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Asymmetric Aza-Claisen Rearrangement of Glycolamide and Glycinamide Enolates. Synthesis of Optically Active α-Hydroxy and α-Amino Acids

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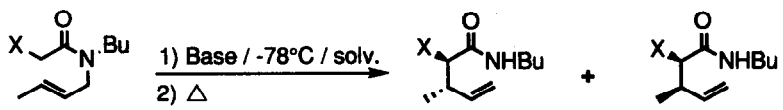
Abstract: *The aza-Claisen rearrangement of the enolates of* N-*crotyl glycolamide and glycinamide proceeded with excellent* syn : anti *(98:2) and facial selectivities (89:11). Optically pure (-)-verrucarinolactone and* D-allo-*isoleucine were derived from the rearrangement products.*

In a previous paper, we described excellent internal asymmetric induction (*syn* : *anti* = up to 99.4 : 0.6)[1,2] and very high substrate-controlled relative asymmetric induction (*RS* : *SR* = 95 : 5)[2,3,4] resulting from the aza-Claisen rearrangement of the enolates of *N*-substituted *N*-(*E*)-2-butenylpropanamides. In order to further test the applicability of this rearrangement, we have extended the reaction to acetamides substituted with a heteroatom at the α-position. This type of the reaction may be useful as the selectivities of the Ireland-Claisen rearrangement of crotyl esters of α-hydroxy or α-amino acids are relatively low.[5,6] The results of our investigation are described herein together with their application to the synthesis of two optically active α-hydroxy and α-amino acids.



1 **2** (*syn*) **2** (*anti*) Scheme 1.

A: X = CH_3 **C**: X = OTBDMS **E**: X = NHBoc
B: X = OH **D**: X = NH_2

General procedure. The starting carboxamides were treated at -78°C with lithium diisopropylamide (LDA) or lithium hexamethyldisilazide (LHMDS) in THF or toluene under Ar atmosphere. After 30 min, the reaction mixture was left at room temperature or heated in a sealed tube. While the diastereomeric ratio in the products was determined by GLC or LC either directly on the reaction mixture or after desilylation, the isolated yield was determined after column chromatography.[2] The structures of the products were confirmed by direct comparison with authentic samples.[7]

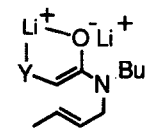
N-(*E*)-2-Butenyl-*N*-butylcarboxamides **1**[a] were subjected to the reaction conditions in order to determine the *syn* : *anti* selectivity of the reaction (Scheme 1). The results are listed in Table 1 together with that of *N*-(*E*)-2-butenyl-*N*-butylpropanamide (**1A**) reported earlier.[1]

Table 1. Aza-Claisen Rearrangement of Enolates of α-Hetero-substituted *N*-(*E*)-2-Butenyl-*N*-butylcarboxamides (**1**).

Entry	Amide	Solvent	Base (eq)	Temp. (°C)	Period (h)	Yield (%)	Product	Ratio *syn* : *anti*
1	**1A** (X=CH_3)	THF→ xylene[a]	LDA (1.5)	135	4	92	**2A**	99.5 : 0.5[b]
2	**1B** (X=OH)	toluene	LHMDS (2.2)	80	15	74	**2B**	98 : 2
3	**1B**	THF	LDA (3.0)[c]	160-180	2	65	**2B**	90 : 10
4	**1C** (OTBDMS)	toluene	LHMDS (1.5)	100	15	59	**2C**	98 : 2
5	**1D** (X=NH_2)	〃	〃 (1.2)	r.t.	15	81	**2D**	98 : 2
6	**1D**	〃	〃 (2.2)	〃	4	74	**2D**	96 : 4
7	**1E** (X=NHBoc)	〃	〃 (2.2)	〃	20	no reaction	—	—
8	**1E**	〃	〃 (2.2)	140	2	0[d]	—	—

a. Enolate was prepared in THF and heated in xylene after solvent exchange. b. Ref. 1.
c. Enolate was trapped as TMS ether before heating. d. no recovery of **1E**.

