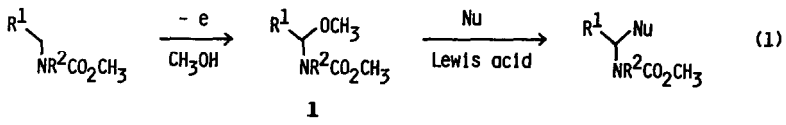
Tetrahedron Letters, Vol.29, No.2, pp 231-234, 1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

NEW SYNTHESIS OF β-AMINO ACIDS BY NUCLEOPHILIC ADDITION OF ENOLATE ANIONS TO N-METHOXYCARBONYLIMINES GENERATED FROM α-METHOXY CARBAMATES[1]

Tatsuya Shono,* Naoki Kise, Fumio Sanda, Satoru Ohi, and Kenji Tsubata
Department of Synthetic Chemistry, Faculty of Engineering,
Kyoto University, Yoshida, Sakyo, Kyoto 606, Japan

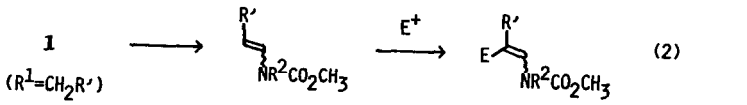
Summary The nucleophilic addition of enolate anions of alkyl acetates to N-methoxycarbonylimines generated from α-methoxy carbamates gave β-amino acid derivatives (3) and enantioselective synthesis (72-90%ee) of 3 was achieved by using chiral 2-methyloxazolines instead of acetates.

Our previous studies on anodic α-methoxylation of carbamates and subsequent acid catalyzed substitution of the α-methoxy group by a variety of nucleophiles have extensively been applied to synthetic problems (eq. 1).[2] Lewis acid catalyzed transformation of the α-methoxy carbamates to enecarbamates and subsequent reaction of the latter compounds with electrophiles have also been applied to synthesis of a variety of compounds (eq. 2).[3]



(1)

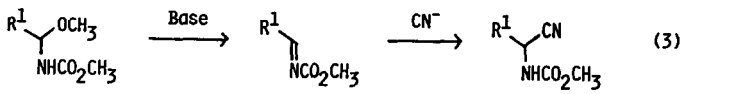
1



(2)

Recently, we have found that the α-methoxylated carbamates obtained from aliphatic primary amines show another type of interesting reaction with nucleophiles under basic conditions.

Namely, in the first place we found that treatment of the α-methoxylated carbamates with cyanide anion in the presence of a base gave the corresponding α-cyano carbamates in reasonable yields (e.g. R^1=Et, Y=98%). The mechanism of this reaction is not the common S_N2 type substitution reaction but a base catalyzed elimination of methanol followed by the addition of cyanide anion to the resulting N-methoxycarbonylimines (eq. 3).



(3)

1 (R^2=H)

Hence, in the next place we have studied the possibility of addition of an enolate anion to the N-methoxycarbonylimine to develop a new method for the synthesis of β-amino acid, and found that an enolate anion generated from an acetate smoothly added to the N-methoxycarbonylimine as the results are summarized in Table 1.[4]

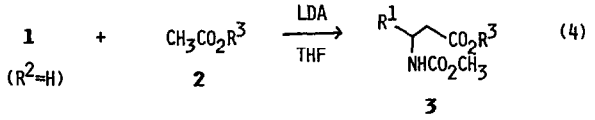


Table 1

Run	R^1	R^3	Temp. (°C)	Yield of 3 (%)[a]
1	1a CH_3	2a *t*-Bu	-70 — 0	3a 78
2	1b *i*-Pr	2a *t*-Bu	-70 — 0	3b 87
3	1a CH_3	2b CH_3	-70[b]	3c 70
4	1b *i*-Pr	2b CH_3	-70[b]	3d 76
5	1c Allyl	2b CH_3	-70[b]	3e 62
6	1b *i*-Pr	2c L-menthyl	-70[b]	3f 70[c]

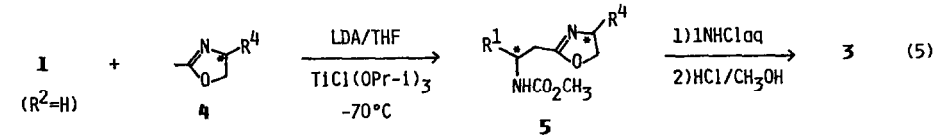
a Isolated yield. Satisfactory spectroscopic and elemental analyses were obtained for all products *b* $TiCl(OPr\text{-}i)_3$ equimolar to 2 was added to the reaction mixture at -70°C and the reaction temperature was kept at -70°C for 7-8 hr. *c* R-3d was obtained in 20%ee after methanolysis of 3f.

