

0040-4039(95)00450-5

Titanium Enolates from Pyroglutamates: Exclusive Formation of $4-\alpha$ Aldol Adducts¹

Dinesh K. Dikshit* and Saroj N. Bajpai Medicinal Chemistry Division, Central Drug Research Institute, Lucknow-226001,India

Abstract : Aldol reactions of pyroglutamate derived titanium enolate give exclusively $4-\alpha$ adducts.

In recent years pyroglutamates have been increasingly used as chiral starting material for the synthesis of bio-active natural products². The lithium enolate chemistry of pyroglutamates has been extensively utilized³ for functionalization at C-4. While the stereochemical outcome at C-4 in the reaction of Li enolates of pyroglutamates with arylmethylhalides is exclusively 4- α , alkylations with other halides and aldol reactions of such enolates are known to give a mixture of 4- α and 4- β products⁴. Use of boron, tin and titanium enolates is known to enhance the diastereofacial selectivity in aldol reactions by making the enolate geometry more rigid⁵. Recently, Evans et al have described the direct generation of titanium enolates by titanium tetrachloride and an amine base⁶. In the present communication we wish to report for the first time the generation of titanium enolate of pyroglutamates and their reaction with aldehydes to give exclusively 4- α adducts.

Thus the methyl N-carboethoxypyroglutamate $(1a)^7$ derived titaniumtrichloroenolate, prepared using the methodology described in literature⁶, reacted with carbonyl electrophiles to



(i) TiCl₄, DIPEA, CH₂Cl₂ -78°C, 3 hr. (ii) R²(C=O)R³, -78°C, 1.5 hr. (iii) H₂, 10% Pd-C, Abs. MeOH, 50 psi., 5 hr.

2	а	ь	c	đ	e	f	g
R ²	p-MeO-Ph	Ph	p-Cl-Ph	Styryl	Bu ^t	(CH ₂) ₄	Ph
R ³	Н	н	Н	н	н		Н

Scheme 1	l
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give, after chromatographic separation, exclusively $4-\alpha$ adducts $2a-g^{8,9,10}$ in good yields (Scheme-1). The stereochemical assignments in these compounds were made on the basis of chemical shifts patterns¹¹ and NOE data in the PMR spectra of 2a-g, and by transforming 2g by hydrogenolysis to give 3^{12} . Reaction of this enolate with cyclopentanone also gave a single adduct 2f which was presumed to have $4-\alpha$ stereochemistry.

Attempts to alkylate these enolates using similar conditions, with benzylbromide, allylbromide and ethyl bromoacetate were not successful. This was not unexpected as titanium enolates show better reactivity towards carbonyl electrophiles.

This paper thus describes a new methodology for the synthesis of 4α - substituted pyroglutamates which otherwise can not be obtained in high *d.e.*

References:

