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REGIOSELECTIVE MONO-ADDITION OF LITHIUM ENOLATES TO N-CARBAMOYL-L-PYROGLUTAMATES

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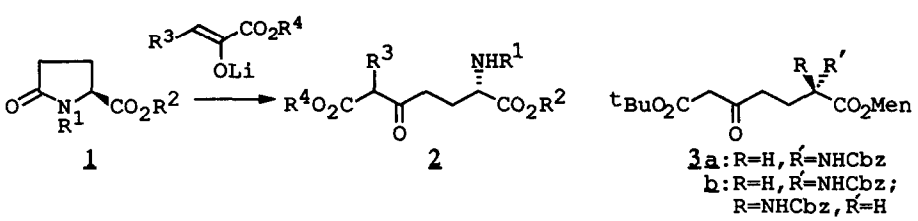
Abstract: Regioselective mono-addition of lithium enolate of esters to N-carbamoyl-L-pyroglutamates (1) gave excellent yields of (2S)-5-oxoamino acid derivatives (2) which were found to be an effective synthon for syntheses of carbapenams and carbapenems.

N-Carbamoyl-L-pyroglutamates (1) have been proven to be the effective chiral templates for the synthesis of nitrogen-containing natural products.[1] We have shown that lithium diisopropylamide (LDA) deprotonates only at C-4 of pyroglutamates (1) in spite of well known enolization of esters.[1] According to the above finding, we planned the ester enolate addition at C-5 of pyroglutamates (1) with the concept of direct modification with the least epimerization at C-2. Here we wish to describe the regioselective mono-addition reaction of lithium enolate of esters to N-carbamoyl-L-pyroglutamates (1) to afford 5-oxoamino acid derivatives (2) in excellent yields as shown in Table 1. Because of having the 4-oxoamide structure, the esters (2) will be used as an effective synthon of pyrrolidine derivatives or carbapenams. As a typical procedure, t-butyl acetate (0.54 ml, 4.00 mmol) in THF (4 ml) was added to LDA in THF (48 ml) prepared from diisopropyl amine (0.68 ml, 4.80 mmol) and 15% n-butyl lithium in n-hexane (3.07 ml, 4.80 mmol) at -78 °C. After stirring the mixture for 30 min, pyroglutamate (1a, 1.41 g, 4.00 mmol) in THF (15 ml) was added. The reaction mixture was stirred for 30 min at -78 °C, and then quenched with AcOH-MeOH (1:1, 2ml). Silica gel chromatography (n-hexane-EtOAc, 4:1 elution) of the crude product afforded the keto-ester (2a, 1.65 g), $[\alpha]_D^{20}$ -4.58° (c 1.27, $CHCl_3$).

The preservation of the optical activity throughout the reaction was confirmed by ^{13}C NMR (125.65 MHz). Proton-decoupled ^{13}C DEPT[2] spectrum of



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3a: R=H, R'=NHCbz
b: R=H, R'=NHCbz; R=NHCbz, R'=H

(-)-Menthyl ester (3a) prepared from the pyroglutamate (1i, R^1=Boc, R^2=(-)-menthyl) and the ester enolate (R^3=H, R^4=^{t}Bu) showed no signal due to the (2R)-isomer as shown in Fig. 1.[3,4] The 5-oxoamino acid derivative (2c) was found to be an effective synthon for a synthesis of carbapenem antibiotic PS-5 which will be described in an accompanying report.

Table 1. Reaction of Pyroglutamates (1) with Ester Enolates

1	R^1	R^2	R^3	R^4	2(%)
1a	Cbz	Bzl	H	^{t}Bu	95
1b	Cbz	Bzl	Me	^{t}Bu	93
1c	Cbz	Bzl	Et	^{t}Bu	81
1d	Cbz	Bzl	^{i}Pr	^{t}Bu	83
1e	Cbz	Bzl	Bzl	^{t}Bu	81
1f	Cbz	Me	H	^{t}Bu	84
1g	Cbz	Me	Et	Bzl	71
1h	Boc	Bzl	H	^{t}Bu	97

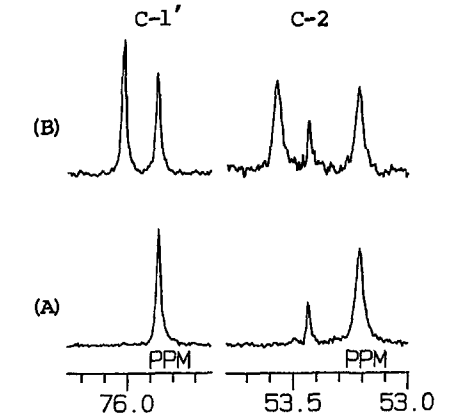

Fig. 1. Proton-Decoupled DEPT Spectra of 3a (A) and 3b (B).

References and Notes

1. T. Ohta, A. Hosoi, T. Kimura, and S. Nozoe, Chemistry Lett., 2091 (1987); T. Ohta, A. Hosoi, and S. Nozoe, Tetrahedron Lett., 29, 329 (1988).
2. D. T. Pegg, D. M. Doddrell, and M. R. Bendall, J. Chem. Phys., 77, 2745 (1982).
3. (-)-Menthyl (-)-(S)-2-benzyloxycarbamido-6-t-butoxycarbonyl-5-oxoheptanoate (3a): $[\alpha]_D^{25}$ -32.2° (c 1.28, $CHCl_3$); δ_H ($CDCl_3$, 500 MHz) 0.74 (3H, d, J=6.8 Hz), 0.88 (3H, d, J=6.8 Hz), 1.46 (9H, s), 3.33 (2H, s), 4.28-4.38 (1H, m), 4.72 (1H, dt, J=4.3, 11.1 Hz), 5.10 (2H, s), 5.46 (1H, d, J=7.7 Hz), 7.35 (5H, s); δ_C ($CDCl_3$, 125.65 MHz, DEPT) 16.3, 20.70, 21.96, 23.34, 26.16, 26.63, 27.96, 27.99, 28.08, 28.30, 31.38, 34.11, 38.62, 40.59, 46.84, 50.56, 53.21, 67.00, 75.86, 128.12, 128.20, 128.53; (-)-Menthyl (RS)-2-benzyloxycarbamido-6-t-butoxycarbonyl-5-oxoheptanoate (3b): δ_H ($CDCl_3$, 500 MHz) 0.73, 0.74 (3H, each d, J=6.8 Hz), 0.89 (3H, d, J=6.8 Hz), 0.91 (3H, d, J=6.8 Hz), 1.45, 1.46 (9H, each s), 3.32, 3.33 (2H, each s), 4.28-4.37 (1H, m), 4.72, 4.67 (1H, each dt, J=4.3, 11.1 Hz), 5.09 (2H, s), 5.44, 5.46 (1H, each d, J=7.7 Hz), 7.34, 7.35 (5H, each s); δ_C ($CDCl_3$, 125.65 MHz, DEPT) 15.83, 16.23, 20.70, 20.81, 21.94, 21.96, 23.01, 23.34, 26.06, 26.16, 26.34, 26.63, 27.95, 28.30, 28.35, 28.37, 31.38, 31.40, 34.11, 38.62, 40.59, 40.66, 46.83, 50.53, 50.56, 53.21, 53.57, 67.01, 75.87, 76.02, 128.09, 128.12, 128.19, 128.20, 128.53, 128.56.
4. DEPT conditions: θ $\pi/4$, acquisition time 1.311 s, repitition delay 4.689 s, scans 256.

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