A procedure using *t*-butyl acetate is shown below as one of the examples

A mixture of 1a (5 mmol) and *t*-butyl acetate (2a, 6 mmol) in THF (5 ml) was added to a solution of LDA (12 mmol) in THF-hexane (15 ml) at -70°C The temperature was gradually raised to 0°C and the mixture was stirred for an additional 2 hr After usual work-up, the product 3a was isolated by kugel rohr distillation (120°C/2 mmHg) in 78% yield.

Methyl acetate gave a poor result (yield 10%) probably due to rather easy selfcondensation of the acetate, while the addition of $TiCl(OPr\text{-}i)_3$[6] to the reaction mixture at -70°C gave satisfactory results

Our next aim was to extend this reaction to the enantioselective synthesis of optically active β-amino acids Since anions generated from chiral 2-methyloxazolines seem to be effective chiral nucleophiles[9,10] and equivalent to the enolate anion of an acetate, several types of chiral oxazoline were then prepared from easily available α-amino alcohols The reactions of these oxazoline anions with 1 were studied under the same reaction conditions as those described in Table 1 to achieve an enatioselective synthesis (eq 5). The results are shown in Table 2



Although each type of the chiral oxazolines showed a moderate extent of diastereoselectivity, most of them were not always satisfactory. The chiral oxazoline 4e prepared from L-valinol, however, showed sufficiently high selectivity

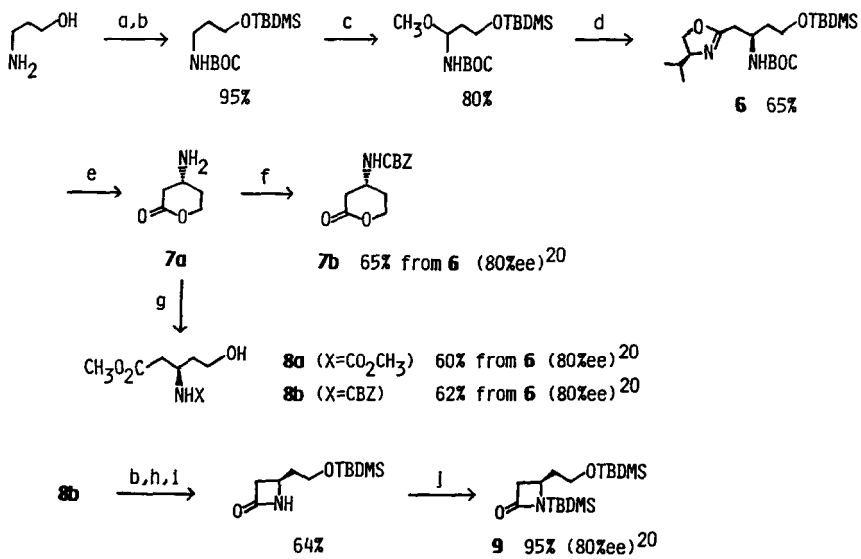
Since one of the most important uses of β-amino acids is their ability to form

Table 2

Run	R^1	R^4	Yield of 5 (%)[a]	ee of 3 (%)[b]
1	1b i-Pr	4a CH_2Ph (S)	5a 50	3d 44 (R)
2	1b i-Pr	4b i-Bu (S)	5b 47	3d 50 (R)
3	1b i-Pr	4c Ph (R)	5c 45 (76)[c]	3d 54 (40)[c] (S)
4	1b i-Pr	4d Et (R)	5d 46	3d 60 (S)
5	1b i-Pr	4e i-Pr (S)	5e 40 (86)[c]	3d 90 (83)[c] (R)[d]
6	1a CH_3	4e i-Pr (S)	5f 63 (83)[c]	3c 76 (63)[c] (R)[e]
7	1c Allyl	4e i-Pr (S)	5g 54	3e 72 (R)[f]

a Isolated yields. Satisfactory spectroscopic and elemental analyses were obtained for all compounds. *b* Determined by chiral shift reagent $Eu(hfc)_3$ *c* The reaction was carried out at -30°C. *d* $[\alpha]_D^{20}$ +34 7° (c3 0, $CHCl_3$). See ref. 11. *e* $[\alpha]_D^{20}$ +20 0° (c2.0, $CHCl_3$). See ref 13 *f* $[\alpha]_D^{20}$ +3.9° (c3.0, $CHCl_3$). See ref 15.

β-lactams, this new reaction may offer an effective method of enantioselective synthesis of carbapenem antibiotics. Our studies on the synthesis of key intermediates[17] 7b[18] and 9[19] are described in Scheme 1 as typical examples

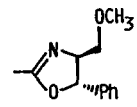


(a)$(BOC)_2CO$,$CHCl_3$,reflux,3h,(b)TBDMSCl,imidazole,DMF,0°C,2h, (c)-e,0.04M Et_4NOTs/CH_3OH,8F/mol,(d)4e,LDA/THF,TiCl(OPr-i)$_3$,-70°C, 8h,(e)1NHCl,reflux,2h,(f)CBZCl,$NaHCO_3$aq,0°C,1h,(g)CH_3CO_2Cl or CBZCl, $NaHCO_3$,CH_3OH,r.t.,3h,(h)H_2(1atm),Pd/C,CH_3OH,r.t.,1h,(i)LDA/THF,0°C, 2h,(j)TBDMSCl,Et_3N,DMF,r.t.,1h.

