33*, 440.

(16) Roberto, B.; Corrado, P. *Tetrahedron Lett.* **1994**, *35*, 5731.

(17) Monson, R. S. *Tetrahedron Lett.* **1971**, 567.

S0022-3263(96)00153-3 CCC: $12.00

Table 1. Synthesis of Enecarbamates

entry	carbamate	n	Lactamol[a] (conditions) % Yield[b]	dehydration conditions[c]	enecarbamate structure	no.	% yield[b]
1		1	(a) 95	A		1	70
2			(b) 96	B		1	0
3				C		1	15
4				D		1	40
5				E		1	0
6		2	(a) 90[d]	A		2	95
7			(b) 83[d]	B		2	90
8				C		2	50-60
9				D		2	82
10				E		2	87
11		3		A		3	77
12			(a) 87	B		3	52
13			(b) 89	C		3	0
14				E		3	85
15		-	(a) 88	A		4	70
16			(b) 85-90				
17		1	(a) 90	A		5	85
18			(b) 88				
19		2	(a) 90	A		6	80
20		1	(a) 88	A		7	80
21			(b) 75				
22		2	(a) 85	A		8	88

[a] (a) = DIBAL, toluene, -78°C. (b) = superhydride, THF. [b] Yields are based upon isolated and purified products. [c] Reaction conditions: A = HMPA , 160-190°C, 2-4 hrs. B = MsCl, Et_3N, DMAP, CH_2Cl_2, 25°C. C = MsCl, Et_3N, H_2O, CH_2Cl_2, 25°C. D = Ac_2O, DMAP, Basic Al_2O_3, CH_2Cl_2, heat. E = *p*-TsOH/toluene, reflux. [d] Yields are based upon crude products >95% pure by NMR analysis.

This route to enecarbamates provides for a number of interesting synthetic possibilities. Reduction of Boc protected ethyl pyroglutamate affords a functionalized enecarbamate **4** (entry 15) while alkylation of the Boc protected lactams prior to reduction and dehydration provides a simple entry into 3-alkyl substituted enecarbamates **5**-**8**. Deprotonation (−78 °C, THF) of Boc-protected 2-pyrrolidinone with lithium diisoproylamide (LDA) or lithium hexamethyldisilazide (LHMDS) followed by alkylation with methyl iodide or allyl iodide afforded the 3-alkyl lactams in excellent yields (89%). Under similar reaction conditions, the enolate anions of the Boc protected 2-piperidinone gave only recovered starting material. Warming the reaction mixtures to room temperature afforded predominantly bis-alkylation products which could not be minimized by inverse addition techniques.[18] Treatment of the enolate anion with alkyl halides between −50 °C and −20 °C provided optimal yields of Boc protected 3-alkyl-2-piperidinones (3-Me, 65%; 3-allyl, 75%) along with significant amounts of the starting material (20−30%). Reduction of the 3-alkyl lactams (entries 17−22) and subsequent dehydration proceeded uneventfully, affording similar overall yields (80−88%) of enecarbamates for both the five- and six-membered lactams (entries 17, 19, 20, and 22).

The reduction procedure can be adapted to the sequence employed in the electrochemical oxidation route. Treatment of Boc protected 2-pyrrolidinol with NaH and MeI (THF, 25 °C) affords the N,O-mixed acetal in 70−80% yields which gives modest yields (40%) of enecarbamates upon treatment with solid ammonium chloride. The lower yields (40% vs 70%) may reflect the greater acid sensitivity of the *tert*-butyl carbamate as compared to the methyl carbamate. Alternatively, acetal formation can be induced by $NaBH_4$ reduction in alcohol with very careful control of pH, although this procedure is often problematic and difficult to control.[19]

The current procedure fails in two variations. First, it does not work with acyclic Boc protected amides because of the lability of the intermediate hemiaminals. Acyclic enecarbamates are available via Curtius rearrangement of unsaturated acyl azides which nicely complements the current method for preparation of cyclic enecarbamates.[7c] Second, although the addition of Grignard or organocerium reagents to the lactam carbonyl proceeds efficiently, the intermediate carbamate protected carbinol amines fragment to the ring opened product.[20] Efforts to trap the intermediate lactamols resulting from organometallic 1,2-additions were unsuccessful.

