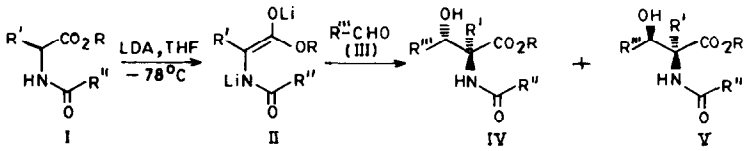
Tetrahedron Letters,Vol.29,No.25,pp 3109-3110,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

1,2-ADDITION OF α-AMINO ACID DERIVATIVES TO CONJUGATED ALDEHYDES: SYNTHESIS OF β-SUBSTITUTED SERINES[1]

Dinesh K. Dikshit* and Sangeeta Singh
Central Drug Research Institute, Lucknow 226 001, INDIA

SUMMARY: *Reaction of C,N-dianions of N-acyl α-amino acid esters with conjugated aldehydes at -78°C give threo- and erythro-β-substituted serine derivatives in excellent yields.*

C,N-Dianions and hard anions derived from α-amino acid derivatives are known to react with aldehydes to give β-substituted serines[2a-f]. Though anions derived from benzylidine -amino acid esters[3] have been shown to undergo Michael addition reactions with conjugated carbonyl compounds, there is no report describing such reaction of dianions with conjugated carbonyl compounds. We now report that such dianions undergo 1,2-addition reactions with conjugated aldehydes rather than 1,4-addition, thus providing an excellent route to β-vinyl and ethynyl serines. (Scheme-1)



Scheme - 1

	a	b	c	d	e	f	g
R	Me	Me	Me	Me	Et	Me	Et
R'	H	H	Me	Me	H	Me	H
R"	Ph	OBzl	OBzl	OBzl	OBzl	OBu^t	OBzl
R"'	CH_2 = CH	CH_2 = CH-	CH_2 = CH-	PhCH = CH-	PhCH = CH-	$Me_3SiC \equiv C$-	$Me_3SiC \equiv C$-

The following procedure is representative: a solution of Bz-Gly-OMe (0.02M) in 100ml. anhyd. THF was added slowly using double ended needle and rubber septa to a solution of Lithium diisopropylamide (0.044M) in 150 ml THF at -78°C. The resulting pale yellow solution of the dianion was stirred at this temperature for 2 hr and to this at -78°C freshly distilled acrolein (.04M, excess) dissolved in 100 ml THF was added. The resulting mixture was stirred at -78°C for additional 2 hr and then quenched with 20% MeOH-H_2O followed by the addition of 400 ml ether. The organic layer was washed successively with ice cold 0.1N HCl and water. Concentration of the organic layer after usual work up gave a residue (4.24g) which was chromatographed over a column of silica gel using hexane-EtOAc (10%) as eluant to give an oily mixture of IVa+Va 1.77g (46% yield) separated by chromatography of their TBS ethers to give IVa and Va[5].

In a similar reaction of CBz-Gly-OMe and acrolein an unseparable oily mixture of dl.N-CBz-β-vinylserine-OMe (IVb & Vb)[6,7] was obtained. Cinnamaldehyde and 3-trimethylsilylpropynal also reacted with Gly and Ala derivatives to give IVd-g, Vd-g (1:1) in good yields. The stereochemical assignments of IV and V were made on the basis of the chemical shift of 3-H[1f].

In order to study the reaction of these dianions with conjugated ketones, a representative candidate (IIc) was reacted with but-3-ene-2-one and in this case no 1,2-addition product could

be detected. However, the expected, 1,4-addition product was obtained in reasonable yield.

The present procedure provides an excellent route for synthesizing β-vinyl and ethynyl serines in good yields, a class of compounds which have recently been synthesized by allylic oxidation of allyl glycine derivative in poor yield[6].

REFERENCES AND NOTES

1. Communication No.3673 from Central Drug Research Institute, Lucknow-226001, INDIA.

2. (a) T. Nakatsuka, T. Miwa and T. Mukaiyama, Chem. Lett. (1981) 279, (1982) 145; (b) A. Shanzer, L. Somekh and D. Butina, J. Org. Chem. (1979) **44**, 3967; (c) Y. Ozaki, S. Maeda, M. Miyoshi and K. Matsumoto, Synthesis (1979) 216; (d) G. Guanti, L. Banfi, E. Narisano and C. Scolastico, Tet. Lett. (1984) **25**, 4693; (e) M. Jung and M.J. Miller, Tet. Lett. (1985) **26**, 977; (f) A.M. Touzin, Tet. Lett. (1975) 1477.

