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THE OXIME REARRANGEMENT CYCLIZATION. ALKENYL, STYRYL AND VINYL CHLORIDE TERMINATORS IN THE SYNTHESIS OF Δ^1-PYRROLINES

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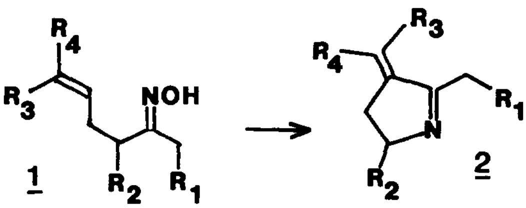
Abstract: Functionalized γ,δ -unsaturated oximes, constructed by regiospecific alkylation of appropriate oximes, may be rearranged and cyclized to Δ^1-pyrrolines in good yield.

The cationic cyclization of nitrilium ions to form Δ^1-pyrrolines has been known for some time.[1] The process has not seen significant utilization in organic synthesis because of the limitations on structural variety achievable by synthesizing the nitrilium ion via a Ritter reaction. We have recently reported the X-ray crystal structure of a Δ^1-pyrroline formed by cationic cyclization of a nitrilium ion generated stereospecifically from a ketoxime.[2] We now report the results of our initial investigation into the generality of the process. Initially, we chose a terminator functionality (i.e., a trisubstituted olefin) which was not expected to be particularly efficient, either as a nucleophile or as a functional group which might be expected to afford a minimum number of products.[3] Ultimate success of the rearrangement-cyclization with a historically poor terminator would be an encouragement for future work with more efficient terminators.

Oxime 1a was treated with several Lewis acids (PCl_5, P_2O_5, $AlCl_3$, $SnCl_4$, and $ZnBr_2$) in several refluxing solvents (toluene, glyme, ether, acetonitrile, nitromethane, carbon tetrachloride, and ethylene chloride). P_2O_5 was found to be the most satisfactory reagent. Yields of isolated product were 73% in CCl_4, 67% in toluene, and 69% in glyme. Since only 70-80% of oxime 1a exists in the E orientation[4] necessary for Beckmann rearrangement to the appropriate nitrilium ion, the yields shown are actually quite good. Efforts aimed at manipulating the geometry of the oxime in order to achieve a higher proportion of E isomer are currently underway.

The vinyl chloride group and the styryl group were tested as terminators. 1,3-Dichloro-2-butene and trans-cinnamyl chloride were alkylated with acetone oxime dianion (2 equiv. n-BuLi/THF/-78°) to afford 2b and 2c, respectively.[5] Oxime 1b was isomerized predominantly to its E geometrical isomer during the course of short column chromatography on



a) $R_1=R_2=H$, $R_3=R_4=CH_3$
b) $R_1=R_2=H$, $R_3=CH_3$, $R_4=Cl$
c) $R_1=R_2=R_3=H$, $R_4=C_6H_5$
d) $R_1=R_3=H$, $R_2=CH_3$, $R_4=C_6H_5$
e) $R_1=R_3=R_4=CH_3$, $R_2=H$
f) $R_1=H$, $R_2=R_3=R_4=CH_3$

silica gel.[6] Oxime *Z-1c* isomerized spontaneously to *E-1c*, in spite of several attempts to isolate the Z isomer. Rearrangement cyclization ($P_2O_5/C_6H_5CH_3$/reflux) of *1b* afforded *2b* as a mixture of E and Z isomers in 50% yield, while similar treatment of *1c* afforded *2c* in 50% yield.[5] It is noteworthy that the vinyl chloride functionality failed to participate in a biomimetic polyene cyclization.[7]

The ultimate success of a cyclization sequence aimed at natural products synthesis will depend to a large extent on the ability of the methodology to allow incorporation of substituents on the newly formed ring in a general way. The recently demonstrated facility of oximes for regiospecific alkylation[8] suggested their use in the construction of substrates since *an alkylation step might be used for convenient introduction of substituents before the cyclization is accomplished*. Having established with reasonable surety the general efficacy of the reaction, we therefore turned our attention to this problem. Z-2-Butanone oxime[8c] was alkylated (2 equiv. *n*-BuLi/THF/-78°) with *trans*-cinnamyl chloride to afford *1d* in 90% yield,[5] as a mixture of oxime geometrical isomers which isomerized to E-*1d* during short column chromatography.[6] Rearrangement cyclization (P_2O_5/CCl_4/reflux) afforded *2d* in 82% yield.[5] Moreover, alkylation of *1a* (2 equiv. BuLi/THF/-78°) with methyl iodide afforded a 4:1 mixture of *1e* and *1f* (98% yield),[5] reflecting the 4:1 ratio of E-*1a* to Z-*1a*. This mixture of *1e* and *1f* was immediately subjected (without purification) to rearrangement-cyclization conditions (P_2O_5/CCl_4/reflux) which provided a 44% yield of *2e* after short column chromatography.[5,6]

Thus, isomerization of the oxime may be utilized to acquire the geometry required for cyclization (e.g., Z-*1d* → E-*1d* → *2d*) or the rearrangement-cyclization may be conducted after alkylation and before isomer equilibration occurs (e.g., E-*1a* → E-*1e* → *2e*).

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FOOTNOTES

1. Meyers, A. I., and Sircar, J. C., in *The Chemistry of Cyano Group*, Rappoport, Z., ed., Interscience, New York, 1970, pp. 341-421.
2. R.E. Gawley, E.J. Termine, and K. D. Onan, *J. Chem. Soc., Chem. Comm.*, *1981*, 568-569.
3. In carbocyclic cationic cyclizations, trisubstituted alkenes afford a multiplicity of products; in iminium ion cyclizations, product multiplicity is reduced but the yields are low (40%). See Cope, A. C., and Burrows, W. D., *J. Org. Chem.*, *31*, 3099-3103 (1966).
4. Isomer ratios were determined by integration of the appropriate peaks in the NMR, see Karabatsos, G.J., and Taller, R.A., *Tetrahedron*, *24*, 3347-3360 (1968). The isomer ratio (E-*1a*/Z-*1a*) was variable from batch to batch.
5. Structural assignments for all new compounds are consistent with ^{1}H NMR, IR, and high-resolution MS of chromatographically homogeneous samples.
6. Hunt, B. J., and Rigby, W., *Chem. and Ind.*, *1967*, 1868-1869.
7. Johnson, W. S., et al, *J. Am. Chem. Soc.*, *102*, 7800-7802 (1980)
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