In summary, a rapid and convenient procedure has been developed for the conversion of Boc-protected lactams into enecarbamates that does not require electrochemical oxidation. The procedure is versatile in that it

(18) Fisher, M. J.; Overman, L. E. *J. Org. Chem.* **1990**, *55*, 1447.

(19) Nagasaka, T.; Tamano, H.; Hamaguchi, F. *Heterocycles* **1986**, *24*, 1231.

(20) Giovannini, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1989**, *54*, 228.

can accommodate additional functionality and provides opportunities for the introduction of substituents at the 3-position of the conjugated enecarbamate.

Experimental Section

General. NMR spectra were recorded as $CDCl_3$ solutions. THF and ether were distilled over sodium−benzophenone ketyl. Diisopropylamine, TMEDA, triethylamine, hexamethylphosphoric triamide (HMPA), and 1,1,1,3,3,3-hexamethyldisilazane (HMDS) were distilled over calcium hydride and stored over 4 Å molecular sieves. Methanesulfonyl chloride (MsCl) and acetic anhydride were distilled and stored in a dry box. All Boc protected amides were prepared according to literature procedures.[8b,21] Alkyllithium reagents were titrated before use.[22] DIBAL and Super-Hydride (1.0 M solutions) were purchased from Aldrich. Products were purified by flash column chromatography (FCC) on silica gel (230−400 mesh) eluting with ethyl acetate/petroleum ether (ethyl acetate: 20−25%, v/v for the lactamols and 5−10% for the enecarbamates). Elemental analyses were performed by Atlantic Microlab, Inc.

General Procedure for Alkylation of Boc-Protected Lactams. To a stirred solution of diisopropylamine (1.1 mmol) in THF (2.0 mL) was added *n*-BuLi (1.1 mmol) dropwise at 0−5 °C under nitrogen. The reaction mixture was stirred for 15 min cooled to −78 °C whereupon addition of lactam (1.0 mmol) in THF (2.0 mL) was achieved *via* cannula. The solution turned pale yellow in color and was stirred at −78 °C for 1.0 h. The electrophile (1.5 equiv) was added at −78 °C (−50 °C for the piperidine derivative with slow warming to −20 to −25°C) and stirred for 30 min. The reaction was quenched with saturated NH_4Cl (−78 °C for pyrrolidine derivative, −25 °C for piperidine derivative) and extracted with ether, and the ether extracts were washed with saturated NH_4Cl (2 times), dried over $MgSO_4$ and concentrated *in vacuo*. Products were purified by medium pressure liquid chrohmatography (silica gel, 30% EtOAc/petroleum ether).

***N*-(*tert*-Butoxycarbonyl)-3-methyl-2-pyrrolidinone.** The product was isolated as a colorless oil in 89% yield after MPLC purification: IR (neat) 1795, 1753, 1727 cm^{-1}; ^1H NMR δ 1.08 (d, J = 8.3 Hz, 3 H), 1.40 (s, 9 H), 1.44−1.55 (m, 1 H), 2.00−2.14 (m, 1 H), 2.33−2.50 (m, 1 H), 3.40−3.50 (m, 1 H), 3.55−3.66 (m, 1 H); ^{13}C NMR δ 15.2, 26.2, 27.8, 38.4, 44.2, 82.5, 150.3, 176.5; mass spectrum, *m*/*z* (relative intensity) EI 198 (1, M+1), 158 (29), 143 (9, $M^+ - C_4H_9$), 112 (23), 98 (03, $M^+ - C_5H_9O_2$), 57 (100, C_4H_9).

***N*-(*tert*-Butoxycarbonyl)-3-allyl-2-pyrrolidinone.** The product was isolated as a colorless oil in 91% yield after MPLC purification: IR (neat) 1795, 1761, 1719, 1029, 961, 930 cm^{-1}; ^1H NMR δ 1.33 (s, 9 H), 1.44−1.58 (m, 1 H), 1.86−2.10 (m, 2 H), 2.33−2.47 (m, 2 H), 3.38 (q, J = 6.0 Hz, 1 H) 3.56 (dt, J = 3.0 Hz, J = 9.0 Hz, 1 H), 4.80−4.91 (m, 2 H), 5.50−5.65 (m, 1 H); ^{13}C NMR δ 23.5, 27.5 (27.9), 34.1, 42.6, 44.0, 82.1, 116.7 (118.6), 132.5 (134.4), 149.7, 174.8 (for pair of rotamers); mass spectrum, *m*/*z* (relative intensity) EI 225 (1, M^+), 169 (47, $M^+ - C_4H_8$), 152 (11, $M^+ - C_4H_9O$), 125 (15), 109 (10), 81 (16), 57 (100, C_4H_9).

