Communications

Diastereoselective Azidations of (*S*)-4-Carboethoxymethyloxazolidin-2-one for 4-Oxy-2,3-diaminobutanoates

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Received January 29, 2002

Keywords : Azides, Diamines, Oxazolidinones.

Vicinal diamine moiety has been found in diverse classes of biologically active compounds including antibiotics, antifungal dipeptides, and alkaloids.[1] Also, recent advance in asymmetric synthesis requires more practical route to enantiopure vicinal diamine derivatives for use as chiral auxiliaries or metal ligands of asymmetric catalysts.[2] In the synthesis of peptidomimetics for rational design of a therapeutic agent, α,β-diamino acids can be employed to establish the optimum conformation and the binding site of a protein for high binding affinity and selectivity against a target protein.

Several methods for α,β-diaminobutanoic acid, the simplest α,β-diamino acid present as a key structural element of the known natural products, have been reported. These methods include Mitsunobu reaction of threonine for the introduction of second amino group,[3] and asymmetric Michael addition of chiral amine to unsaturated ester followed by trapping the resulting enolate with trisyl azide.[4] Also, stereoselective synthesis of four isomers of 2,3-diaminobutanoic acid from *t*-butyl crotonate utilizing the asymmetric aminohydroxylation has been reported.[5] Synthesis of more complex vicinal diamino acid derivatives requires the fuctionalization of γ-position of 2,3-diaminobutanoic acid. Many synthetic methods have been studied for the diamine derivatives,[2] but more efficient enantioselective method for unsymmetrical diamine with modifiable backbone and different amine protecting groups still needs to be developed.

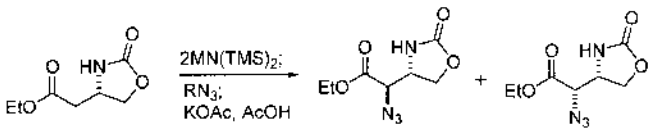
In our previous reports, we prepared (*S*)-4-carboethoxymethyloxazolidin-2-one (**1**) from L-aspartic acid in three steps. And the condition for highly diastereoselective alkylation of the enolate dianion of β-amidoester **1** and the application to the synthesis of indolizidine alkaloids has been reported.[6] In continuation of this study, we attempted the azidation of **1** to provide an ester with α,β-dinitrogenated and γ-oxygenated with different types of protections respectively in a stereoselective manner.

Thus, the enolate dianion of **1**, prepared by addition to two equivalents of metal hexamethyldisilazide in THF at -78 °C, was reacted with tosyl azide to give a chromatographically inseparable diastereomeric mixture of **2**. When the metal cation of the base is lithium or sodium in the azide transfer reaction, extensive decomposition of the triazene intermediate to diazo compound was observed.[7] This decomposition was easily avoided by addition of KOAc/AcOH to the reaction mixture before the aqueous workup. As summarized in Table 1, *anti*/*syn* diastereoselectivity was maximized with the use of sodium enolate as we observed in the case of the alkylation of **1**. In an attempt to improve the selectivity, bulky azide transfer reagent, trisyl azide, was used to give almost the identical result as in the case of tosyl azide.

For the direct amination of **1**, diisopropyl azodicarboxylate (DIAD) was reacted at -78 °C to give *anti*-hydrazinocarboxylate **3a** as a single isomer, but with a modest 52% yield (Scheme 1).[8] For the *syn*-selective α-azidation, enolate halogenation and azide displacement was studied. When the Li-enolate dianion of **1** was treated with 1,2-diiodoethane at -78 °C, a diastereomeric mixture of **3b** (*anti*:*syn* = 10:1) was obtained. Since the α-iodoimide is known to be configurationally unstable in the enolate iodination of *N*-acyl-2-oxazolidinones, partial epimerization of the iodinated product **3b** can not be excluded.[7] Thus, the Li-enolate was treated with bulky bromonium source, 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCD), at -45 °C to give exclusively *anti*-bromide **3c** which was easily displaced with azide ion to diastereomerically pure *syn*-azide **2b**.

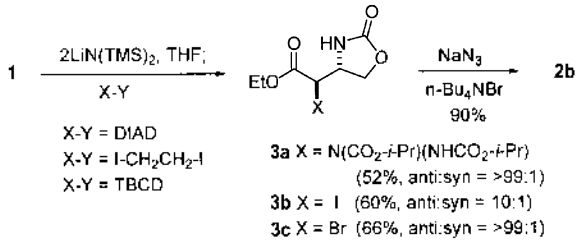
We next briefly examined the synthetic utility of azide **2a** for a potential intermediate of biotin synthesis.[9] The dia-

Table 1. Diastereoselective azidation of the enolate dianion of **1** with tosyl and trisyl azides

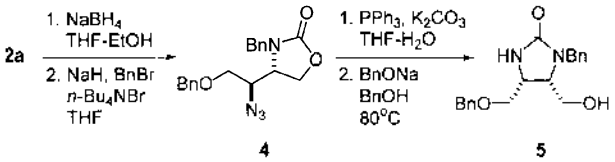


1 **2a** **2b**

	R = Tosyl		R = Trisyl	
M	yield (%)	anti:syn	yield (%)	anti:syn
Li	90	5:1	80	3:1
Na	86	7:1	89	7:1
K	84	5:1	84	4:1



Scheme 1



Scheme 2

stereomeric mixture of **2a** and **2b**, generated from Li-enolate of **1** and TsN_3, was reduced to alcohols with $NaBH_4$ followed by *N,O*-bisbenzylation to give a chromatographically separable mixture of azide **4** (58%) and its diastereomer (11%). Azide **4** was reduced under Staudinger condition,[10] and the resulting crude polar amino product was rearranged to cyclic urea **5** with NaOBn in BnOH under heating at 80 °C in 60% overall yield.

In summary, we studied diastereoselective α-azidation of a chiral β-amino ester, readily available from L-aspartic acid, to develop an easy access to 4-oxy-2,3-diaminobutanoic acid derivatives. This will provide an alternative approach to various vicinal diamines.

Acknowledgment. This work was financially supported by the Korea Research Foundation Grant (KRF-2000-015-DP0254).

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11. Selected spectral data. **2a**: R_f = 0.38 (2:1, EtOAc/hexanes); IR (neat, cm^{-1}) 3311, 2966, 2122, 1746; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.82 (s, 1H), 4.48 (t, J = 9 Hz, 1H), 4.31 (q, J = 7 Hz, 2H), 4.23 (t, J = 6 Hz, 2H), 4.18 (m, 1H), 1.36 (t, J = 7 Hz, 3H). **2b**: R_f = 0.38 (2:1, EtOAc/hexanes); $[\alpha]_D^{20}$ -143 (c 3.7, $CHCl_3$); IR (neat, cm^{-1}) 3270, 2984, 2120, 1754, 1742; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.80 (s, 1H), 4.54 (t, J = 9 Hz, 1H), 4.31 (q, J = 7 Hz, 2H), 4.23 (m, 2H), 4.09 (d, J 6 Hz, 1H), 1.35 (t, J 7 Hz, 3H). **3c**: R_f 0.42 (2:1, EtOAc/hexanes); $[\alpha]_D^{20}$ 9.2 (c 2.1, $CHCl_3$); IR (neat, cm^{-1}) 3263, 2981, 1764, 1730; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.93 (s, 1H), 4.56 (m, 1H), 4.37 (m, 3H), 4.27 (q, J = 7 Hz, 2H), 1.31 (t, J = 7 Hz, 3H).