Diastereoselectivity in the Reaction of 2-Piperidineacetates

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In the reactions of the enolates of various 2-piperidineacetates with iodomethane or trisyl azide, the *anti* isomer was always predominant over the *syn* one, independent of the stereochemistry of the piperidineacetates. The piperidineacetates having OTBDMS moiety at C_5 proceeded more diastereoselectively than the compounds without the substituent. The diastereoselectivity could be explained by perpendicular model for the electrophilic substitution reaction.

Introduction

Reactions of enolates with electrophiles have been well established as important synthetic methods for C-C, C-O and C-N bond forming reactions. The control of diastereoselectivity in alkylation, azidation and oxidation reactions remains one of the most challenging problems in this field.[1,2,3]

Dealing with stereochemical issues in the synthesis of antitumor agent DKP 593A, isolated from the soil microorganism *Streptomyces griseoluteus*,[4] we have been interested in the control of diastereoselectivity in the reaction of the enolate of 2-piperidineacetates with some electrophiles.

A piperidineacetate was used as a starting material in the preparation of many biologically active compounds such as streptolutin, lupinine and sedamine.[5] However, relatively few examples have previously been reported for the diastereoselective reactions at the α-position of piperidineacetates.[5,6,7]

Allylation of the lithium enolate derived from methyl 2-(*N*-*t*-butyloxycarbonyl)piperidineacetate with allyl bromide gave the mixture of *anti* and *syn* isomer in a ratio of 86 : 14.[5c] In the reaction of methyl 2-(*N*-benzyloxycarbonyl)piperidineacetate with KHMDS and 2,4,6-triisopropylbenzenesulfonyl azide (trisyl azide), the corresponding *anti* azide was predominant over the *syn* isomer in a ratio of 78 : 22.[6] The *anti* preference was also shown in the azidation of 2-[*N*-methoxycarbonyl-5-(*t*-butyldimethylsilyloxy)piperidin-2-yl]-acetate.[7]

The high diastereoselective reaction of piperidineacetates has been explained by favorable association between the anionic center and the carbamate group,[5,6] while some reactions follows Cram's model. In this paper, we have examined whether the reactions follow the chelation control or not, and have attempted to control the ratio of *syn* and *anti* stereochemistry at the α-position of various 2-piperidineacetates.

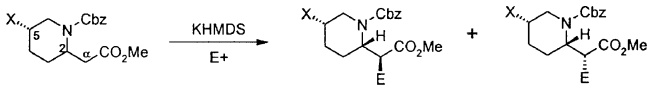
Results and Discussion

An ester enolate of a piperidineacetate was generated by the treatment with KHMDS in THF at -78 °C, and the enolate was then reacted with some electrophiles, such as methyl iodide and trisyl azide to give an α-methylpiperidineacetate and an α-azidopiperidineacetate. The diastereomeric ratio was determined by ^{1}H NMR spectrum of the ester methyl proton as in methyl 2-(*N*-benzyloxycarbonyl)piperidineacetate and methyl *trans*-2-[*N*-benzyloxycarbonyl-5-(*t*-butyldimethylsilyloxy)piperidin-2-yl]acetate, but by HPLC for methyl *cis*-2-[*N*-benzyloxycarbonyl-5-(*t*-butyldimethylsilyloxy)piperidin-2-yl]acetate.

As shown in Table 1, the *anti* isomer was preferred to the *syn* isomer, irrelevant to the stereochemistry of the piperidine ring. From the entries 2 and 3, the optically active compound showed almost the same diastereoselectivity as the racemate. The *trans* isomer showed slightly lower diastereoselectivity than the corresponding *cis* isomer. The piperidineacetates having OTBDMS moiety at C_5 showed higher diastereoselectivity than the compounds without the substituent (entries 4, 5, 6, 7 and 8).