***N*-(*tert*-Butoxycarbonyl)-3-methyl-2-piperidinone.** The product was obtained as a colorless oil in 65% yield after MPLC purification: IR (neat) 1778, 1736 cm^{-1}; ^1H NMR δ 1.22 (d, J = 8.3 Hz, 3 H), 1.55 (s, 10 H), 1.80−1.94 (m, 2 H), 1.97−2.03 (m, 1 H), 2.47−2.58 (m, 1 H), 3.58−3.66 (m, 1 H), 3.75−3.86 (m, 1 H); ^{13}C NMR δ 16.3, 22.1, 27.8, 28.4, 38.4, 45.6, 82.3, 152.8, 174.5; mass spectrum, *m*/*z* (relative intensity) EI 214 (04, M + 1), 186 (36, M + 1 − CO), 170 (2), 140 (16), 112 (36, $M^+ - C_5H_9O_2$), 87 (12), 57 (100, C_4H_9), 41 (42).

***N*-(*tert*-Butoxycarbonyl)-3-allyl-2-piperidinone.** The product was obtained as a colorless oil in 75% yield after MPLC purification: IR (neat) 1778, 1727, 984, 915 cm^{-1};^1H NMR δ 1.50 (1.51) (br s 10 H), 1.72−1.94 (m, 2 H), 1.94−2.10 (m, 1 H), 2.16−2.33 (m, 1 H), 2.39−2.58 (m, 1 H), 2.61−2.75 (m, 1 H), 3.53−3.67 (m, 1 H), 3.67−3.80 (m, 1 H), 5.00−5.14 (m, 2 H), 5.70−5.92 (m, 1 H); ^{13}C NMR δ 21.5, 25.4, 27.9, 35.3, 43.2, 45.6, 82.3 (82.6), 116.9 (118.5), 133.6 (135.8), 152.8, 173.4 (for pair of rotamers); mass spectrum, *m*/*z* (relative intensity) EI 240 (3, M + 1), 95 (15,), 59 (21), 57 (100, C_4H_9).

Reduction of Lactams with DIBAL (Procedure a). The general procedure for preparation of lactamols from Boc protected lactams is illustrated for N-(*tert*-butoxycarbonyl)valerolactam. To a stirred solution of the carbamate (4.47 g, 22.48 mmol) in 120 mL of dry THF at −78 °C (2-propanol dry ice bath) under a N_2 atmosphere was added a 1 M hexane solution of DIBAL (33.7 mL, 33.7 mmol) dropwise or in portions over a 5 min period. The reaction mixture was stirred for 2 h and then quenched with a saturated potassium acetate solution (50 mL) at −78 °C. The solution was transferred to a flask (500 mL) containing saturated NH_4Cl:ether (400 mL, 1:3, v/v). The solution was warmed to rt and stirred until a thick white gel formed at the bottom, and the mixture was then filtered through Celite. The aqueous layer was extracted with ether (3 × 50 mL), and the combined organic phase was washed with saturated NH_4Cl (2 × 100 mL) and dried over anhydrous K_2CO_3. Concentration *in vacuo* afforded crude lactamol in high yield (90−95%). The crude product was relatively clean as indicated by TLC and NMR analysis. Purification by silica gel column chromatography (20% ethyl acetate/petroleum ether, v/v) gave an analytically pure sample (4.25 g, 94%).