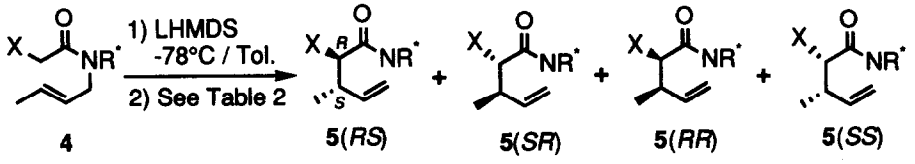
The experimental results shown in Table 1 can be summarized as follows. i) Excellent *syn* selectivity (98 : 2) was observed for nearly all cases. ii) The presence of an OH or particularly a NH_2 group at the α-position of acyl group facilitates the rearrangement (entries 2 and 5 vs. entry1), possibly due to the intermediacy of a dianionic species, such as **3**. In fact, **1D** rearranges much faster with 2 equivalents of LHMDS than with 1 equivalent (entry 6 vs. entry 5). iii) The protection of the free OH or NH_2 group decelerates the reaction (entries 4, 7 and 8), contrary to the rearrangement of ester enolates.[5,6] This is especially dramatic for amino protection **1E** (entries 7 and 8). iv) Trapping of enolate as TMS ether and subsequent thermal rearrangement (entry 3) also decelerates the reaction and lowers the yield and selectivity as in α-alkyl derivatives.[1,2] This is again contrary to the reaction of ester enolates: their trapping as silyl ethers is usually necessary for satisfactory results.[5,6] Thus, the best method is simply to prepare amide enolates without any protection of the OH or NH_2 group present, and, if necessary, heat them under basic conditions (entries 2 and 5).



Y= O^- or N^-H

3

The facial selectivity of the reaction, which is also moderate in the Ireland-Claisen rearrangement,[9] was investigated using an (*R*)- or (*S*)-1-phenethyl group as a chiral auxiliary on the amide nitrogen (Scheme 2). Thus, **4B-D** were subjected to the reaction under similar conditions to those used previously to afford diastereomeric mixtures of the rearranged products **5** (Table 2).



Scheme 2.

A~D See Scheme 1.

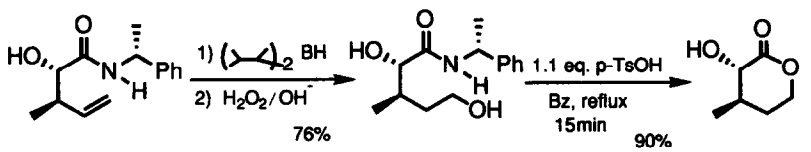
Table 2. Asymmetric Aza-Claisen Rearrangement of *N*-2-Butenyl-*N*-1'-phenethylcarboxamides **4**.

Entry	Substrate	Temp. (°C)	Period (h)	Yield (%)	product	Ratio *RS SR RR SS*
1	**4A**: X=CH_3, R*=(*S*)-1'-phenethyl	120	6	85	**5A**	89 : 11 : 0 : 0 [a]
2	**4B**: X=OH, R*=(*R*)-1'-phenethyl	80	15	95	**5B**	13 : 86 : 0 : 0.8
3	**4C**: X=OTBDMS, R*=(*R*)-1'-phenethyl	120	6	62	**5C**	33 : 67 : 0 : 0
4	**4D**: X=NH_2, R*=(*S*)-1'-phenethyl	r.t.	15	89	**5D**	89 : 11 : 0 : 0

a) Ref. 2 and 3.

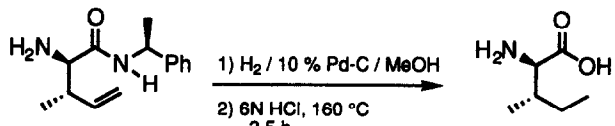
The reactions with the unprotected OH or NH_2 compound (**4B** and **4D**) went smoothly and diastereomeric mixtures were obtained in excellent yields. *Anti* products (*RR* and *SS*) were either not detected (entries 1, 3, 4) or obtained in < 1% yield (entry 2), showing higher internal asymmetric induction than *N*-butyl amides. The facical selectivity was 6.6~8.1, a value similar to that for alkyl derivative **4A**. The protection of hydroxyl group (**4C**) lowered both the facial selectivity and the chemical yield (entry 2 vs. entry 3).