This result was very disappointing in the preparation of streptolutin and antitumor agent DKP 593A, which require *syn*(*threo)* relationship between C_2 and C_α.[4,7] The *syn* isomer may be obtained by employing a chiral auxiliary.[1m] Since the disubstituted compound gave almost one isomer, lupine or 2-piperdylglycine may be synthesized as an optically pure form by removal of the hydroxy moiety at C_5.[5c,9]

Table 1. Diastereoselectivity of 2-Piperidineacetates

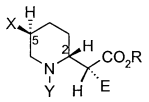


anti(C_2C_α=*SS*) *syn*(C_2C_α=*SR*)

Entry[a]	X	E	C_2	C_2/C_5	Product (C_2C_α) *anti*	*syn*
1	H	Me	-	-	78	22
2[b]	H	N_3	-	-	78	22
3	H	N_3	*S*	-	80	20
4	OTBDMS	Me	*S*	*cis*	95	5
5	OTBDMS	N_3	*S*	*cis*	95	5
6	OTBDMS	Me	*R*	*trans*	90	10
7	OTBDMS	N_3	*R*	*trans*	90	10
8[c]	OTBDMS	N_3	*R*	*trans*	95	5
9[d]	H	Me	-	-	78	22
10[d]	H	N_3	-	-	78	22

[a]The solvent was THF, and the yields of the reactions were over 80%. [b]Data from ref. 6. [c]Data from ref. 7. The *N*-protecting group was CO_2Me instead of Cbz. [d]The solvent was THF-HMPA.

Table 2. Comparison of Conformations in Chiral *trans*-2-Piperidineacetates



X	Y	E	R	C_5-C_2	ΔH_f^o (Kcal/mol)[c]
OH[a]	-H·HCl	H	H	eq-eq	-
OTBDMS[b]	H	H	Me	eq-eq	-
OTBDMS	Cbz	H	Me	eq-eq	-245.72
				ax-ax	-249.06
OTBDMS	Cbz	Me	Me	eq-eq	-240.92
				ax-ax	-247.64
OTBDMS	Cbz	N_3	Me	eq-eq	-161.46
				ax-ax	-164.89
OH[a]	CO_2Me	$NH_3^+Cl^-$	Me	ax-ax	-

[a]X-ray analysis.[7] [b]^{1}H NMR. [c]MNDO calculation.

The high diastereoselectivity has been explained based on perpendicular (Cram's) model or eclipsed (chelation) model with the consideration of the chirality of neighboring center, although the stereochemical relationship such as *cis* or *trans* and equatorial or axial was involved. Due to $A^{1,3}$-allylic strain in carbamates of 2-substituted piperidine, the methoxycarbonylmethyl group in the *cis* disubstituted piperidineacetate occupies axial position.[5c,9] Based on the X-ray crystallographic analysis,[7] both substituents in the *trans* isomer occupied axial position although the substituents were rather bulky. As shown in Table 2, ^{1}H NMR analysis or MNDO calculation suggested that the diaxial occupation was preferred in the conformation of several *trans* disubstituted piperidineacetates.

Based on the study of the methylation of enolates derived from β-substituted ester (Figure 1), eclipsed model (A) was favored for a chelated enolate, and perpendicular model (B) for a non chelated enolate.[2,3a] The *anti* preference could be explained by either model in the electrophlic substitution reaction of 2-piperidineacetates.

However, the chelation is not quite stable because the chelation of the metal between the enolate and the oxygen of carbamate forms a 8-membered ring. On the other hand, the perpendicular model causes a 1,3-diaxal repulsion between two axial hydrogens in the ring and the vinyl hydrogen of the enolate, judging from a molecular model.

