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A Mild Method for the Efficient [3,3]-Sigmatropic Rearrangement of *N,O*-Diacylhydroxylamines

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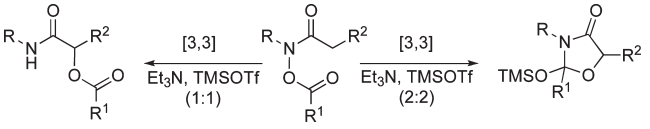
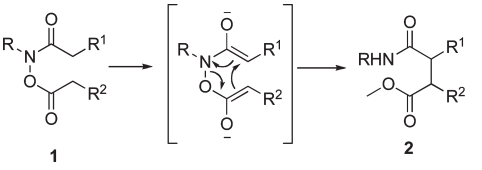


A mild, general method for the [3,3]-sigmatropic rearrangement of *N,O*-diacylhydroxylamines, employing a combination of mild base and Lewis acid, is described. Employing stoichiometric amounts of reagents with respect to substrate provides α-acyloxyamides, whereas an excess of reagents favors formation of cyclic ortho-amides.

The [3,3]-sigmatropic rearrangement[1,2] of *N,O*-diacylhydroxylamines (e.g., **1**, Scheme 1) was first reported by Endo in 1994.[3] Under their reported conditions, the dienolate was generated at low temperature which then rearranged to give products **2** in modest to good yields.

Several years later, Clark's group reported that under forcing thermal conditions[4] or employing an organic base,[5] an alternative rearrangement can occur as shown in Scheme 2. Thus, under Clark's conditions, selective amide

SCHEME 1. Endo's [3,3]-Sigmatropic Rearrangement of *N,O*-Diacylhydroxylamines[3]



SCHEME 2. Alternative [3,3]-Sigmatropic Rearrangement of *N,O*-Diacylhydroxylamines[5]

enolization of **3** generates the corresponding enol and/or enolate which then rearranges to give α-acyloxy products **4**. These products can easily be hydrolyzed to give synthetically useful 2-hydroxyamides and acids.[6] Since that report, Clark has published a series of studies, exploring the use of different bases in order to improve the generality of the process.[7] Two main issues with regard to substrate structure were noted by this group. The first involved the acidity of the α protons required to undergo enolization. It was found that only activated systems (i.e., allylic and benzylic) would undergo rearrangement.

In order to overcome this problem, a catalytic method based on the use of highly basic phosphazenes in refluxing toluene for extended periods of time was developed. Under these conditions, even unactivated systems rearranged. However, with such unactivated substrates, the steric nature of the *N*-alkyl substituent played a significant role in promoting or hindering the rearrangement. Thus, it was observed that as the substituent decreased in steric demand so did the yield. Whereas *N*-*tert*-butyl-containing substrates gave good yields after rearrangement, *N*-*sec*-butyl and *N*-*iso*propyl gave modest yields and *N*-methyl failed to react at all.

We were interested in establishing whether milder conditions than those previously described could be developed for this class of rearrangements. We did this with a view toward expanding the scope of the rearrangement to include as wide a range of substrates as possible.

The rearrangement of *N,O*-diacylhydroxylamines employing varying ratios of a mild base, Et_3N, and TMSOTf as silylating agent was examined first (Scheme 3). These conditions are similar to those reported by Miller's group for the rearrangement of *N,N′*-diacylhydrazides[8] and

(1) For general reviews on [3,3]-sigmatropic rearrangements: (a) Enders, D; Knopp, M; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, *7* (7), 1847–1882. (b) Nowicki, J. *Molecules* **2000**, *5*, 1033–1050. (c) Allin, S. M.; Baird, R. D. *Curr. Org. Chem.* **2001**, *5*, 395–415. (d) Nubbemeyer, U. *Synthesis* **2003**, *7*, 961–1008.

(2) For general reviews on hetero-[3,3]-sigmatropic rearrangements, see: (a) Blechert, S. *Synthesis* **1989**, 71–82. (b) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423–1452. (c) Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579–586.

