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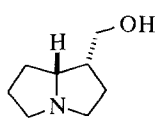
Studies on the Diastereoselective Alkylation of Enolate Dianion of (*S*)-4-Carboethoxymethyl-2-oxazolidinone

Deok-Chan Ha,* Kun-Eek Kil, Kwang-Sun Choi, and Hye-Sang Park

Department of Chemistry, Korea University, 5-1-2 Anam-Dong, Seoul, Korea 136-701

Abstract: Diastereoselective alkylation of enolate dianion of (*S*)-4-carboethoxymethyl-2-oxazolidinone has been studied. The increased *anti*-selectivity in the presence of HMPA was explained by stereoelectronic effect of the electron-rich nitrogen atom of the oxazolidinone amidate.

Chirality transfer in the α-alkylation of ester having heteroatom substituted at the β-position has found an extensive use in the synthesis of optically active natural products.[1] The stereochemical outcome in the alkylation process was appropriately rationalized with stereoelectronic or chelation effects of the heteroatom substituted at the β-position of the ester.[2,3] Lindelofidine (**1**), tashiromine (**2**), and lupinine (**3**) are typical examples of pyrrolizidine, indolizidine, and quinolizidine alkaloids, respectively, possessing hydroxymethyl group and their diastereomers were also naturally isolated.[4] For synthesis of these nitrogen-fused bicyclic alkaloids, cyclic carbamate **4** can be a common synthetic intermediate and might be prepared through diastereoselective alkylation of chiral ester **5**. Intramolecular chelation between enolate oxygen and oxazolidinone nitrogen of **5** would direct the alkylation process at the sterically less demanding enolate π-face. In this letter, we report our initial findings on the stereochemical behavior in the α-alkylation of a new chiral ester **5**.



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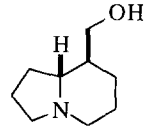

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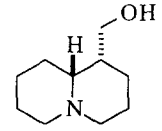

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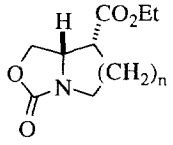

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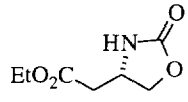

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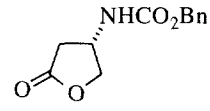


6

Lactone **6**, prepared conveniently from L-aspartic acid using a known procedure, was treated with NaOEt in ethanol at rt to give oxazolidinone **5** in 70% yield.[5-7] Enolate dianion of the ester **5**, generated by using two equivalents of lithium or sodium hexamethyldisilazide in THF at -78°C, was reacted with alkyl halides to

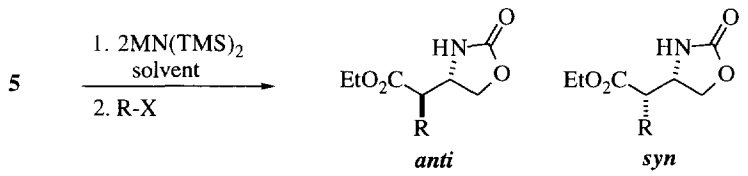
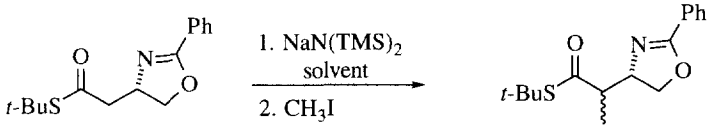


Table 1. Yields and Diastereoselectivities in Alkylations of Enolate Dianion generated from **5**