To establish the absolute stereochemistry[7] and demonstrate the usefulness of the reaction, the major products **5B**(*SR*) and **5D**(*RS*) were converted to the compounds of known absolute configuration. Thus, the major product **5B**(*SR*) purified easily by silica-gel column chromatography was converted to the dihydroxy amide **6** which on subsequent acid hydrolysis yielded (-)-verrucarinolactone (**7**) [$[\alpha]_D^{23}$ -9.8 (c 0.73, $CHCl_3$), lit $[\alpha]_D^{23}$ -9±1 (c 1.0, $CHCl_3$)[10]](Scheme 3).



Scheme 3.

The major product **5D**(*RS*) purified similarly was converted to *D-allo*-isoleucine (**8**) [$[\alpha]_D^{23}$ -37.7 (c 2.0, 6N HCl), lit $[\alpha]_D^{23}$ -38.4 (c 4.0, 6N HCl)[11]] in two steps (catalytic hydrogenation and acid hydrolysis)(Scheme 4).



5D(*RS*) **8** Scheme 4.

Thus, the relative asymmetric induction (the facial selectivity) in the present reactions was demonstrated to follow the general trend of the aza-Claisen rearrangement and the reactions are shown to be useful enough for the stereoselective synthesis of natural products.

REFERENCES AND NOTES

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3. Tsunoda, T.; Sakai, M.; Sasaki, O.; Sako, Y.; Hondo, Y.; Itô, S. *Tetrahedron Lett.* **1992**, *33*, 1651-1654.
4. The relative asymmetric induction was improved from the reported ratio (~90 : 10) by utilizing 2,2-dimethyl-1-phenylpropanamine (Tsunoda, T.; Hishiki, T.; Itô, S. to be published).
5. Although the Ireland-Claisen rearrangement of some allylic glycolates, especially TMS ethers, were reported to proceed with very high yields and excellent stereoselectivity (Gould, T. J.; Balestra, M.; Wittman, M. D.; Gary, J. A.; Rossano, L. T.; Kallmerten, J. *J. Org. Chem.* **1987**, *52*, 3889-3901. Also ref 7.), they are rather unsatisfactory in many cases. For example, (*E*)-2-butenyl glycolate was rearranged to 2-hydroxy-3-methyl-4-pentenoic acid in 38% yield with a low (2.4 : 1) diastereoselectivity (Bartlett, P. A.; Tanzella, D. J.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3941-3945).
6. The Ireland-Claisen rearrangement of allylic esters of *N*-protected α-amino acids proceeded in moderate to good yields and diastereoselectivity. For example, (*E*)-2-butenyl *N*-(*t*-butoxycarbonyl)glycinate yielded 2-*t*-butoxycarbonylamino-3-methyl-4-pentenoic acid in 60-65% yield and *syn* : *anti* ratio of 9 : 1(Bartlett, P. A.; Barstow, F. *J. Org. Chem.* **1982**, *47*, 3933-3941).
7. Relative configuration of the products was established as follows. The authentic sample of **2B** and **5B** was prepared by standard procedure from the 2-hydroxy-3-methyl-4-pentenoic acid (*syn* : *anti* = 9 : 1) obtained by the Fujisawa version of the Ireland-Claisen rearrangement of crotyl glycolate (Sato, T.; Tajima, K.; Fujisawa, T. *Tetrahedron Lett.* **1983**, *24*, 729-730), while **2C** and **5C** were converted to **2B** and **5B**, respectively, by desilylation. The authentic sample of **2D** and **5D** was prepared from 2-*t*-butoxycarbonylamino-3-methyl-4-pentenoic acid (*syn* : *anti* = 3 : 1) (cf. ref. 6.).
8. The *E* isomers (>99.5% by GLC), purified by $AgNO_3$-SiO_2 column chromatography and subsequent distillation, were employed for the reaction.
9. For asymmetric rearrangement of glycolate ester, see Kallmerten, J.; Gould, T. J. *J. Org. Chem.* **1986**, *51*, 1152-1155.
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