Reduction of Lactams with Super-Hydride (Procedure b). To a stirred solution of Boc protected lactam (1.0 mmol) in THF (15.0 mL) was added lithium triethylborohydride (1.2 mmol, 1.0 M solution in THF) at −78 °C, under nitrogen. The reaction mixture was stirred at −78 °C for 20−30 min and then quenched with a saturated $NaHCO_3$ solution at −78 °C, followed by treatment with 30% aqueous H_2O_2 for 15−20 min at −20 to 0 °C. The aqueous phase was extracted with CH_2Cl_2, and the organic phase dried and concentrated to give 90−95% yield of crude product. In later experiments, the solution was not treated with H_2O_2 and the lactamols were isolated in pure form by flash column chromatography.

***N*-(*tert*-Butoxycarbonyl)-2-pyrrolidinol.** Both procedures a and b gave the desired lactamol which upon FCC gave 90−95% yield of pure material as a colorless oil: IR (neat) 3446 (s), 1702 (s) cm^{-1}; ^1H NMR δ 1.47 (1.50) (s, 9H), 1.72−2.16 (m, 4 H), 3.19−3.38 (m, 1 H), 3.40−3.61 (m, 1 H), 3.14 (3.87) (br s, 1 H), 5.27−5.53 (m, 1 H); ^{13}C NMR δ 22.6 (21.9), 28.4, 32.6 (33.4), 45.8 (45.6), 79.9 (80.2), 81.5 (81.3), 155.0 (pair of rotamers).

***N*-(*tert*-Butoxycarbonyl)-2-hydroxypiperidine.** Both procedures a and b gave the lactamol in 83−90% yield as a colorless oil, which required no further purification: IR (neat) 3446 (s), 1702 (s) cm^{-1}; ^1H NMR δ 1.44 (s, 9 H), 1.49 - 1.94 (m, 7 H), 3.08 (dt, J = 3.0 Hz, J = 12.9 Hz, 1 H), 3.80 (br d, J = 12.9 Hz, 1 H), 5.71 (d, J = 2.7 Hz, 1 H); ^{13}C NMR δ 17.6, 24.7, 28.2, 30.5, 38.9, 74.2, 79.9, 155.2.

***N*-(*tert*-Butoxycarbonyl)-2-hydroxyhexahydroazepine.** Both procedures a and b gave 85−90% yield of the lactamol, which required no further purification. Spectroscopically clean samples were obtained by passing the crude sample through silica gel by flash chromatography which gave 90−95% yield of the lactamol as a white solid: IR (neat) 3446 (s), 1685 (s) cm^{-1}; ^1H NMR δ 1.13−1.83 (m, 7 H), 1.47 (1.50) (s, 9 H), 2.00−2.30 (m, 1 H), 3.00−3.16 (m, 1 H), 3.19 (3.88) (br s, 1 H), 3.61 (3.77) (br d, J = 16.6 Hz, 1 H), 5.53−5.63 (5.38−5.53) (m, 1 H); ^{13}C NMR δ 22.7, 28.3, 29.2, 29.5, 34.1 (34.5), 40.7 (41.1), 79.3, 79.8 (80.0), 155.0 (156.0) (pair of rotamors).

Ethyl *N*-(*tert*-Butoxycarbonyl)-(S)-(−)-2-hydroxypyrrolidine-5-carboxylate. Both procedures a and b gave, after FCC, lactamol in 85−90% yield as a colorless oil: IR (neat) 3455 (s), 1744 (s), 1710 (s) cm^{-1}; ^1H NMR δ 1.30 (t, J = 6.0 Hz, 3 H), 1.43 (1.45, 1.50) (s, 9 H), 1.88−2.05 (m, 2 H), 2.05-2.44 (m, 2 H), 4.19 (q, J = 2.4 Hz, 2 H), 4.27−4.38 (m, 1 H), (5.50) 5.60 (dt, J = 3.0 Hz, J = 6.0 Hz, 1 H); ^{13}C NMR δ 14.0, 26.9, 27.8 (28.0), 32.2 (33.4), 59.0 (59.4), 60.9 (61.1), 80.6 (80.8), 82.1, 153.1 (153.6), 172.8 (173.1) (diastereomers + rotamers).