- (a) This paper, CDRI communication No.5353, is dedicated to Dr. Nitya Anand on his 70th birthday.
 (b) This work was supported by a research grant from the Department of Science & Technology, Delhi. Award
- of a CSIR research associate fellowship to SNB is gratefully acknowledged.
- 2. (a) Ikota, N. Tetrahedron Lett. 1992, 33, 2553.(b) Langlois, N.; Andriamialisoa, R.Z. ibid 1991, 32, 3057.
- (a) Ezquerra,J.; Mendoza,J.De.; Pedregal,C.; Ramirez,C. Tetrahedron Lett. 1992, 33, 5589.(b) Jain, S.; Sujatha,K.; Krishna, K.V.R.; Roy,R.; Singh,J.; Anand,N. Tetrahedron 1992,48, 4985.
- (a) Ezquerra, J.; Pedregal, C.; Rubio, A.; Yruretagoyena, B.; Escribano, A.; Ferrando, F.S. Tetrahedron 1993, 49, 8665. (b) Dikshit D.K.; Panday, S.K. J. Org. Chem. 1992, 57, 1920. (c) Baldwin, J.E.; Miranda, T.; Moloney; M., Hokelek, T. Tetrahedron 1989,49, 2459.
- (a) Heathcock, C.H. Aldrichimica Acta 1990, 23,99. (b) Evans, D.A.; Howard, P.Ng.; Clark, J.S.; Rieger, D.L. Tetrahedron 1992, 48, 2127. (c) Siegel, C.; Thornton, E.R. J. Am. Chem. Soc. 1989, 111,5722.
- 6. Evans, D.A.; Bilodeau, M.T.; Somers, T.C.; Clardy, J.; Cherry, D.; Kato, Y. J. Org. Chem. 1991, 56, 5750 and references cited therein.
- 1a was prepared according to the procedure described in Rigo, B.; Lespagol, C.; Pauly, M. J. Het. Chem. 1988, 25,49.
- 8. Presence of the presumed $4-\beta$ adduct (5%) was detected only in the PMR spectrum of crude 2e.
- 9. Though we have not assigned the stereochemistry of the carbinolic center in 2a-g, based on the J values of carbinolic protons it appears to be opposite to that of adducts derived from Li enolates of pyroglutamate. Aldol adducts derived from titanium enolates are reported to be predominantly syn-, while anti- adducts are obtained with lithium enolates.
- 10. Typical procedure : Using a syringe and rubber septum, a solution of TiCl₄ (5.49 ml, 5.39 mmol, 1M in CH₂Cl₂) was added dropwise to a magnetically stirred solution of methyl N-ethoxycarbonylpyroglutamate (1.07 gm, 4.97 mmol) in dry CH₂Cl₂ (25 ml) at -78°C under N₂, giving a yellow slurry. After 5 min. diisopropylethylamine (1.04 ml, 5.96 mmol) was added dropwise over a period of 15 min. The resulting violet coloured solution was stirred at -78°C under N₂ for 3hr. A solution of p-methoxybenzaldehyde (0.73ml, 5.96 mmol) in CH₂Cl₂ (5 ml)was added over a period of 10 min. and stirring continued at -78°C for 1.5 hr. The reaction was terminated by addition of a saturated aq. solution of NH₄Cl. The usual workup followed by flash chromatography (ethyl acetate:hexane (15:85)) gave the product 2a. Yield 740 mg (69%), m.p.90-92°C. IR: 1742, 1720, 1614 cm⁻¹. PMR(CDCl₃): δ 1.35 (t, J=6Hz, 3H, CH₃), 1.72-1.78 (m, 1H, 3'-H), 1.92-2.04 (m, 1H, 3-H), 2.96-3.04 (m, 1H, 4H), 3.77 (s, 3H, OCH₃), 3.82(s, 3H, CH₃), 4.35 (q, J=6Hz, 2H, CH₂CH₃), 4.59 (dd, J=8,2 Hz, 1H, 2-H), 4.75 (d, J=10Hz, 1H, CHOH), 6.90 (d, J=7Hz, 2H, ArH), 7.28 (d, J=7Hz, 2H, ArH). ¹³C NMR:δ 14.99, 25.55, 48.99, 52.71, 55.26, 56.75, 63.46, 74.68, 76.70, 77.33, 77.99, 114.94, 127.85, 132.22, 152.76, 159.76, 170.99. 175.27. Mass: m/z 351(M⁺). Anal. Calcd. for C₁₇H₂₁NO₇: C, 58.11; H, 6.02; N, 3.98. Found: C, 58.04; H, 6.38; N, 3.79. [α]²² -61.42 (c, 0.6, CHCl₃).
- 11. In the PMR spectrum of 4- α benzyl compounds both hydrogens at C-3 come as a multiplet while in 4- β both appear as multiplet at different positions as observed by us^{4b} and Ezquerra et al^{4a}.
- 12. 3 was found to be identical with the sample^{4b} made previously. However the PMR data of 3 as reported by Ezquerre etal.^{4a} appears to be that of the ethyl ester.

(Received in UK 10 January 1995; revised 6 March 1995; accepted 10 March 1995)