When the reaction was carried out in HMPA-THF to exclude a chelation, the *anti* preference was also observed

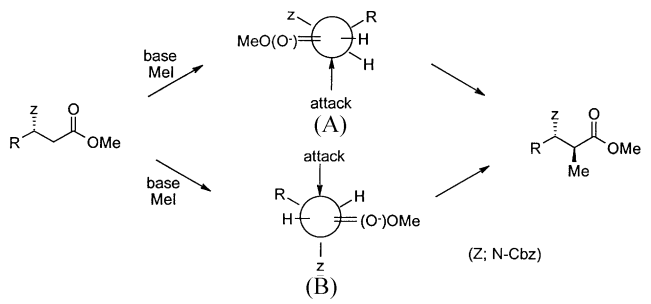


Figure 1. Eclipsed model for chelation (A), and perpendicular model (B) for non-chelation in the electrophilic reaction.

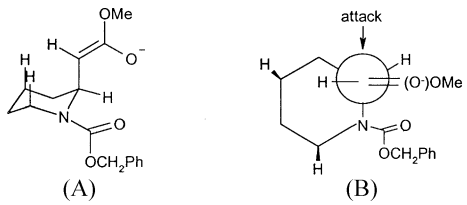


Figure 2. Enolate at axial position (A), and perpendicular model (B) in the electrophilic reaction of 2-piperidineacetate.

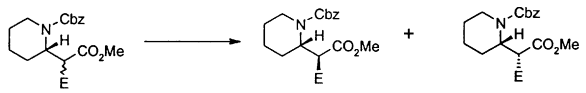
(entries 9 and 10 in Table 1). Thus the high diastereoselective reaction can be rationalized by perpendicular model. Since one side of the enolate is shielded by the *N*-Cbz group, approach by the incoming electrophile would occur from the opposite side of the *N*-Cbz group (Figure 2).[5c,6,7]

In the electrophilic substitution reaction, protonation of the enolate takes place in the same stereochemical feature as alkylation of the enolate does.[2a] As shown in Table 3, the ratio of *anti* to *syn* isomer may not be changed in the deprotonation of α-methylpiperdineacetates with KHMDS or LiOMe followed by protonation with acetic acid (entry 1), while the ratio was changed to 1 : 1 in equilibration of α-azidopiperidineacetates with DBU or KOH at room temperature (entries 5 and 6).

When the α-azidopiperidineacetate was treated with a strong base(KHMDS), unknown compounds were produced (entry 4). Highly bulky substituents at the axial position prevent deprotonation and protonation with the α-methylpiperdineacetate. For the azido compound, azido and methoxycarbonyl groups may show almost the same stereoelectronic effect (entries 5 and 6).

In conclusion, the *anti* isomer was always predominant over the *syn* isomer in the reaction of 2-piperidineaceates, regardless of the presence or the stereochemistry of the substituent at the C_5 position. The diastereoselectivity slightly depends on electrophiles, whereas structural changes have a considerable amount of influence. The eletrophilic substitution reaction presumably followed perpendicular model; the

Table 3. Equilibration at the α-position[a]



anti *syn*

Entry	E	Equilibration condition[c]	product *anti*	product *syn*
1	CH_3	A	74	26
2	CH_3	B	76	24
3	CH_3	C	71	29
4[b]	N_3	A	-	-
5	N_3	B	58	42
6	N_3	C	43	57

[a]The substrate was the mixture of *anti* and *syn* isomer in a ratio of 78 : 22 in all cases. [b]The major product was an unknown compound. [c]Epimerization condition A; deprotonation with KHMDS and protonation with AcOH. B; reflux with DBU. C; saponification with KOH followed by methylation with CH_2N_2.

high diastereoselectivity was governed by steric bulkiness of the *N*-Cbz group.

Experimental Section

All chemicals were reagent grade (Aldrich Chemical Co.) and were used as purchased without further purification. The syntheses of chiral and achiral methyl 2-(*N*-benz-yloxycarbonyl)piperidineacetates have been reported previously.[6~9]

NMR spectra were recorded on a Varian Gemini 2000 (200 MHz) spectrometer. Chemical shifts for ^{1}H NMR spectra were reference to TMS and measured with respect to the residual protons in $CDCl_3$, and ^{13}C chemical shifts were also reported relative to $CDCl_3$. Analytical HPLC was performed on a 4.6 mm×250 mm silica gel column using UV detection.