***N*-(*tert*-Butoxycarbonyl)-3-methylpyrrolidin-2-ol.** Both procedures a and b gave after MPLC purification a colorless oil in 90% yield (65:35 mixture of diastereomers): IR (neat) 3446, 1702 cm^{-1}; ^1H NMR δ 0.97 (1.03) (d, J = 8.3 Hz, 3 H), 1.40 (1.42) (br s, 10 H), 1.58−1.80 (m, 1 H), 1.92−2.22 (m, 1 H), 3.02−3.22 (m, 1 H), 3.25−3.50 (m, 1 H), 4.89 (4.97) (br s, 1 H), 5.11 (5.20) (br s, 1H); ^{13}C NMR δ 12.8 (16.4), 28.3, 29.3 (29.8, 30.2), 37.7 (38.5, 39.7, 40.4), 44.2 (44.6, 45.0, 45.3), 79.7 (79.8, 80.0), 82.3

(21) Tamm, C.; Matthes, M.; Ackermann, J. *Helv. Chim. Acta* **1990**, *73*, 122.

(22) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

(87.6), 153.7 (155.2) (diastereomers + rotamers); mass spectrum characteristic of enecarbamate **5** was obtained.

***N*-(*tert*-Butoxycarbonyl)-3-methylpiperidin-2-ol.** Procedure a was followed which upon purification by MPLC gave 85% yield of a 64:36 mixture of diastereomers as a colorless oil: IR (neat) 3429, 1685, cm^{-1}; ^1H NMR δ 1.42 (1.44) (d, J = 8.3 Hz, 3 H), 1.44 (1.36) (br s, 11 H), 1.55−1.72 (m, 2 H), 1.80−1.97 (m, 1 H), 2.91−3.11 (m, 1 H), 3.63−3.72 (m, 1 H), 5.27 (br s, 1 H), 5.44 (br s, 1 H); ^{13}C NMR δ 17.9, 25.3, 25.66 (26.0), 28.3, 35.3, 38.6 (38.7), 74.1, 79.7 (79.8), 155.2 (diastereomers); mass spectrum characteristic of enecarbamate **6** was obtained.

***N*-(*tert*-Butoxycarbonyl)-3-allylpyrrolidin-2-ol.** Both procedures a and b gave a colorless oil in 88% yield upon MPLC purfication (68:32 mixture of diastereomers): IR (neat) 3438, 1702, 976, 915 cm^{-1}; ^1H NMR δ 1.47 (1.44, 1.50) (br s, 11 H), 1.97−2.36 (m, 4 H), 3.33−3.50 (m, 2 H), 4.05 (3.16) (br s, 1 H), 5.00−5.14 (m, 2 H), 5.72−5.88 (m, 1 H); ^{13}C NMR δ 27.6, 28.3, 37.2, 44.6 (44.7), 45.2 (45.4), 80.0 (80.3, 81.3), 85.7 (85.9), 116.5 (116.0), 135.9 (136.6), 155.1 (153.3) (diastereomers + rotamers); mass spectrum characteristic of enecarbamate **7** was obtained.

***N*-(*tert*-Butoxycarbonyl)-3-allylpiperidin-2-ol.** Procedure a was followed which on purification gave a colorless oil in 88% yield (60:40 mixture of diastereomers): IR (neat) 3435, 1702, 991, 912 cm^{-1}; ^1H NMR δ 1.44 (1.47) (br s, 11 H), 1.63−2.22 (m, 4 H), 2.25−2.42 (m, 1 H), 3.10−3.22 (m, 1 H), 3.39−3.58 (m, 1 H), 3.80 (3.08) (s, 1 H), 4.91−5.10 (m, 2 H), 5.20 (5.30) (s, 1H), 5.70−5.88 (m, 1H); ^{13}C NMR δ 27.5, 28.3, 32.7, 43.1, 44.0, 44.9 (45.2), 79.8 (80.1), 81.3, 115.5 (115.7), 136.7 (136.8) 154.9 (153.3) (diastereomers); mass spectrum characteristic of enecarbamate **8** was obtained.

Dehydration of Lactamols in HMPA.[17] Procedure A. The reaction was carried out by modification of Monson's procedure. HMPA (5.0 mL) was added via syringe to a dry 25 mL flask containing lactamol (1.0 mmol) under N_2. The flask was heated in an oil bath at 160−180 °C for 1−5 h depending upon the type of lactamol. Increasing the oil bath temperature to >210 °C may lead to undesired decomposition products. The progress of the reaction is accompanied by a color change from colorless to a pale or dark yellow solution, and the reaction can be monitored by TLC (10% ethyl acetate/petroleum ether). After the mixture was cooled to rt, saturated NH_4Cl was added and the aqueous layer was extracted with ether (4 × 10 mL). The combined organic phase was washed with saturated NH_4Cl (4 × 20 mL) to remove residual HMPA, dried over K_2CO_3, and concentrated *in vacuo*. Purification of enecarbamates by silica gel chromatography gave analytically pure samples.

