Tetrahedron Letters, Vol. 33, No. 38, pp. 5589-5590, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Regioselective Nucleophilic Attack on N-BOC-Pyroglutamate Ethyl Ester

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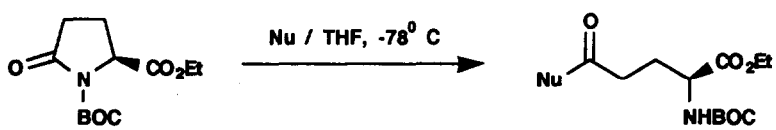
Key words: *Pyroglutamate, Amino Acid, Asymmetric Synthesis*

Abstract: *N-BOC ethyl pyroglutamate undergoes regioselective ring opening with different nucleophiles without racemization at the chiral centre.*

α-Amino acids constitute useful starting materials for the synthesis of enantiomerically pure compounds, because the chiral centre present in the naturally occurring α-amino acids provides a useful building block for asymmetric synthesis.[1] N-protected pyroglutamate esters have often been employed in the synthesis of optically active natural products containing the pyrrolidine ring, such as (-)-domoic acid,[2] (-)-kainic acid,[3] (+)-deoxynojirimycin,[4] and the *Monomorium minutum* ant venom alkaloids.[5]

N-protected pyroglutamate can be viewed as an internally protected form of the γ-carboxylic group of glutamic acid, allowing an easy differentiation of both carboxy groups of the amino acid. Thus, ring opening to mixed diesters can be achieved by reaction with alcohols with the aid of cyanide as a catalyst.[6] Also, N-BOC ethyl pyroglutamate undergoes ring opening with Grignard reagents[7] and ester lithium enolates[8] with excellent regioselectivity. A further recent development extends this type of ring opening to 1,3-dithiane addition, on a pyroglutamate derivative in which the ester was reduced and protected prior to nucleophilic attack.[9] We wish to report here that these extra steps are unnecessary, since N-BOC ethyl L-pyroglutamate can react regioselectively at the amide function with a range of C-nucleophiles (Scheme I).



1 **(Scheme I)** 2

Reactions of Boc-protected[10] ethyl L- pyroglutamate (**1**) with C-nucleophiles (Table I) afforded compounds (**2a-e**) in good yields.

To investigate the optical purity of the compounds, the D-enantiomers of (**2a**), (**2b**), and (**2d**) were also prepared from N-BOC ethyl D-pyroglutamate.[11] ^{1}H-NMR Spectra of both enantiomeric series were registered after addition of the chiral shift reagent (+)-Eu(tfc)$_3$. The (e.e.) was ≥ 95% in all cases.

Tautomeric equilibria I / II in compounds (**2a**) and (**2b**) were strongly shifted to form I, as shown by heteronuclear NOE difference experiments.[12] Thus, irradiation of H-4 in (**2a**) caused a 44% enhancement of only the most downfield shifted carbon signal (Scheme II).

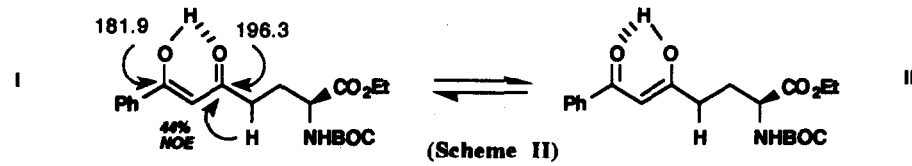
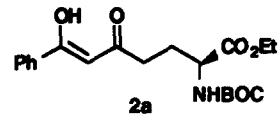
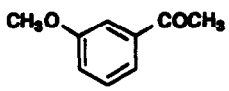
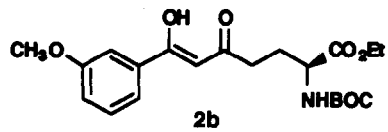
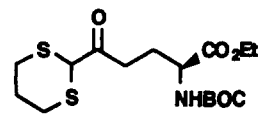
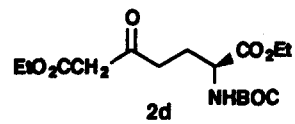
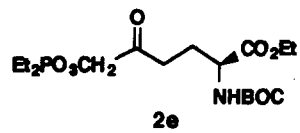


Table I. Reaction of (1) with Nucleophiles[a]

Reagent	Compound[b]	Yield	M.p.	$[\alpha]_D^{25}$
$PhCOCH_3$	 **2a**	78	80-82°C	+16.7°
	 **2b**	61	(c)	+15.5°
	 **2c**	72	86-88°C	+10.8°
CH_3CO_2Et	 **2d**	77	(c)	+4.1°
$CH_3PO_3Et_2$	 **2e**	60	(c)	+0.9°

(a) Typical procedure: To freshly prepared LDA (2 mmol) in THF (4 mL) was added the reagent (2 mmol) in THF (2 mL) at -78° C. After 45 min, (1) (1.94 mmol) in THF (3 mL) was added dropwise, and the mixture was maintained for 30 min at -78° C, and at r.t. for 3-4 h. Work-up: i) Quenching with aq. NH_4Cl. ii) Extraction with CH_2Cl_2 (3x5 mL). iii) Column chromatography (silica gel, CH_2Cl_2/MeOH 95:5).
(b) All new compounds were characterized by a full complement of analytical and spectroscopic data.
(c) Oil.

References and Notes

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(11) $[\alpha]_D$ values for **2a**, **2b**, and **2c** were -17.0°, -15.4°, and -3.9°, respectively.
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(Received in UK 29 May 1992)