A Remarkable Base-Induced Rearrangement of Hydroxy Oxazolines to Amido Tetrahydrofurans

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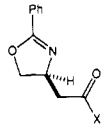
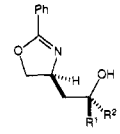
Summary: Asymmetric β-hydroxy oxazolines have been shown to rearrange at room temperature to isomeric tetrahydrofurans when deprotonated with potassium hydride in tetrahydrofuran.

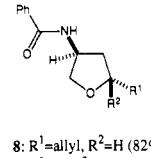
In the course of our investigations on the asymmetric elaboration of enantiomerically pure oxazoline **1**, we observed varying amounts of undesirable contaminants accompanying some of these transformations.[1] Invariably, these contaminants appeared when the reaction proceeded through an anionic intermediate resulting from an addition reaction at the acyl carbon and were found to be isomers of the protonated alkoxide intermediate.[2] In an effort to understand the nature of this undesirable reaction pathway, the formation of the isomeric contaminant was encouraged through the deprotonation of several β-substituted hydroxy oxazolines. Compounds **3–7** were prepared from thiolester **1** or the derived aldehyde **2**[3] and a study was undertaken to define reaction conditions which would favor the formation of the isomeric materials. It was found that efficient isomerization of these β-hydroxy oxazolines could be achieved through generation of their potassium alkoxides (KH) in tetrahydrofuran at room



1: X=S^{t}Bu
2: X=H

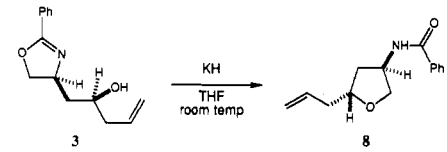


3: R^1=allyl, R^2=H
4: R^1=H, R^2=allyl
5: R^1=H, R^2=H
6: R^1=R^2=allyl
7: R^1=R^2=Me



8: R^1=allyl, R^2=H (82%)
9: R^1=H, R^2=allyl (65%)
10: R^1=H, R^2=H (87% at 40% conversion)
11: R^1=R^2=allyl (65%)
12: R^1=R^2=Me (100%)

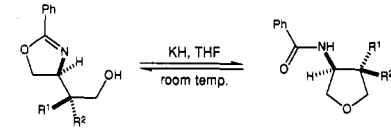
temperature.[5] For example, subjecting *syn*-allylated compound **3** to these conditions afforded an isomeric product in 82% yield as a crystalline material. While spectroscopic analysis (NMR, IR, UV, mass spectra) of this product proved inconclusive, single-crystal X-ray analysis revealed that a rearrangement had taken place to afford an asymmetric amido tetrahydrofuran **8** (eq 1). Subjecting compounds **4–7** to these reaction conditions led to similar results, yielding asymmetric tetrahydrofuran



3 8 (1)

products **9**, **11**, and **12** in good to excellent yields. The only exception to efficient isomerization was the unsubstituted substrate **5**, which proceeded only to 40% completion even at extended reaction times (the yield of **10** reflects recovered starting material).[6] This remarkable, and unprecedented, base-mediated rearrangement strikingly contrasts with the few previously reported thermal rearrangements of β-hydroxy-substituted oxazolines which afford isomeric β-hydroxy-substituted oxazines.[7]

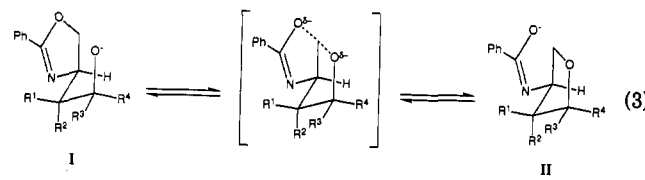
To further probe the generality of this rearrangement, isomeric methylated substrates **13** and **14** were prepared[8] and submitted to the rearrangement conditions. This led only to recovered oxazoline in the case of **13** and to a 2:1 mixture of oxazoline **14**:tetrahydrofuran **17** in 75% yield in the case of *cis* isomer **14** (eq 2).[9] *Furthermore,*



13: R^1=H, R^2=Me
14: R^1=Me, R^2=H

15: R^1=H, R^2=Me
17: R^1=Me, R^2=H (2)

submitting tetrahydrofuran 17 to the isomerization conditions (KH, THF) led to the same 2:1 mixture of 14:17 (75%). As a consequence of these results, the mechanism of this rearrangement may be speculated to involve a *reversible* cyclization process of the type described in eq 3, the position of the equilibrium being



I II (3)

determined by the relative stabilities of the alkoxide **I** and amide anion **II**. Available data suggest that the relative thermodynamic stabilities of alkoxides and amide anions are comparable,[10] consistent with the favorable equilibria observed for compounds **3**, **4**, **6**, and **7**. Steric

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(1) For previous work, see: (a) McGarvey, G. J.; Williams, J. M.; Hiner, R. N.; Matsubara, Y.; Oh, T. *J. Am. Chem. Soc.* **1986**, *108*, 4943. (b) McGarvey, G. J.; Hiner, R. N.; Williams, J. M.; Matsubara, Y.; Poarch, J. W. *J. Org. Chem.* **1986**, *51*, 3742. (c) McGarvey, G. J.; Wilson, K. J.; Shanholtz, C. E. *Tetrahedron Lett.* **1992**, *32*, 2641.

