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ANIONIC HETERO[3,3]REARRANGEMENTS. *N,O*-DIACYLHYDROXYLAMINES TO SUCCINIC ACID DERIVATIVES

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N,O-Diacylhydroxylamines rearrange under basic conditions to afford 2,3-disubstituted succinic acid derivatives. The rearrangement can be rationalized in terms of [3,3]sigmatropic shifts of ester-amide dienolated *N,O*-diacylhydroxylamines.

KEYWORDS [3,3]sigmatropic rearrangement; enolate; *N,O*-diacylhydroxylamine; C-C bond formation

An aliphatic version of the Claisen rearrangement has been developed by means of *in situ* formation of the [3,3]rearrangement precursors, i.e., allyl vinylether systems.1) Examples include the exchange of amide acetals2) or ethyl orthoacetate3) with allyl alcohols and subsequent formation of γ,δ-unsaturated amides or esters upon rearrangement. An important example was reported by Ireland and Mueller, who demonstrated Claisen rearrangement of acylated allyl alcohols by the use of lithium dialkylamide bases for the generation of ester enolates.4) The 3-aza-4-oxa[3,3]sigmatropic rearrangement of *N,O*-divinylhydroxylamine, which has been estimated to be exothermic,5) seems to be widely applicable for synthesis. However, its application has been restricted to aromatic rearrangements6) because of the instability of the requisite *N,O*-divinylhydroxylamine systems. In this paper, we wish to report an anionic 3-aza-4-oxa[3,3]sigmatropic rearrangement of ester-amide dienolated *N,O*-diacyl-*N*-alkylhydroxylamines to succinic acid derivatives.

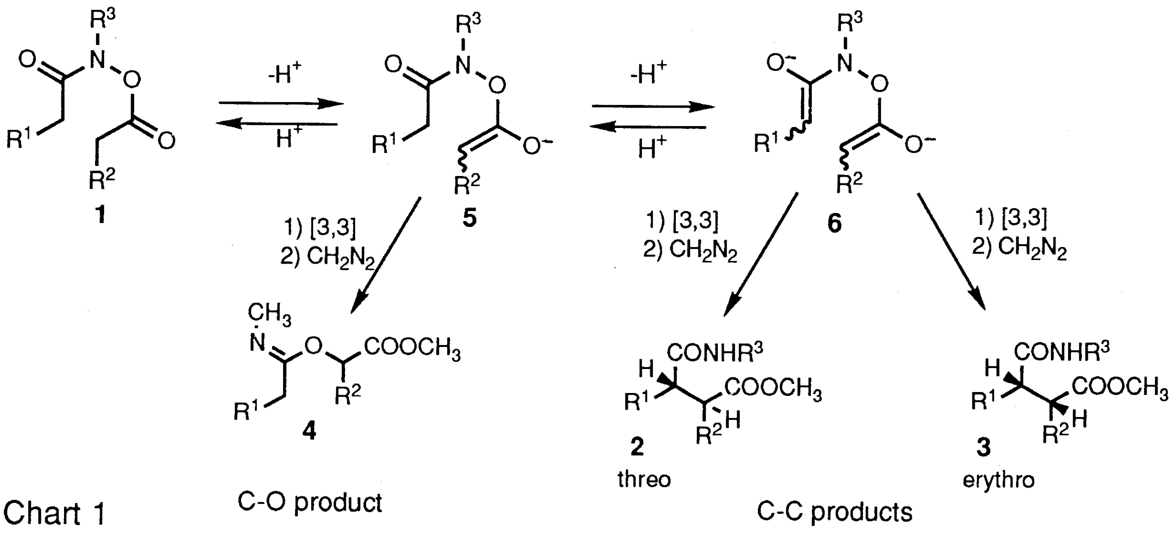

Chart 1

The scope of the [3,3]sigmatropic rearrangement of *N,O*-diacylhydroxylamines was tested by using the *N,O*-diacyl-*N*-alkylhydroxylamines (**1**).[7] Treatment of *N,O*-diacetyl-*N*-methylhydroxylamine (**1a**) with 2.5 eq of potassium hexamethyldisilazide (KHMDS) or lithium diisopropyl amide (LDA) in THF at -78°C for 2 h followed by esterification with diazomethane did not give the expected succinic acid derivative (Table I, entries 1,2). In order to elucidate the favorable intermediate structure for [3,3]sigmatropic shifts, we examined the reaction from two viewpoints, *i.e.* the stability of the dienolate intermediate and the conformational character of the intermediate.