(3) (a) Endo, Y.; Uchida, T.; Hizatate, S.; Shudo, K. *Synthesis* **1994**, 1096–1105. (b) Uchida, T.; Endo, Y.; Hizatate, S.; Shudo, K. *Chem. Pharm. Bull.* **1994**, *42* (2), 419–421. For Endo's previous anionic [3,3]-sigmatropic rearrangements of either *O*- or *N*-acylhydroxylamines, see: (c) Endo, Y.; Hizatate, S.; Shudo, K. *Tetrahedron Lett.* **1991**, *32* (24), 2803–2806. (d) Endo, Y.; Hizatate, S.; Shudo, K. *Synlett* **1991**, *9*, 649–650.

(4) Al-Faiyaz, Y. S. S.; Clark, A. J.; Filik, R. P.; Peacock, J. L.; Thomas, G. H. *Tetrahedron Lett.* **1998**, *39*, 1269–1272.

(5) Clark, A. J.; Al-Faiyaz, Y. S. S.; Broadhurst, M. J.; Patel, D.; Peacock, J. L. *J. Chem. Soc., Perkin Trans. 1.* **2000**, 1117–1127.

(6) There are few synthetic methods available for the synthesis of 2-hydroxyamides; see: (a) Seebach, D; Scheiss, M. *Helv. Chim. Acta* **1983**, *66*, 1618–1623. (b) Hoffman, R. V.; Nayyar, N. K.; Chen, W. *J. Org. Chem.* **1992**, *57*, 5700–5707.

(7) Clark, A. J.; Al-Faiyaz, Y. S. S.; Patel, D.; Broadhurst, M. J. *Tetrahedron Lett.* **2001**, *42*, 2007–2009.

(8) Miller, S. J.; Bayne, C. D. *J. Org. Chem.* **1997**, *62*, 5680–5681.

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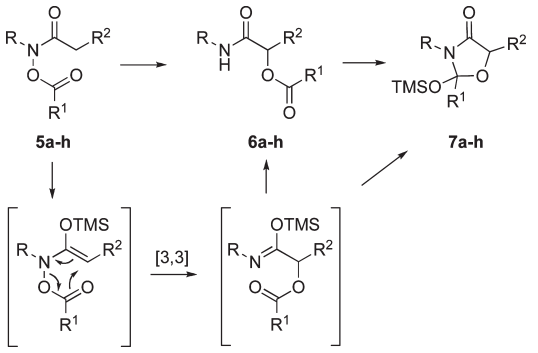
TABLE 1. Results for the [3,3]-Sigmatropic Rearrangement of *N*,*O*-Diacylhydroxylamines 5a−h (See Scheme 3)

compd	R	R^1	R^2	TMSOTf/Et_3N	**6**/**7**[a]	total yield (%)
5a	Me	Ph	Ph	1:1	1:0	75
5a	Me	Ph	Ph	2:2	1:10	90
5b	Me	Bn	Ph	1:1	10:1	90
5b	Me	Bn	Ph	2:2	0:1	85
5c	Me	$(CH_2)_2CH{=}CH_2$	$CH_2CH{=}CH_2$	1:1	1:0	25
5c	Me	$(CH_2)_2CH{=}CH_2$	$CH_2CH{=}CH_2$	2:2	1:0	60
5d	Bn	Ph	Ph	1:1	1:0	40
5d	Bn	Ph	Ph	2:2	1:4	90
5e	Bn	Ph	Me	1:1	1.2:1	70
5e	Bn	Ph	Me	2:2	1:1.5	75
5f	Bn	Ph	*i*-Pr	1:1	1:0	10
5f	Bn	Ph	*i*-Pr	2:2	1:0	50
5g	Bn	Ph	$CH_2CH{=}CH_2$	1:1	1:0	45
5g	Bn	Ph	$CH_2CH{=}CH_2$	2:2	1:0	70
5h[b]	*t*-Bu	Ph	Ph	1:1	1:0	5[d]
5h[c]	*t*-Bu	Ph	Ph	2:2	2:1	25[d]

[a]Product ratios determined by ^{1}H NMR spectroscopy; [b]7 d. [c]Reflux. [d]Yield estimated by ^{1}H NMR spectroscopy and crude isolation.