entry	R-X[a]	solvent[b]	M	condition (°C, h)[c]	yield (%)[d]	*anti* : *syn*[e]
1	CH_3I	THF	Li	-43, 2	85	51 : 49
2	CH_3I	THF-HMPA	Li	-43, 2	78	66 : 34
3	CH_3I	THF	Na	-43, 2	85	95 : 5
4	CH_3I	THF-HMPA	Na	-43, 2	70	95 : 5
5	CH_3CH_2I	THF	Li	-23, 10	64	84 : 16
6	CH_3CH_2I	THF-HMPA	Li	-23, 10	82	92 : 8
7	CH_3CH_2I	THF	Na	-23, 10	70	96 : 4
8	$PhCH_2Br$	THF	Li	-43, 3	79	90 : 10
9	$PhCH_2Br$	THF-HMPA	Li	-43, 2	84	92 : 8
10	$PhCH_2Br$	THF	Na	-43, 3	98	96 : 4
11	CH_2=$CHCH_2Br$	THF	Li	-43, 3	84	85 : 15
12	CH_2=$CHCH_2Br$	THF-HMPA	Li	-43, 2	91	91 : 9
13	CH_2=$CHCH_2Br$	THF	Na	-43, 4	84	95 : 5
14	$(CH_3)_2C$=$CHCH_2Br$	THF	Li	-43, 3	77	89 : 11
15	$(CH_3)_2C$=$CHCH_2Br$	THF-HMPA	Li	-43, 3	96	93 : 7
16	$(CH_3)_2C$=$CHCH_2Br$	THF	Na	-43, 4	91	98 : 2
17	$ClCH_2CH_2CH_2I$	THF	Li	-23, 3	68	84 : 16
18	$ClCH_2CH_2CH_2I$	THF-HMPA	Li	-23, 3	73	95 : 5
19	$ClCH_2CH_2CH_2I$	THF	Na	0, 3	80	97 : 3
20	$ClCH_2CH_2CH_2I$	THF-HMPA	Na	-23, 3	32	95 : 5

[a] Two equivalents of alkyl halide were used. [b] Two equivalents of HMPA were added after generation of the enolate. [c] After alkyl halide was added, the reaction mixture was stirred for 1h at -78°C and ran at the indicated condition [d] Isolated yields after silica gel chromatography and all products were characterized by their ^{1}H-NMR, IR, and mass spectra. [e] The ratio was determined by integration of ^{1}H-NMR spectra.

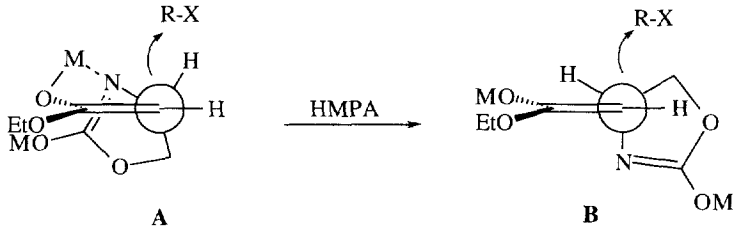


(eq.1)

7 **8**

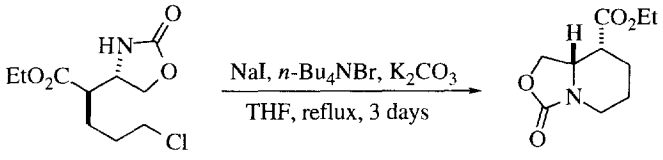
solvent	*anti* : *syn*
THF	95 : 5
THF-HMPA	10 : 90

observe the effects of the counter cation of base and HMPA (Table 1).[8,9] The use of sodium enolate showed better diastereoselectivity than lithium enolate in these chelate-controlled alkylations. Interestingly, *anti*-selectivity of lithium enolate has been improved in the presence of HMPA. This behavior is quite different from McGarvey's results where enolate of oxazoline thioester **7** displayed *anti*-selectivity in THF but *syn*-selectivity when HMPA was added to the enolate (eq.1).[5b] The change in selectivity between these oxazolidinone and oxazoline enolates may be resulted from different stereoelectronic effects exerted by the β-substituents of the esters. In THF, the intramolecularly chelated *Z*-enolate, like conformer **A**, is alkylated at the sterically less demanding face to give *anti* products. In the presence of HMPA, where intramolecular chelation is improbable, most electron-rich β-substituent is aligned perpendicular to the plane of the enolate. In the case of the enolate dianion from **5**, amidate nitrogen disposes perpendicularly as in conformer **B** to give *anti* product while homoallylic participation of oxygen lone pair of the oxazoline ring is important in **7** to give *syn* product.[2b] As expected, sodium enolates in the presence of HMPA produced the same stereochemical results as in the cases of lithium enolate-HMPA with the decreased yields (entries 4 and 20, Table 1).