3. G. Stork, Y.W.L. Ambrose and A.M. Touzin, J. Org. Chem. (1976) **41**, 3491.

4. **IVa**, m.p. 82-4°C, yield 20.5%, IR(KBr) 1660, 1760, 3400 cm^{-1}; PMR($CDCl_3$)δ 3.74 (3, s, OMe), 4.67-4.71 (1, dd, J=7 & 4 Hz, 2-H), 4.94-5.07 (1, dd, J=4 & 7 Hz, 3-H), 5.19-5.47 (2, m, 5-H), 5.69-6.09 (1, m, 4-H), 6.92-7.17 (1, b, NH), 7.25-7.88 (5, m, Ar-H); m/z = 249(M^+), 219, 193, 105, 77; **Va**, oil, yield 16.5%, IR(Neat) 1680, 1760, 3200 cm^{-1}; PMR ($CDCl_3$)δ 3.70 (3, s, OMe), 4.60-5.00 (2, m, 2-H & 3-H), 5.01-5.50 (2, m, 5-H), 5.60-6.20 (1, m, 4-H), 6.70-6.95 (1, bd, J = 9 Hz, NH), 7.20-7.80 (5, m, ArH); m/z = 249(M^+), 193, 105; **IVb & Vb**, oil, yield 60%, IR(Neat) 1740, 3400 cm^{-1}; PMR($CDCl_3$)δ 3.60 (3, s, OMe), 4.15-4.71 (2, m, 2&3-H), 5.12-5.40 (2, m, 5-H), 5.10 (2, s, CH_2Ph) 5.50-6.15 (1, m, 4-H), 7.28 (5, s, ArH); m/z = 279, 223, 91; **IVc & Vc**, oil yield 65%, IR(Neat) 1740, 3400 cm^{-1}; PMR($CDCl_3$)δ 1.53 (3, s, Me), 3.68 (3, s, OMe), 4.30 (1, d, J=9 Hz, 3-H), 5.01 (2, s, CH_2Ph), 5.12-5.30 (1, m, 5-H), 5.40-5.92 (1, m, 4-H), 7.27 (5, s, ArH); m/z = 171, 91; **IVd**, oil,yield 32%, IR(Neat) 1700-1725, 3430 cm^{-1}; PMR($CDCl_3$) 1.60 (3, s, Me), 3.68 (3, s, OMe), 4.20 (1, d, J=6 Hz, 3-H), 4.60 (1, bs, OH), 5.12 (2, s, CH_2Ph), 5.90 (1, bs, NH), 6.05 (1, dd, J=6 & 17 Hz, 4-H), 6.73 (1, d, J=17 Hz, 5-H), 7.20 (10, bs, ArH); m/z = 369, 237, 191; **Vd**, oil,yield 26%, IR(Neat) 1700-1720, 3440 cm^{-1}; PMR($CDCl_3$)δ 1.52 (3, s, Me), 3.70 (3, s, OMe), 4.48 (1, d, J=6 Hz, 3-H), 5.05 (2, s, CH_2Ph), 5.60 (1, bs, NH), 6.10 (1, dd, J=6& 17 Hz, 4-H), 6.60 (1, d, J=17 Hz, 5-H), 7.20 (10, bs, ArH); **IVe**, m.p. 89-90°C, yield 54.8%, IR(KBr) 1680, 1740, 3000, 3300, 3400 cm^{-1}, PMR($CDCl_3$)δ 1.12 (3, t, J=7 Hz, CH_2CH_3), 3.35 (1, b, OH), 4.09 (2, q, J=7 Hz, CH_2CH_3), 4.55 (2, m, 2&3-H), 5.00 (2, s, CH_2Ph), 5.78 (1, d, J=9 Hz, NH), 6.08 (1, dd, J=6&17 Hz, 4-H), 6.60 (1, d, J=17 Hz, 5-H), 7.20 (10, bs, ArH); m/z = 237, 91; **Ve**, oil,yield 17%, IR(Neat) 1700, 1740, 3000, 3450, 3500 cm^{-1}, PMR($CDCl_3$) 1.20 (3, t, J=7 Hz, CH_2CH_3), 4.15 (2, q, J=7 Hz, CH_2CH_3), 4.45 (1, m, 2-H), 4.72 (1, m, 3-H), 5.00 (2, s, CH_2Ph), 5.50 ((1, b, OH), 5.70 (1, d, J=9 Hz, NH), 6.12 (1, dd, J=6&17 Hz, 4-H), 6.60 (1, d, J=17 Hz, 5-H), 7.20 (10, bs, ArH); **IVf**, m.p. 79-80°C, yield 30%, IR(KBr) 1700-1720, 2200, 3000, 3400, 3500 cm^{-1}, PMR($CDCl_3$ lock at 7.27)δ 0.12 (9, s, SiMe), 1.42 (9, s, Bu^t), 1.60 (3, s, Me), 3.78 (3, s, OMe), 4.75 (1, bs, 3-H), 5.62 (1, bs, NH); **Vf**, m.p. 96-98°C yield 35%, (IR(KBr) 1720, 2200, 2950, 3300, 3450 cm^{-1}; PMR($CDCl_3$, lock at 7.27)δ 0.12 (9, s, $SiMe_3$), 1.45 (9, s, Bu^t), 1.53 (3, s, Me), 3.78 (3, s, OMe), 4.65 (1, bs, 3-H), 5.08 (1, bs, NH); **Vg**@, m.p. 75-77°C, yield 47%, IR(KBr) 1720-40, 2200, 3000, 3400 cm^{-1}, PMR($CDCl_3$)δ 0.1 (9, s, $SiMe_3$), 1.22 (3, t, J=8 Hz, CH_2CH_3), 4.15 (2, q, J=8 Hz, CH_2CH_3), 4.56 (1, dd, J=4&9 Hz, 2-H), 4.72 (1, d, J=4 Hz, 3-H), 5.08 (2, s, CH_2Ph), 5.20 (1, b, NH), 7.30(5, s, ArH). @In this case **IVg** could not be detected.

5. (a) P.M.R. Spectra of crude reaction products showed that **IVa-f** and **Va-f** were formed in approx. 1:1 and constitute 80% of the crude.

   (b) TBS ethers were prepared using imidazole, DMF and TBS-Cl and chromatographed on silica gel: aq.HF-CH_3CN was used to cleave TBS group.

6. Y. Ohfune and H. Nishio, Tet. Lett. (1984), **25**, 4133.

7. Though the mixture of dl-**IVb** & **Vb** showed PMR and HPLC patterns identical to the authentic l-sample kindly provided by Prof. Ohfune, they could not be crystallized.

(Received in UK 25 March 1988)