(2) These compounds were found to elute faster by thin layer chromatography and their isomeric character was established by mass spectral analysis.

(3) Compounds **3** and **4** were readily prepared via the previously reported diastereoselective allylation of aldehyde **2** (X = H),[4] while compounds **5**, **6**, and **7** could be routinely derived from the thiolester **1** (X = S^{t}Bu) through reduction with $NaBH_4$ or bis-alkylation with the appropriate Grignard reagent.

(4) Overly, K. R.; Williams, J. M.; McGarvey, G. J. *Tetrahedron Lett.* **1990**, *31*, 4573.

(5) The use of sodium or lithium salts did not affect rearrangement. The rearrangement was not subject to appreciable solvent effects, nor was it facilitated by the inclusion of ion complexing agents such as HMPA or 18-crown-6.

(6) The oxazoline to product ratio remained unchanged even after exposure to the reaction conditions for several days.

(7) Wong, C. M.; Ho, T. L.; Niemczura, W. P. *Can. J. Chem.* **1975**, *53*, 3144.

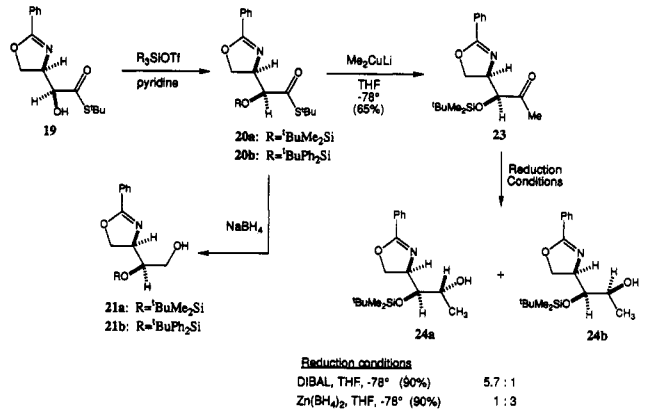
(8) Substrates **13** and **14** were prepared via diastereoselective methylation of the thiolester **1** (X = S^{t}Bu)[1a] followed by reduction ($NaBH_4$, THF).

(9) The structure of **17** confirmed through single-crystal X-ray analysis.

(10) Representative pK_as: ^{n}PrOH (16.1), ^{i}PrOH (17.1), ^{t}BuOH (~19), acetanilide (~17.6). See: Challis, B. C.; Challis, J. A. In *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon Press: New York, 1975; Vol. 2, Chapter 9.9.

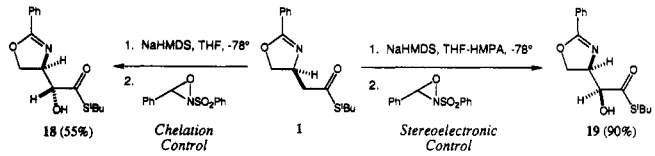
0022-3263/93/1958-6180$04.00/0

Scheme I



effects may also contribute to the explanation of the fact that no rearranged *cis*-tetrahydrofuran was observed from **13**, while the more stable *trans* product is observed in the thermodynamic mixture derived from **14**.

Anticipating the use of this rearrangement for the synthesis of novel furanoid carbohydrates, the preparation of more highly oxidized substrates was examined. It was found that the sodium enolate of the thiolester **1** (X = S^{t}Bu) could be conveniently oxidized using the Davis reagent.[11] Applying the reaction conditions previously demonstrated to select for *syn* and *anti* alkylation products of thiolester **1**[1a] allowed the preparation of alcohol **18** (55%) or **19** (90%) in greater than 95% diastereoselectivity (eq 4). Protection of the *cis* alcohol **19** as its ^{t}BuMe$_2$Si ether



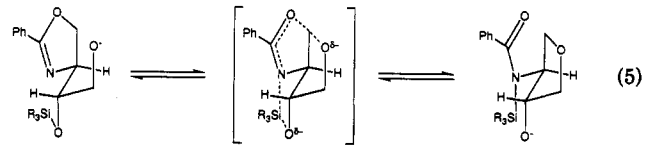
(4)

20a (see Scheme I) followed by exposure to NaBH$_4$ over a period of 2 days led to a 1.5:1 mixture of oxazoline **21a**: tetrahydrofuran **22a** in 92% yield. However, submission of **21a** to the rearrangement conditions (KH, THF) afforded a 1:4 mixture of products favoring the isomeric tetrahydrofuran **22a** in 79% combined yield. It is noteworthy that the bulkier ^{t}BuPh$_2$Si-protected alcohol **21b** almost exclusively favors the corresponding oxygen heterocycle **22b** in 50% isolated yield (**21b**:**22b** = 1:99). Once