A **B**

The diasteromeric mixture **9** (entry 19, Table 1) was cyclized with the usual procedure and diastereomerically pure bicyclic oxazolidinone **10** was obtained in 73% yield. The stereochemistry of chiral centers in **10** was clearly established by NOE enhancement experiments between C(8)-H and C(8a)-H.



9 **10**

In summary, the highly diastereoselective α-alkylation of a new chiral ester readily available from L-aspartic acid was studied and the effect of HMPA on the improved *anti*-selectivity in the alkylation process was described. This method can provide an easy access to nitrogen-containing heterocycles in a stereoselective manner. Further synthetic applications to alkaloid natural products will be reported in due course.

Acknowledgment. Financial support from Korea Science and Engineering Foundation, and Ministry of Education through Basic Research Institute Program is gratefully acknowledged.

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6. Carboxylic acid of **5** has very recently been reported utilizing similar synthetic method, see Murray, P. J.; Starkey, I. D. *Tetrahedron Lett.* **1996**, *37*, 1875-1878.
7. **5**: colorless oil; R_f = 0.35 (EtOAc/Hexane = 2:1); $[\alpha]^{20}_D$ = -45.3 (c 0.8, $CHCl_3$); IR (CH_2Cl_2, cm^{-1}) 3340, 1742, 1245; ^{1}H-NMR (300MHz, $CDCl_3$) δ 6.24 (br s, 1H), 4.57 (t, *J* = 7 Hz, 1H) 4.03-4.30 (m, 4H), 2.58 (dd, *J* = 17, 7 Hz, 1H), 2.50 (dd, *J* = 17, 7 Hz, 1H), 1.27 (t, *J* = 7 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 13.7, 39.4, 48.8, 60.9, 69.5, 159.7, 170.6; HRMS *m/z* calcd for $C_7H_{11}NO_4$ *m/e* 173.0688, found 173.0674
8. For diastereoselective hydroxylation of enolates generated from N-protected aspartate diesters, see (a) Sardina, F. J.; Paz, M. M.; Fernandez-Megia, E.; de Boer, R. F.; Alvarez, M. P. *Tetrahedron Lett.* **1992**, *32*, 4637-4640. (b) Hanessian, S.; Vanasse, B. *Can. J. Chem.* **1993**, *71*, 1401-1406.
9. Experimental procedure for **9**: To a solution of $NaN(TMS)_2$ (3.2 mmol) in 7 mL of THF cooled at -78°C under argon atmosphere was added 0.28g (1.6 mmol) of **5** in 4 mL of THF over a 5-min period followed by stirring for 1h at -78°C. A solution of 1-chloro-3-iodopropane (0.35 mL, 3.2 mmol) in 4 mL of THF was added over a 5-min period followed by stirring for 1h at -78°C and 3h at 0°C. The mixture was quenched with 50 mL of sat. NH_4Cl solution and extracted three times with 50-mL portions of CH_2Cl_2. After drying ($MgSO_4$), the solvents were evaporated and the residue was chromatographed (SiO_2, EtOAc/hexane = 1:1) to give 0.32g (80%) of **9** as a colorless oil. R_f = 0.41 (EtOAc/Hexane = 2:1); $[\alpha]^{20}_D$ = 8.5 (c 2.4, $CHCl_3$); IR (CH_2Cl_2, cm^{-1}) 3290, 1746, 1637; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7 Hz, 3H), 1.73 (m, 2H), 1.84 (m, 2H), 2.60 (m, 1H), 3.56 (t, *J* = 6 Hz, 1H), 4.09 (m, 1H), 4.27-4.15 (m, 3H), 4.52 (t, *J* = 7 Hz, 2H), 5.54 (br s, 1H); HRMS *m/z* calcd. for $C_{10}H_{17}NO_4Cl$+H 250.0847, found 250.0829.

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