SCHEME 3. [3,3]-Sigmatropic Rearrangement of *N*,*O*-Diacylhydroxylamines 5a−h with Et_3N and TMSOTf



Kamimura's group for the formation of cyclic orthoamides from α-hydroxyamides.[9,10]

Thus, **5a** was first treated with 1 equiv each of Lewis acid and base at −78 °C and then stirred overnight at room temperature. The rearranged product **6a** was obtained in 75% yield. When a 1-fold excess of base and silylating agent was employed, a 10:1 ratio of **7a**/**6a** was obtained in 90% yield. With these encouraging results in hand, we examined variations in substituents R, R^1, and R^2 as well as ratios of reagents to substrate. This correlation between major products and reagent to substrate ratios was found to hold in most cases. The results are collected in Table 1.

Compound **5b** followed the trend established by the initial experiment, giving products **6b** or **7b**[11] in excellent yields depending on the number of equivalents used. The rearrangement was also attempted at lower temperature but resulted in no reaction. For those cases where both the ester and amide moieties bear acidic α-protons, i.e., **5b** and **5c**, only the amide moiety undergoes enolization under these conditions.[9,10] This observation is important as it precludes the possibility of the alternative, "Endo", rearrangement[3] occurring. Also noteworthy is the successful rearrangement of **5c**, where both acyl substituents are allylic, and R = Me, as such unactivated systems were inaccessible employing base catalysis alone.

Compounds **5d**−**g**, all bearing the more synthetically useful *N*-benzyl substituent, were prepared and rearranged in order to establish the generality of this new method. As evident from Table 1, our conditions were able to rearrange both activated and nonactivated systems. In line with the literature,[7] branched substituent **5f** reacted sluggishly, though with excess reagent, a 50% yield was obtained. Substrate **5h** proved the most difficult to rearrange, requiring a 7 days at room temperature, or overnight reflux, to provide, at best, only poor yields (25%) of impure material.

Hence treating *N*,*O*-diacylhydroxylamines with 1 equiv each of TMSOTf and base produces silyl ketene aminals, which can then undergo [3,3]-sigmatropic rearrangement to give the corresponding silyliminoethers. Without significant excess of TMSOTf quenching of the reaction yields **6**. However, where an excess of TMSOTf is present a second product, **7**, is generated and, in some cases, becomes the major product (Scheme 3). Although the precise mechansim of formation of this second product has not been studied, it is noteworthy that Kamimura[9,10] has demonstrated that α-hydroxyamides are readily converted into cyclic orthoamides under conditions similar to those employed in this study.

Finally, we briefly evaluated the use of a chiral *O*-acyl moiety to induce diastereoselectivity during the rearrangement (Scheme 4). The reaction proceeded in modest yield but provided essentially an equal mixture of the two diastereomers. Separation of the two compounds was easily achieved with column chromatography.

Assignment of the stereochemistry of each diastereomeric product could be achieved by acylation of mandelamide. Thus, reaction of *N*-benzyl-(*S*)-mandelamide (**11**) with (*S*)-(*O*-methyl)mandelic acid (**12**) gave a product which was identical in every way with **10**, generated by rearrangement of **8** (Scheme 5). The same process was repeated to confirm diastereomer **9**.

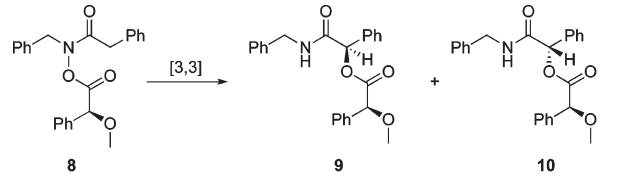
In conclusion we have developed a new, reliable protocol for the [3,3]-sigmatropic rearrangement of *N*,*O*-diacylhydroxylamines. This pathway allows for milder reaction conditions and a wider substrate range than previously possible.

(9) Kamimura, A.; Omata, Y.; Kakehi, A.; Shirai, M. *Tetrahedron* **2002**, *58*, 8763–8770.

(10) (a) Omata, Y; Kakehi, A; Masashi, S; Kamimura, A. *Tetrahedron Lett*. **2002**, *43*, 6911–6914. (b) Kamimura, A.; Omata, Y.; Keiichi, T.; Shirai, M. *Tetrahedron* **2003**, *59*, 6291–6299. (c) Kamimura, A.; Tanaka, K.; Hayashi, T.; Omata, Y. *Tetrahedron Lett*. **2006**, 3625–3627.