21a: R^1='BuMe$_2$Si, R^2,R^3=H
21b: R^1='BuPh$_2$Si, R^2,R^3=H
24a: R^1='BuMe$_2$Si, R^2=H, R^3=CH$_3$
24b: R^1='BuMe$_2$Si, R^2=CH$_3$, R^3=H

22a: R^1='BuMe$_2$Si, R^2,R^3=H
22b: R^1='BuPh$_2$Si, R^2,R^3=H
25a: R^1='BuMe$_2$Si, R^2=H, R^3=CH$_3$
25b: R^1='BuMe$_2$Si, R^2=CH$_3$, R^3=H

again, the identical mixture of isomers could be generated in each case through exposure of the tetrahydrofuran isomer **22** to the basic rearrangement conditions. As indicated by the reduction of **21a**, the rearrangement of these silyl ethers was found to be relatively facile compared to the examples previously described. It is tempting to attribute the relative ease of these rearrangements to participation of the silicon protecting group in the fashion depicted in eq 5.[12]



(5)

Finally, a more stereochemically complex example was examined. Compound **20a** was directly converted into the corresponding methyl ketone **23** (Me$_2$CuLi) for subsequent reduction (Scheme I). Some degree of diastereoselectivity could be exercised in these reductions as DIBAL favored the *anti,syn* isomer **24a** in a ratio of 5.7:1, while reduction with Zn(BH$_4$)$_2$ selected for the *syn,syn* isomer **24b** in 3:1 diastereoselectivity. Though inseparable, these mixtures were subjected to the rearrangement conditions and the relative quantities of the oxazolines and tetrahydrofurans were assessed when the reaction reached its steady state.[13] Neither isomer showed a strong thermodynamic preference for the tetrahydrofuran products (**24a**:**25a** = 45:55, **24b**:**25b** = 60:40), presumably reflecting the steric influences of the additional methyl substituent.

Recent interest in the therapeutic exploitation of unnatural analogs of nucleosides in the treatment of human diseases, notably those resulting from HIV infection,[14] has stimulated effort to develop concise synthetic access to asymmetric furanoid compounds. To date, most of these approaches have relied on manipulation of naturally occurring carbohydrates, oxidation of acyclic olefins, or stereoselective electrophilic cyclization processes.[15] The present methodology offers a new approach to such heterocycles that may have their asymmetry readily obtained from amino acids. It is noteworthy that examples of 3-amino isomers of furanosides have been shown to have value as hydrolytically stable anti-HIV agents.[16] Further work addressing the scope and applications of this remarkable rearrangement will be forthcoming.

Acknowledgment. The financial support of the National Institutes of Health is gratefully acknowledged.

Supplementary Material Available: General experimental procedures, physical data, and X-ray crystallographic data (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information. The author has deposited atomic coordinates for structures **8** and **17** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(11) Davis, F. A.; Viswakaarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241. See also: Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346.

(12) For previous examples of silicon migration, see: (a) Dodd, G. H.; Golding, B. T.; Iounnou, P. V. *J. Chem. Soc., Perkins Trans. I* **1976**, 2273. (b) Mulzer, J.; Schollhorn, B. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 431.

(13) These quantities were obtained by ^{1}H NMR integration, HPLC, and weights of the chromatographically purified starting materials and diastereomeric products.

(14) For reviews: (a) Wells, K. H.; Byrne, B. C.; Poiesz, B. J. *Semin. Oncol.* **1990**, *17*, 295. (b) Sarin, P. S. *Ann. Rev. Pharmacol.* **1988**, *28*, 411. (c) De Clercq, E. *Anticancer Res.* **1987**, *7*, 1023.

(15) For some recent examples, see: (a) Lipshutz, B. H.; Barton, J. C. *J. Am. Chem. Soc.* **1992**, *114*, 1084. (b) Kang, S. H.; Hwang, T. S.; Kin, W. J.; Lim, J. K. *Tetrahedron Lett.* **1991**, *32*, 4015. (c) Walba, D. M.; Przybyla, C. A.; Walker, C. B. *J. Am. Chem. Soc.* **1990**, *112*, 5624. (d) Mihelich, E. D. *J. Am. Chem. Soc.* **1990**, *112*, 8995. (e) Semmelhack, M. F.; Zhang, N. *J. Org. Chem.* **1989**, *54*, 4483. For a review: Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321.

(16) (a) Huruya, D. M.; Sluboski, B. C.; Tam, S. Y.; Todaro, L. J.; Weigele, M. *Tetrahedron Lett.* **1989**, *30*, 6259. (b) Norbeck, D. W.; Spanton, S.; Broder, S.; Mitsuya, H. *Tetrahedron Lett.* **1989**, *30*, 6263.