Dehydration of Lactamols with MsCl/DMAP/Et_3N.[14] Procedure B. To a stirred solution of lactamol (1.0 mmol) in CH_2Cl_2 (5 mL) were added triethylamine (3.0 mmol) and DMAP (5 mg, 4 mol %). The mixture was cooled to −5 °C in an ice bath, and MsCl (1.5 mmol) was added dropwise to the solution. The mixture was stirred for 1−4 h depending upon the type of substrate. The reaction was quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2. The organic phase was washed with saturated NH_4Cl (4 × 10 mL), water, dried over K_2CO_3, and concentrated *in vacuo*.

Dehydration in Ac_2O/DMAP/basic Al_2O_3.[16] Procedure D. To a stirred solution of lactamol (1.0 mmol) in dry ether (10 mL) at rt under N_2 were added anhydrous acetic anhydride (15.0 mmol) and catalytic amount of DMAP. The reaction mixture was stirred for 3 h. After removal of solvent *in vacuo*, the crude acetate was dissolved in CH_2Cl_2 and treated with DMAP (1.5 mmol)/basic alumina (0.3 g) and heated to reflux for 10 h. The alumina was then filtered off and the organic layer washed with water, dried over K_2CO_3, and concentrated *in vacuo*. Purification by silica gel column chromatography gave an analytically pure sample.

***N*-(*tert*-Butoxycarbonyl)-2-pyrroline (1).** Procedure D was followed, and the reaction mixture was heated at reflux for 16-20 h. Workup and concentration *in vacuo* followed by purification via FCC gave a pure analytical sample (40%) of **1** as a colorless oil: IR (neat) 1702, 1628 cm^{-1}; ^1H NMR δ 1.44 (s, 9 H), 2.53−2.66 (m, 2 H), 3.61−3.66 (m, 2 H), 4.95 (br d, J = 12.6 Hz, 1 H), 6.41 (6.54) (br s, 1 H); ^{13}C NMR δ 28.2 (28.4), 29.5, 44.6 (45.0), 79.7, 107.3, 129.6, 151.4 (pair of rotamers); mass spectrum, *m/z* (relative intensity) EI 169 (10, M^+), 113 (36, $M^+ - C_4H_8$), 96 (22, $M^+ - C_4H_9O$), 68 (63, $M^+ - C_5H_9O_2$), 57 (100, C_4H_9). Anal. Calcd for $C_9H_{15}O_2N$: C, 63.91; H, 8.88. Found: C, 63.81; H, 8.89.

***N*-(*tert*-Butoxycarbonyl)-1,2,3,4-tetrahydropyridine (2).** Procedures A and B gave satisfactory yields (90−95%). Purification by FCC gave an analytically pure sample (90%) of **2** as a colorless oil: IR (neat) 1709, 1659 cm^{-1}; ^1H NMR δ 1.42 (s, 9 H), 1.66−1.80 (m, 2 H), 1.90−2.00 (m, 2 H), 3.41−3.55 (m, 2 H), 4.66−4.77 (4.78−4.90) (m, 1 H), 6.65 (6.77) (br d, J = 8.0 Hz, 1 H); ^{13}C NMR 21.4 (21.6), 28.2, 41.3, 42.4, 80.3, 105.0 (105.4), 125.2 (125.5), 152.2 (for pair of rotamers); mass spectrum, *m/z* (relative intensity) EI 183 (09, M^+) 127 (59, $M^+ - C_4H_8$), 110 (20, $M^+ - C_4H_9O$), 82 (58, $M^+ - C_4H_9O_2$), 57 (100, C_4H_9). Anal. Calcd for $C_{10}H_{17}O_2N$: C, 65.56; H, 9.29. Found C, 65.30; H, 9.29.