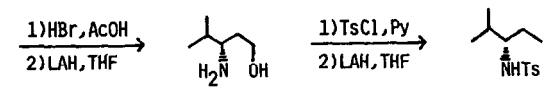
Scheme 1

References and Notes

1. Electroorganic Chemistry. 111.
2. a) T. Shono, Y. Matsumura, and K. Tsubata, *J. Am. Chem. Soc.*, 103, 1172 (1981). b) *idem, Tetrahedron Lett.*, 22, 2411 and 3249 (1981). c) T. Shono, K. Tsubata, and N. Okinaga, *J. Org. Chem.*, 49, 1056 (1984). d) T. Shono, Y. Matsumura, K. Uchida, and H. Kobayashi, *ibid.*, 50, 3243 (1985).
3. T. Shono, Y. Matsumura, K. Tsubata, Y. Sugihara, S. Yamane, T. Kanazawa, and T. Aoki, *J. Am. Chem. Soc.*, 104, 6697 (1982).
4. D. J. Hart *et al.* have been reported the reaction of imines with ester enolates.[5] In this reaction, however, imines are limited to those non-enolizable to the corresponding enamines.
5. a) D. C. Ha, D. J. Hart, and T. K. Yang, *J. Am. Chem. Soc.*, 106, 4819 (1984). b) D. J. Hart, C. S. Lee, W. H. Pirkle, M. H Hyon, and A. Tsipouras, *ibid.*, 108, 6054 (1986).
6. $TiCl(OPr\text{-}i)_3$ has been known as an effective reagent for the conversion of Li-enolate to Ti-enolate.[7] In our other study,[8] we found that the addition of $TiCl(OPr\text{-}i)_3$ allowed the reaction of 1 with Li-enolate to proceed at lower temperature (-70°C).
7. M. T. Reets and R. Peter, *Tetrahedron Lett.*, 22, 4691 (1981).
8. Unpublished.
9. a) A. I. Meyers and G. Knaus, *Tetrahedron Lett.*, 1974, 1333. b) A. I. Meyers and Y. Yamamoto, *J. Am. Chem. Soc.*, 103, 4278 (1981).
10. A. I. Meyers *et al.* reported the aldol reaction of lithium azaenolate of 10 (18-25%ee).[9a] The reaction of 10 with 1b gave S-3d in only 20%ee.
11. The absolute configuration of 3d was confirmed by its transformation to 11. $[\alpha]_D^{20}$ -14 0° (c2 5, EtOH) (Lit.[12] -16.7°).

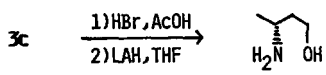


10



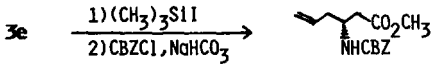
11

12. A. Romeo, V. Tortorella, and G. D. Maio, *Ricerca sci* 29, 2253 (1951).
13. The absolute configuration of 3c was assigned by its conversion to 12 $[\alpha]_D^{20}$ -8.2° (c1.0, EtOH) (Lit.[14] -11.2°).



12

14. R. Kinas, K. Pankiewics, and W. J. Stec, *J. Org. Chem.*, 42, 1650 (1977).
15. The absolute configuration of 3e was decided by its transformation to 13 $[\alpha]_D^{20}$ +3.2° (c2.0, $CHCl_3$) (Lit [16] +4 7).



13

16. M. Ohno, S. Kobayashi, T. Izawa, and Y. Wang, *Nippon Kagaku Kaishi*, 1983, 1299.
17. Carbapenem antibiotics such as thienamycin, PS-5, and carpetimycin A were synthesized from 7b[18] and 9.[19]
18. T Iimori, Y. Takahashi, T. Izawa, S. Kobayashi, and M. Ohno, *J. Am. Chem Soc.*, 105, 1659 (1983).
19. K. Okano, T. Izawa, and M. Ohno, *Tetrahedron Lett.*, 24, 217 (1983).
20. The ee of 8a was found to be 80% by the method using $Eu(hfc)_3$. The optical purities of 7a,b, 8b, and 9 were not able to be determined directly, but they are reasonably believed to be the same as 8a since the processes used to transform 7a to 7b, 8a,b, and 9 will not change the optical purity. 8a· $[\alpha]_D^{20}$ +12.4° (c0.5, $CHCl_3$). 7b. $[\alpha]_D^{20}$ +3.6° (c1.0, $CHCl_3$) (Lit.[18] +4.7°). 9 $[\alpha]_D^{20}$ -41.4° (c1.5, $CHCl_3$) (Lit.[19] -49.2°).

(Received in Japan 2 October 1987)