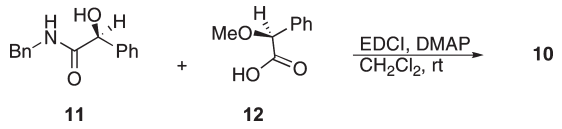
(11) Most of the cyclic orthoamides were stable in solution. However, **7b** proved to be the exception and decomposed when left overnight in a $CDCl_3$ solution.

SCHEME 4. [3,3]-Sigmatropic Rearrangements of *N*,*O*-Diacylhydroxylamine 8 Bearing a Homochiral *O*-Acyl Group



TMSOTf/Et_3N	Conditions	**9:10**	Yield (%)
1:1	R.t., 17h	1.2:1	50
1:1	Reflux, 17h	1:1	65

SCHEME 5. Chemical Proof of the Stereochemistry of Rearrangement Product 10



Experimental Section

Typical Procedures for the [3,3]-Sigmatropic Rearrangement of *N*,*O*-Diacylhydroxylamines under Conditions Which Provide Either Product 6 or 7. Preparation of 2-(Methylamino)-2-oxo-1-phenylethyl Benzoate (6a). Under an argon atmosphere, *N*-(benzoyloxy)-*N*-methyl-2-phenylacetamide (**5a**) (200 mg, 0.743 mmol) was dissolved in 3 mL of dry DCM and the temperature lowered to −78 °C. To this, TMSOTf (135 μL, 0.743 mmol) was added, followed 5 min later by NEt_3 (104 μL, 0.743 mmol). After being stirred at this temperature for 30 min, the reaction was removed from the cooling bath, allowed to warm to room temperature, sealed and left to stir overnight. The reaction was quenched by pouring directly onto a silica gel plug and eluted with EtOAc. Solvent removal in vacuo left a white solid which upon spectroscopic analysis, proved to be pure **6a** (150 mg, 75%): mp 142−143 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10−8.14 (m, 2H), 7.28−7.65 (m, 8H), 6.37 (s, 1H), 6.20 (brs, 1H), 2.90 (d, J = 4.8, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 169.1, 165.1, 135.8, 133.8, 130.0, 129.5, 128.9, 128.8, 128.8, 127.5, 76.1, 26.4; FT-IR ν_{max}/cm^{-1} 3311, 3092, 3065, 3036, 2949, 1725, 1661, 1561, 1496, 1449, 1315, 1245, 1113, 1025, 985, 708, 683; ESI-HRMS m/z 270.1124, 292.0947 ($C_{16}H_{15}NO_3 + H^+$ requires 270.1130, $C_{16}H_{15}NO_3 + Na^+$ requires 292.0950).

Preparation of 3-Methyl-2,5-diphenyl-2-(trimethylsilyloxy)-oxazolidin-4-one (7a). *N*-(Benzoyloxy)-*N*-methyl-2-phenylacetamide (**5a**) (100 mg, 0.371 mmol) was dissolved in 1.5 mL of dry DCM and the temperature lowered to −78 °C. To this was added TMSOTf (135 μL, 0.743 mmol), followed 5 min later by NEt_3 (104 μL, 0.743 mmol). After being stirred at this temperature for 30 min, the reaction was removed from the cooling bath, allowed to warm to room temperature, sealed, and left to stir overnight. The reaction was quenched by pouring directly onto a silica gel plug and eluted with EtOAc. Solvent removal in vacuo left a white solid which upon spectroscopic analysis showed a 10:1 mixture of **7a**/**6a** in a combined 90% yield. Column chromatography (20% EtOAc/hexane) afforded **7a** as a white solid (102 mg, 80%): mp 62−63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20−7.62 (m, 10H), 5.52 (s, 1H), 2.70 (s, 3H), 0.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 169.5, 139.5, 135.5, 129.5, 128.9, 128.7, 128.7, 128.4, 127.0, 126.9, 126.8, 110.7, 78.6, 25.7, 1.2; FT-IR ν_{max}/cm^{-1} 3035, 2957, 1716, 1424, 1231, 1090, 1062, 1035, 869, 839, 760, 698; ESI-HRMS m/z 342.1519 ($C_{19}H_{23}NO_3Si + H^+$ requires 342.1525).

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Supporting Information Available: Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.