***N*-(*tert*-Butoxycarbonyl)-4,5,6,7-tetrahydroazepine (3).** Procedure A was followed, and the reaction mixture was heated for 1 h. Purification by FCC gave **3** in 77% yield as a colorless oil: IR (neat) 1702, 1659 cm^{-1}; ^1H NMR δ 1.48 (s, 9 H), 1.63−1.83 (m, 4 H), 2.13−2.21 (m, 2 H), 3.61−3.70 (m, 2 H), 4.90−5.00 (m, 1 H), 6.48 (br s, 1 H); ^{13}C NMR 26.1, 28.0, 28.3, 38.9, 46.8, 80.1, 113.9, 130.5, 153.6; mass spectrum, *m/z* (relative intensity) EI 197 (13, M^+), 141 (78, $M^+ - C_4H_8$), 124 (15, $M^+ - C_4H_9O$) 96 (17, $M^+ - C_4H_9O_2$), 57 (100, C_4H_9). Anal. Calcd for $C_{11}H_{19}O_2N$: C, 67.00; H, 9.65. Found: C, 66.75; H, 9.75.

Ethyl *N*-(*tert*-Butoxycarbonyl)-(*S*)-(−)-2-pyrroline-5-carboxylate (4). Procedure A gave crude material in 80% yield which upon FCC afforded pure **4** in 70% yield as a colorless oil: IR (neat) 2987 (s), 1761 (s), 1719 (s) 1634 (m) cm^{-1}; ^1H NMR δ 1.18 (t, J = 6.0 Hz, 3 H), 1.34 (1.39) (s, 9 H), 2.58 (t, J = 15.0 Hz, 1 H), 2.98 (q, J = 15.0 Hz, 1 H), 4.20 (q, J = 6.9 Hz, 1 H), 4.41−4.61 (m, 1 H), 4.86 (d, J = 13.2 Hz, 1 H), 6.55 (6.42) (br s, 1 H); ^{13}C NMR δ 13.9 (14.0), 27.9 (28.1), 34.1 (35.3), 57.7 (58.2), 60.9, 80.6 104.8, 129.8 (129.9), 151.2, 171.4 (171.7) (pair of rotomers); mass spectrum *m/z* (relative intensity) EI 241 (1.6, M^+), 185 ($M^+ - C_4H_8$), 168 ($M^+ - C_4H_9O$), 141 (9, $M^+ - C_5H_8O_2$), 112 (5, $M^+ - C_7H_{13}O_2$), 96 ($M^+ - C_7H_{13}O_3$), 68 (100, $M^+ - C_8H_{13}O_4$). Anal. Calcd for $C_{12}H_{19}O_4$: C, 59.75; H, 7.88. Found: C, 59.86: H, 7.98.

***N*-(*tert*-Butoxycarbonyl)-3-methyl-2-pyrroline (5).** Procedure A was followed, and the reaction mixture was heated for 1 h. Purification by FCC gave **5** in 85% yield as a colorless oil: IR (neat) 1702 (s), 1628 (m) cm^{-1}; ^1H NMR δ 1.42 (s, 9 H), 1.65 (s, 3 H), 2.38−2.55 (m, 2 H), 3.58−3.75 (m, 2 H), 6.11 (6.23) (s, 1 H); ^{13}C NMR δ 13.5, 28.4, 33.1 (34.1), 45.2 (45.7), 79.6, 118.1, 124.1, 151.4 (151.7) (for pair of rotamers); mass spectrum, *m/z* (relative intensity) EI 183 (15, M^+) 127 (63, $M^+ - C_4H_8$), 110 (21, $M^+ - C_4H_9O$), 82 (57, $M^+ - C_4H_9O_2$), 57 (100, C_4H_9). Anal. Calcd for $C_{10}H_{17}O_2N$: C, 65.57; H, 9.28; N, 7.65. Found: C. 65.44; H, 9.29; N, 7.55.

