Tetrahedron Letters,Vol.24,No.32,pp 3311-3314,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain 

# α-ALKYLATION OF THREONINE

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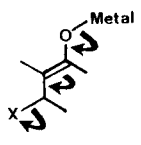
*Abstract: The (S,S)- and the (S,R)-oxazolines 4, both readily available from L-threonine, are deprotonated with lithium diisopropylamide (LDA, → 5) and alkylated diastereoselectively (>95 % ds) to yield the 4.4-disubstituted oxazolines 7. The product of methylation (7a, E = $CH_3$) is shown to be formed with relative topicity ul-1.2.*

Aminoacids are among the least expensive enantiomerically pure starting materials for organic synthesis[2a)] (pool of chiral building blocks[2b)]). In our search for methods of alkylating hydroxy-[3a-d)] and aminoacids[3d-i)] without racemization[4)] and without the use of external chiral auxiliaries[5)], we have now succeeded in converting threonine into α-branched allothreonine derivatives of both senses of chirality. This required to find an enolate derived from threonine, i.e. an enolate bearing a β-leaving group which would not eliminate[3a,b,c,f,i,6)], see 1. After many unrewarding attempts with mono- and di-lithiated derivatives of the oxazoli-

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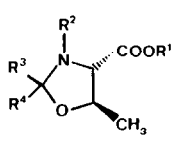


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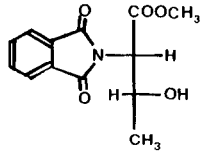


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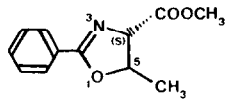


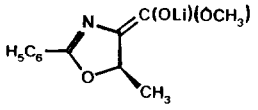

4

**a**: (4S,5R) = trans
**b**: (4S,5S) = cis

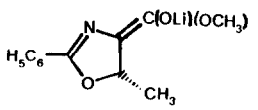
dine 2 and of phthalylthreonine 3, the 2-phenyl-oxazoline 4 turned out to be an ideal precursor[3i)]. Following literature procedures[7)], threonine can be converted either to the *trans*-isomer 4a with retention at both asymmetric carbon atoms[7a)] or to the *cis*-isomer 4b with inversion of configuration at the β-carbon[7b)]. Both diastereomers are of ≥98 % configurational and enantiomeric purity (by capillary GC and specific rotation, see Table).

Addition of 4 to a 10 % molar excess of *ca.* 0.17 M LDA in tetrahydrofuran (THF) with stirring at -75°C generates solutions of the enolate 5. These are stable up to *ca.* -35°C,

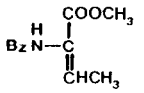
when decomposition with β-elimination begins, leading to the isolation after workup of E/Z--mixtures of methyl α-benzoylamino-crotonate (6). Quenching the enolate solutions with acetic acid or deuteroacetic acid produces *ca.* 1:1-mixtures of unlabelled or of 4-deuterio-*cis*- and -*trans*-oxazolidines 4. In contrast, reactions with carbon electrophiles such as primary and secondary haloalkanes, aldehydes, and ketones lead to the products 7 highly diastereoselec-




(R)-5




(S)-5

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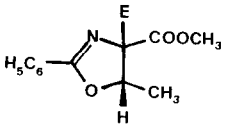
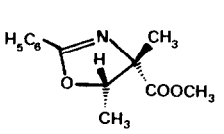
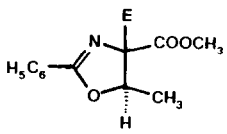


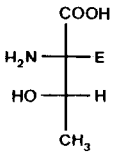

7a




7a (E = $CH_3$)




7b

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tively, see the Table. With the less reactive alkylating reagents, activation by a cosolvent such as hexamethyl phosphoric acid triamide (HMPT) or dimethyl propylene urea (DMPU)[8] greatly improves the yields.

The stereochemical course of methylation of the enolate 5 follows from nuclear *Overhauser* effect (NOE) measurements with the product 7a, E = $CH_3$ (see Table). We assume that the other products 7 are formed in the same way, i.e. with a relative topicity *ul* of the 1.2-induction. This would mean that the directing effect of the substituent on the enolate 5 is opposite to that observed with enolates of 5-substituted alkyl 1.3-dioxolan-4-carboxylates[3b,c,9].