Table I. Anionic [3,3]Rearrangement of N,O-Diacyl-N-alkylhydroxylamines

Entry	Compound	R^1	R^2	R^3	Base	Condition[a]	Yield (%)[b] C-C Product (threo **2** : erythro **3**)	Yield (%)[b] C-O Product **4**
1	**1a**	H	H	CH_3	KHMDS	A	0	0
2	**1a**	H	H	CH_3	LDA	A	0	0
3	**1b**	Ph	H	CH_3	KHMDS	A	17	12
4	**1c**	H	Ph	CH_3	KHMDS	A	47	10
5	**1d**	Ph	Ph	CH_3	KHMDS	A	67 (71:29)	31
6	**1d**	Ph	Ph	CH_3	LDA	A	33 (69:31)	29
7	**1e**	H	H	$CH(CH_3)_2$	KHMDS	A	13	0
8	**1e**	H	H	$CH(CH_3)_2$	LDA	A	12	0
9	**1f**	H	H	$C(CH_3)_3$	KHMDS	B	65	0
10	**1f**	H	H	$C(CH_3)_3$	LDA	A	68	0
11	**1g**	CH_3	CH_3	$C(CH_3)_3$	LDA	A	49 (69:31)	0
12	**1h**	Ph	H	$C(CH_3)_3$	LDA	B	59	0
13	**1i**	H	Ph	$C(CH_3)_3$	LDA	A	74	0
14	**1j**	Ph	Ph	$C(CH_3)_3$	LDA	A	75 (57:43)	0

a) Condition A: Base 2.5 eq. in THF, -78°C, 2h; B: Base 2.5 eq. in THF, -40°C, 2h.
b) Yields are isolated yields.

The presence of a phenyl group enhances the thermodynamic acidity of adjacent protons by 7 pK units.[8] As expected, *N,O*-diphenacetyl-*N*-methylhydroxylamine (**1d**) smoothly rearranged upon treatment with 2.5 eq of KHMDS in THF at -78°C for 2 h, followed by esterification with diazomethane to give the C-C products (**2d** and **3d**) in a yield of 67% (Table 1, entry 5).[9] KHMDS treatment of *N*-phenylacetyl-*O*-acetyl-*N*-methylhydroxylamine (**1b**) and *N*-acetyl-*O*-phenylacetylhydroxylamine (**1c**) also gave the C-C products (**2** and **3**) (Table 1, entries 3,4). In these reactions, α-hydroxyacetic acid derivatives (**4**) were isolated along with the major products (**2** and **3**). The structure of the α-hydroxyacetic acid derivatives (**4**) indicates that the oxygen atom of the amide group rearranges to the carbon atom of the ester enolate. The formation of α-hydroxyacetic acid derivatives (**4**) can be explained in terms of 1,4-dioxa-3-aza[3,3]sigmatropic rearrangement of the ester enolates (**5**). Treatment of **1d** with 1.1 eq of KHMDS at -40°C for 2 h gave the C-C products (**2d** and **3d**, 33 %) and a C-O product (**4d**, 29 %). This is presumably because ester-amide dienolates are readily formed and there is an equilibrium between dienolate and ester enolates.