General Procedure for Methylation and Azidation of 2-Piperidineacetates

Methylation. To a solution of a piperidineacetate (0.300 mmol) in dry THF (2 mL) stirred at -78 °C under N_2 was added 0.5 M KHMDS in toluene (0.545 mL, 0.300 mmol) by syringe and stirring was continued for 30 min at -78 °C. To the resulting enolate was added a solution of methyl iodide (0.142 g, 1.00 mmol) in THF (1 mL), and the reaction temperature was allowed to rise to 0 °C. After stirring for 2 h at 0 °C, aqueous ammonium chloride was added. The mixture was extracted with CH_2Cl_2 and the combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The crude product (85%) was purified by column chromatography and the diastereoselectivity was determined by HPLC and/or ^{1}H NMR.

Methyl 2-(*N*-benzyloxycarbonylpiperidin-2-yl)propanoate (Entry 1 in Table 1). ^{1}H NMR δ 1.14 (d, *J*=6.8 Hz, 3H, CH_3), 1.35-1.85 (m, 6H, H_3, H_4, H_5), 2.93-3.11 (m, 2H, H_α, H_{6a}), 3.50 (*anti*), 3.70 (*syn*) (s, 3H, OCH_3), 4.01-4.18 (m, 1H, H_{6e}), 4.32-4.47 (m, 1H, H_{2e}), 5.01-5.19 (m, 2H, benzyl), 7.36 (bs, 5H, phenyl).

Methyl 2-[(2*S*,5*S*)-*N*-benzyloxycarbonyl-5-(*t*-buthyldimethylsilyloxy)piperidin-2-yl]propanoate (Entry 4 in Table 1). ^{1}H NMR δ 0.02 (s, 6H, Si-CH_3), 0.88 (s, 9H, *t*Bu), 1.14 (d, *J*=7.0 Hz, 3H, CH_3), 1.40-1.90 (m, 4H, H_3, H_4), 2.68-3.12 (m, 2H, H_{6a}, H_α), 3.40-3.65 (m, 4H, H_{5a}, OCH_3), 4.00-4.20 (m, 1H, H_{6e}), 4.20-4.40 (m, 1H, H_{2e}), 5.02-5.20 (m, 2H, OCH_2), 7.34 (bs, 5H, phenyl). ^{13}C NMR δ -6.5, 12.9, 16.3, 24.0, 27.4, 36.2, 44.2, 46.2, 49.8, 51.2, 65.6, 66.0, 126.1, 126.3, 126.8, 135.2, 153.7, 173.1. t_r values for the *cis* isomer on HPLC eluting with 20% EtOAc/*n*-Hex.; 3.48 (*syn*), 4.09 (*anti*), 5.06 (starting material).

Methyl 2-[(2*R*,5*S*)-*N*-benzyloxycarbonyl-5-(*t*-buthyldimethylsilyloxy)-piperidin-2-yl]propanoate (Entry 6 in Table 1). ^{1}H NMR δ 0.03 (s, 6H, Si-CH_3), 0.86 (s, 9H, *t*Bu), 1.17 (d, *J*=7.0 Hz, 3H, CH_3), 1.42-1.69 (m, 3H, H_3, H_{4a}), 2.02-2.22 (m, 1H, H_{4e}), 2.87-3.8 (m, 2H, H_{6a}, H_α), 3.50 (*anti*), 3.70 (*syn*) (s, 3H, OCH_3), 3.81-3.93 (m, 1H, H_{5e}), 3.94-4.13 (m, 1H, H_{6e}), 5.00-5.21 (m, 2H, OCH_2), 7.34 (bs, 5H, phenyl).

