FORMATION OF FUNCTIONALIZED CYCLIC ETHERS BY INTRAMOLECULAR NITRILE OXIDE CYCLOADDITIONS¹a

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Abstract: The reaction of O-trimethylsilyl α -bromo aldoximes with unsaturated alcohols produces oximino ethers which can be readily oxidized with sodium hypochlorite. The transient nitrile oxide intermediate formed undergoes spontaneous cyclization affording fused isoxazolines. MM2 calculations help rationalize the observed stereoselectivity.

Substituted and functionalized tetrahydrofurans and pyrans are of interest as analogs of carbohydrates.² Recently, we reported the synthesis of α -brominated aldoxime derivatives (1) which can be used in reaction with nucleophiles such as vinylazetidines.³ The aminated intermediates served as convenient synthons for intramolecular dipolar cycloadditions.⁴ These results suggested a novel approach to functionalized cyclic ethers via intramolecular nitrile oxide-olefin cycloadditions.⁵ We report here on the reaction of O-trimethylsilyl α -bromo aldoximes 1 with



unsaturated alcohols **3** in the presence of fluoride ion to produce unsaturated ethers **4**. Most likely this reaction involves a nitrosoalkene intermediate (i.e. **2**) since an analogous process is known to occur upon treatment of α -halo oximes with base.⁶ Nitrosoalkenes so generated undergo rapid addition of a variety of nucleophiles resulting in an overall nucleophilic functionalization alpha to the oxime center.⁷⁻¹⁰ In our case the resulting unsaturated ether **4** possesses an aldoxime functionality which can be readily oxidized to a nitrile oxide intermediate that spontaneously cyclizes.

Intramolecular nitrile oxide-olefin cycloadditions (INOC) have been of considerable synthetic and mechanistic interest.⁵ When such reactions are to be employed in the construction of cyclic compounds with well defined stereochemistry, it is most desirable to be able to predict stereo and regioselectivity during ring formation.¹¹ The unsaturated dimethyl substituted oxime 4a was readily converted in 95% yield to the cycloaddition product 5a by treatment with sodium hypochlorite. In a similar manner ring closure with formation of the five-membered cyclic ether took place from 4b to produce 5b as a single diastereomer^{12,13} in 88% yield while the analogous methyl system (i.e. 4c) gave rise to a 2.4:1 mixture of diastereoisomers 5c in 71% yield.¹² Raney-nickel reduction of 5b resulted in isolation of the functionalized THF derivative 7 in 80% yield.¹²

MM2 calculations help rationalize the exclusive formation of cycloadduct **5b** and account for a mixture of isomers with the methyl system (i.e. **5c**). The calculations reveal a 0.96 kcal difference between the two diastereomeric transition states for the phenyl case but only a 0.38 kcal difference for the methyl system.¹⁴ In both cases the lower energy isomer corresponds to the trans diastereomer. This is a subtle effect which is not immediately obvious on inspection of molecular models but for which MM2 calculations serve well to predict stereochemistry in such intramolecular dipolar-cycloadditions.



In order to establish the generality of the reaction, we have investigated the cycloaddition of a number of closely related systems. Treatment of 1c with cyclohexenol followed by NaOCI oxida tion gave the tricyclic ether 8^{12} in 67% yield. The use of propargyl alcohol and propargyl thiol led, via the acetylenic oximes, to fused tetrahydrofurano[3,4-c]isoxazoles 9a and 9b. An analogous reaction occurred with bromo aldoxime 1b giving in 75% yield isoxazole 9c.¹⁵ Reaction of 1-buten-4-ol with α -bromo aldoxime 1b followed by NaOCI oxidation afforded tetrahydropyran derivative 6b, mp 77-79°C, in 40% yield.