Further examples of alkylations of the enantiomeric enolates 5, hydrolyses of the products 7 to free allothreonine aminoacids of type 8, and conversions to other α-alkylated β-heterosubstituted and β.γ-unsaturated aminoacids, as well as alkylations of the corresponding derivative of β-phenyl-serine will be subject of the full paper.

Table. - *Products* 7 *of alkylation of the enolates* 5. - Unless stated otherwise, the yields (y) are those of distilled (Kugelrohr) or flash-chromatographed products. - The diastereoselectivities (% ds)[3d] were determined by capillary GC or $^{13}$C-NMR. - After addition of the alkyl halides to the solution of 5, the mixture was stirred at -75°C for 2 - 4 hr and then allowed to warm to 0°C overnight; the reactions with benzaldehyde and with acetone were quenched with acetic acid after 5 - 10 min. at -75°C. - The $[\alpha]_D$ measurements were all done at ambient temperature.

4a from methyl threoninate·HCl and methyl iminobenzoate[7a], 71 % y, 98.6 % ds, b.p. 105°C/6.10$^{-5}$ Torr, $[\alpha]_D$ = +96.7° (c = 1.18, $CHCl_3$).

4b from methyl N-benzoyl-threoninate and $SOCl_2$[7b], 84 % y, 98.4 % ds, m.p. 74.5-76.5°C, $[\alpha]_D$ = +69.2° (c = 9.0, $C_2H_5OH$).

6, E: m.p. 108.5-109.5°; Z: m.p. 71.5-73.0°C; NMR assignment cf.[10].

7a, E = $CH_3$: from 4a and $CH_3I$, 94 % y, 93.3 % ds, $[\alpha]_D$ = +9.5° (c = 0.98, $CHCl_3$).

7b, E = $CH_3$: from 4b and $CH_3I$, 93 % y, 94.6 % ds, $[\alpha]_D$ = -9.5° (c = 1.14, $CHCl_3$); difference NOE of the 5-CHO with irradiation at 4-C-$CH_3$ frequency.

7a, E = $C_2H_5$: from 4a and $C_2H_5I$, *ca.* 25 % DMPU cosolvent, 91 % y, 94.7 % ds, $[\alpha]_D$ = +55.7° (c = 1.15, $CHCl_3$).

7b, E = $C_2H_5$: from 4b and $C_2H_5I$, *ca.* 17 % HMPT cosolvent, 94 % y, 94.7 % ds, $[\alpha]_D$ = -54.25° (c = 0.91, $CHCl_3$).

7a, E = $CH_2CH_2CH(CH_3)_2$: from 4a and $(CH_3)_2CHCH_2CH_2Br$, *ca.* 17 % HMPT cosolvent, 62 % y, >98 % ds, $[\alpha]_D$ = +65.4° (c = 1.14, $CHCl_3$).

7a, E = $CH(CH_3)_2$: from 4a and 2-iodopropane, *ca.* 17 % HMPT cosolvent, 85 % y, 98.4 % ds, $[\alpha]_D$ = +97.4 (c = 0.99, $CHCl_3$).

7b, E = $CH_2$-CH=$CH_2$: from 4b and allyl bromide, 96 % y, 98.7 % ds, $[\alpha]_D$ = -28.0° (c = 1.17, $CHCl_3$).

7b, E = $CH_2C_6H_5$: from 4b and benzyl bromide, 93 % y, >99 % ds, $[\alpha]_D$ = +4.6° (c = 0.92, $CHCl_3$).

7b, E = $C(OH)(CH_3)_2$: from 4b and acetone, 68 % y, >99% ds, $[\alpha]_D$ = -27.5° (c = 1.22, $CHCl_3$).

7b, E = $CH(OH)C_6H_5$: from 4b and benzaldehyde, 72 % y, ~70 % ds (crude product $^1$H-NMR), only two of the four possible diastereomers are formed: diastereomer A, 20 % y, >99 % configurational purity, $[\alpha]_D$ = +24.9° (c = 1.31, $CHCl_3$); diastereomer B, 52 % y, >99 % configurational purity, $[\alpha]_D$ = +19.5 (c = 0.84, $CHCl_3$).

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(Received in Germany 16 May 1983)