Because a cyclic six-centered intermediate is involved in [3,3]sigmatropic rearrangement, a favorable conformation for [3,3]shifts can be expected by replacing the methyl group on the nitrogen with a sterically bigger substituent. Base treatment of *N,O*-diacetyl-*N*-isopropylhydroxylamine (**1e**) followed by esterification gave the C-C product in low yield (Table I, entries 7,8). Significant improvement was achieved with the *N-tert*-butyl substituent. *N,O*-Diacetyl-*N-tert*-butylhydroxylamine (**1f**) effectively rearranged to the C-C product in 68 % yield (Table 1, entries 9,10). The *N-tert-* butyl derivatives rearranged to give the corresponding C-C products (**2** and **3**) whether the reactant had an α-stabilizing group or not(Table I, entries 11-14).

A reasonable mechanism for the formation of the C-C products would be 3-aza-4-oxa[3,3]sigmatropic rearrangement of an ester-amide dienolate (**6**). The stereochemistry of the products seems to be reflected in the geometry of the transition state which is a mixture of E- and Z-enolates. Because, the thero-erythro ratios unchanged at -78°C in the prolonged reaction times. As described above, the yields of the [3,3]rearrangement are affected by the stabilizing forces due to the α- substituent groups of the enolates. A bulky substituent on nitrogen plays an important role in the constitution of the transition state. When the lifetime of the dienolate is long enough to allow generation of the chair conformation of cyclic six-centered transition state, the [3,3]rearrangement proceeds smoothly. A major side reaction of the present system would be cleavage of the C-O bond to give *N*-acyl-*N*-alkylhydroxylamines and ketenes, sicne the rearrangement precursors, *N,O*-diacyl-*N*-alkylhydroxylamines, correspond to activated esters.10) *N*-Acyl-*N*-alkyl-*O*-methylhydroxylamines and methyl acylates were isolated after treatment with diazomethane.

This aliphatic 3-aza-4-oxa[3,3]sigmatropic rearrangement of an ester-amide dienolate increases the synthetic utility of anionic [3,3]sigmatropic rearrangements initiated by N-O bond cleavage.

REFERENCES AND NOTES

1) For reviews, see F. E. Ziegler, *Chem. Rev.* **88**, 1423 (1988); S. Blechert, *Synthesis*, 1989, 71.
2) D. Felix, K. Gschewend-Steen, A. E. Wick, A. Eschenmoser, *Helv. Chim. Acta*, **52**, 1030 (1969).
3) W. S. Johnson, L. Werthemann, W. R. Bartlett, J. J. Brockson, T. Lee, D. J. Faulkner, M. R. Petersen, *J. Am. Chem. Soc.*, **92**, 741-743 (1970).
4) R. E. Ireland, R. H. Mueller, *J. Am. Chem. Soc.*, **94**, 5897 (1972).
5) J. B. Hendrickson, *Angew. Chem.,Int.Ed.Engl.*, **13**, 47 (1974).
6) For [3,3]sigmatropic shifts of *N*-arylhydroxylamine derivatives, see R. M. Coates, I. Md. Said, *J. Am. Chem. Soc.*, **99**, 2355 (1977) ; S. Blechert, *Tetrahedron Lett.*, **25**, 1547 (1984); Y. Endo, S. Hizatate, K. Shudo, *Tetrahedron Lett.*, **32**, 2803 (1991). For [3,3]sigmatropic shifts of *O*-arylhydroxylamines, see Y. Endo, T. Terashima, K. Shudo, *Tetrahedron Lett.*, **25**, 5537 (1984); Y. Endo, K. Namikawa, K. Shudo, *Tetrahedron Lett.*, **27**, 4209 (1986).
7) *N,O*-Diacyl-*N*-alkylhydroxylamines were prepared by *N*-acylation of *N*-methylhydroxylamine hydrochloride in THF-H_2O, followed by *O*-acylation in benzene or dichloromethane.
8) A. Streitwieser, M. R. Granger, F. Mares, R. A. Wolf, *J.Am.Chem.Soc.*, **95**, 4257 (1973).
9) The procedures employing 2.5 eq of sodium hydride in THF, 2.5 eq of potassium hydride in THF-HMPA, and 2.5 eq of potassium hydride, with 18-crown-6 in THF at 0°C gave no C-C products.
10) The low yield in the rearrangement of **1d** with LDA seems to be caused by the C-O cleavage.

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