Azidation.[6~8] To a stirred solution of a piperidineacetate (0.300 mmol) in THF (2 mL) at -78 °C was added 0.5 M KHMDS in toluene (0.545 mL, 0.300 mmol). The solution was stirred for 30 min at -78 °C followed by treatment, via teflon cannula, with precooled solution of trisyl azide (0.102 g, 0.330 mmol) in toluene (1 mL). The reaction was quenched after 3 min by addition of glacial acetic acid (0.075 mL, 0.330 mmol). The mixture was allowed to reach room temperature and stirring was continued at ambient temperature for an additional hour. The crude product (85%) was purified by column chromatography, and the diastereoselectivity was determined as mentioned above.

Methyl 2-azido-2-[(2*S*,5*S*)-*N*-benzyloxycarbonyl-5-(*t*-buthyldimethylsilyloxy)piperidin-2-yl]ethanoate (Entry 5 in Table 1). ^{1}H NMR δ 0.06, 0.08 (s, 6H, Si-CH_3), 0.90 (s, 9H *t*-Bu), 1.48-2.14 (m, 4H, H_3, H_4), 2.62-2.87 (m, 1H, H_{6a}), 3.50-3.73 (*anti*), 3.75-3.85 (*syn*) (m, 4H, OCH_3, H_{5a}), 4.07-4.30 (m, 2H, H_{6e}, H_α), 5.05-5.20 (m, 2H, benzyl), 7.30 (bs, 5H, phenyl). t_r values for the *cis* isomer on HPLC eluting with 20% EtOAc/*n*-Hex.; 3.65 (*anti*), 4.23 (*syn*), 5.06 (starting material).

Methyl 2-azido-2-[(2*R*,5*S*)-*N*-benzyloxycarbonyl-5-(*t*-buthyldimethylsilyloxy)piperidin-2-yl]ethanoate (Entry 7 in Table 1). ^{1}H NMR δ 0.02, 0.03 (s, 6H, Si-CH_3), 0.88 (s, 9H, *t*-Bu), 1.18-1.40 (m, 1H, H_{3a}), 1.52-1.83 (m, 2H, H_{3e}, H_{4a}), 2.02-2.25 (m, 1H, H_{4e}), 3.02-3.16 (m, 1H, H_{6a}), 3.63 (*anti*), 3.78 (*syn*) (s, 3H, OCH_3), 3.91(bs, 1H, H_{5e}), 3.96-4.17(m, 2H, H_{6e}, H_α), 5.02-5.36 (m, 2H, benzyl), 7.34 (bs, 5H, phenyl).

Epimerization of 2-Piperidineacetates

Method A (deprotonation and protonation with KHMDS or LiOMe). To a solution of a mixture of *anti* and *syn* piperidineacetate (0.300 mmol) in dry THF (2 mL) was added a base (0.300 mmol) at -78 °C under N_2. The reaction was allowed to rise to room temperature and stirring was continued for 2 h. The reaction was quenched by addition of glacial acetic acid (0.075 mL, 0.330mmol) at -78 °C. The mixture was allowed to reach room temperature and sttiring was continued for an additional hour. The diastereoselectivity was determined as mentioned above.

Method B (equilibration with DBU). A mixture of *anti* and *syn* piperidineacetate (0.300 mmol) was dissolved into DBU (5 mL). After strirring for 2 h at room temperature, the diastereoselectivity was determined as mentioned above.

Method C (saponification and esterification). A mixture of *anti* and *syn* piperidineacetate (0.300 mmol) was dissolved into the solution of KOH (0.034 g, 0.606 mmol) in 4 : 1 of MeOH/H_2O (5 mL). After stirring for 3 h at room temperature, the MeOH was removed and the mixture was acidified to pH = 3 with 2N HCl. The crude product was isolated as usual and reacted with CH_2N_2 in ether. The resulting ester was isolated and diastereoselectivity was determined as mentioned above.

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