***N*-(*tert*-Butoxycarbonyl)-3-methyl-2-piperidine (6).** Procedure A gave **6** as a colorless oil in 80% yield, and an analytically pure sample was obtained by passing the crude product through silica gel contained in a pipette (petroleum ether): IR (neat) 1702 (s), 1675 (sh, m) cm^{-1}; ^1H NMR δ 1.43 (s, 9 H), 1.61 (s, 3 H), 1.72−1.83 (m, 2 H), 1.91 (t, J = 6.0 Hz, 2 H), 3.36−3.50 (m, 2 H), 6.45 (6.60) (s, 1 H); ^{13}C NMR δ 21.8, 26.7 (26.9), 28.3, 40.8, 41.8, 79.9 (80.0), 113.9 (114.3), 120.0 (120.3), 152.2 (152.7) (for pair of rotamers); mass spectrum, *m/z* (relative intensity) EI 197 (16, M^+) 141 (100, $M^+ - C_4H_8$), 124 (17, $M^+ - OC_4H_9$), 96 (21, $M^+ - O_2C_5H_9$), 82 (65, $M^+ - O_2C_6H_{11}$), 57 (64, C_4H_9). Anal. Calcd for $C_{12}H_{19}O_2N$: C, 67.00; H, 9.64; N, 7.10. Found: C, 66.83; H, 9.81; N, 6.84.

***N*-(*tert*-Butoxycarbonyl)-3-allyl-2-pyrroline (7).** Procedure A was followed and upon purification gave **7** in 80% yield as a colorless oil: IR (neat) 1702 (s), 1680 (sh, m), 1030 (s), 919 (m) cm^{-1}; ^1H NMR δ 1.42 (s, 9 H), 2.41−2.55 (m, 2 H), 2.75 (d, J = 6.0 Hz, 2 H), 3.61−3.77 (m, 2 H), 5.05 (br d, J = 16.5 Hz, 2 H), 5.66−5.86 (m, 1 H), 6.14 (6.29) (s, 1 H); ^{13}C NMR δ 28.4, 32.9, 45.1 (45.6), 79.7, 116.0, 120.7, 124.4, 135.3, 151.5 (151.7) (for pair of rotamers); mass spectrum, *m/z* (relative intensity) EI 209 (14, M^+), 194 (2.0, M^+), 153 (71, $M^+ - C_4H_8$), 124 (3.0, $M^+ - OC_5H_9$), 108 (34, $M^+ - O_2C_5H_9$), 80 (20, $M^+ - O_2C_7H_{12}$), 57 (100, C_4H_9). Anal. Calcd for $C_{12}H_{19}O_2N$: C, 68.89; H, 9.09; N, 6.69. Found: C, 68.78; H, 9.15; N, 6.63.

***N*-(*tert*-Butoxycarbonyl)-3-allyl-2-piperidine (8).** Procedure A was followed, and the reaction mixture was heated for 1 h. An analytically pure sample was obtained by passing the crude product through pipette filled silica gel column (petroleum

ether), giving **8** in 87% yield as a colorless oil: IR (neat) 1705 (s), 1683 (sh, m), 985 (m), 916 (m) cm^{-1}; ^1H NMR δ 1.41 (s, 9 H), 1.65−1.80 (m, 2 H), 1.90 (t, J = 6.0 Hz, 2 H), 2.63 (d, J = 6.0 Hz, 2 H), 3.34−3.50 (m, 2 H), 4.97 (br d, J = 15.0 Hz, 2 H), 5.61−5.79 (m, 1 H), 6.48 (6.64) (s, 1 H); ^{13}C NMR δ 21.7, 24.9, 28.3, 39.7, 41.0, 42.1, 80.2, 115.7 (116.4), 120.9 (121.2), 136.3, 152.2 (152.7), (for pair of rotamers); mass spectrum, *m/z* (relative intensity) EI 223 (15, M^+), 167 (100, $M^+ - C_4H_8$), 150 (17, $M^+ - OC_4H_9$), 122 (29, $M^+ - O_2C_5H_9$), 95 (22, $M^+ - O_2C_7H_{12}$), 82 (22, $M^+ - O_2C_8H_{13}$), 57 (10, C_4H_9). Anal. Calcd for $C_{13}H_{21}O_2N$: C, 69.95; H, 9.41; N, 6.27. Found: C, 70.17; H, 9.50; N, 6.03.

Acknowledgment. We gratefully acknowledge support by the National Science Foundation (CHE-9408912-001).

Supporting Information Available: Copies of ^{1}H and ^{13}C spectra (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO960153Y