During the course of our studies we found that simple heating of the unsaturated oxime (i.e. **4b**) at 80°C in benzene led in 25% yield to cycloaddition product **11** as a single diastereomer.^{12,16} Grigg and coworkers have previously demonstrated that aldehyde and ketone oximes react with electron deficient olefins to give isoxazolidines in which a second molecule of the olefin is attached to the isoxazolidine nitrogen atom.¹⁷ More recently, the 2-oximes of 1,2,3-tricarbonyl systems have been shown to undergo a proton transfer from oxygen to nitrogen to generate a 1,3-dipole as a reactive intermediate.¹⁸ However, attempts to extend this 1:1-cycloaddition process to other simple aldehyde or keto oximes by the Grigg group were unsuccessful. We believe that the conversion of **4** to **11** involves a thermal tautomeric equilibration¹⁹ of the oxime with its 1,3-dipolar tautomer **10** which subsequently undergoes an intramolecular dipolar-cycloaddition. The facility with which oximino ethers of type **4** undergo 1:1-cycloaddition may be related to the presence of the heteroatom in **4** which promotes the tautomeric equilibration process.



Tetrahydroisoxazoles of type **11** are potential starting materials for the stereospecific formation of 1,3-amino alcohols.

Other aspects of the reaction of oximes possessing olefinic side chains and their application to natural product synthesis will appear in forthcoming papers.

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References and Notes

- 1. a. Cycloadditions 38. For paper 37 see reference 3a; b. Department of Chemistry, Universita di Catania, Catania, Italy. U.C. thanks the NATO Foundation for a travel grant and the M.P.I. for partial financial support.
- J. Yoshimura Adv. Carb. Chem. 42, 69 (1984); M. Bourgeois Helv. Chim. Acta 56, 2879 (1973); ibid. 58, 363 (1975).
- 3. a. A. Hassner, K.S.K. Murthy, A. Padwa, W. H. Bullock and P. D. Stull J. Org. Chem. 53 submitted (1988); b. K.S.K. Murthy and A. Hassner Tetrahedron Lett. 97 (1987).
- 4. A. Padwa in "1,3-Dipolar Cycloaddition Chemistry", A. Padwa, Ed.; Wiley-Interscience, New York, Vol. 2, 1984.
- 5. A. P. Kozikowski Acc. Chem. Res. 17, 410 (1984).
- 6. T. L. Gilchrist Chem. Soc. Rev. 12, 53 (1983).
- 7. W. Hobold; U. Prietz and W. Pritzkow J. Prakt. Chem. 311, 260 (1969).
- 8. K. Wieser and A. Berndt Angew. Chem. Int. Ed. Engl. 14, 70 (1975).
- 9. E. Francotte, R. Merenyi, B. Vandenbulcke-Coyette and H. Viehe Helv. Chim. Acta. 64, 1208 (1981).
- 10. E. T. Kaiser, J. H. Smith and J. H. Heidema J. Am. Chem. Soc. 94, 9276 (1972).
- 11. A. P. Kozikowski and Y. Y. Chen J. Org. Chem. 46, 5248 (1981); A. P. Kozikowski and P. D. Stein J. Am. Chem. Soc. 107, 2569 (1985).
- The cycloaddition products were usually obtained as oils and were purified by flash chromatography over silica gel. All new compounds were characterized by 'H- and ¹³C-NMR and by high resolution mass spectra.
- 13. NMR **5b** (CDCl₃, 300 MHz) δ 3.80 (t, 1H, J=8.7 Hz), 4.06 (dd, 1H, J=12.2 and 8.2 Hz), 4.22 (p, 1H, J=9.4 Hz), 4.43 (t, 1H, J=8.7 Hz), 4.58 (t, 1H, J=8.7 Hz), 5.60 (s, 1H) and 7.2-7.5 (m, 5H); NMR **7** δ 2.86 (m, 1H), 3.86 (dd, 1H, J=11.2 and 5.0 Hz), 3.95 (dd, 1H, J=11.2 and 5.0 Hz), 4.16 (t, 1H, J=9.5 Hz), 4.65 (t, 1H, J=9.5 Hz), 4.74 (s, 1H) and 7.2-7.5 (m, 5H).
- 14. MM2 Calculations were performed on a Vax 11/785 using Model 2.92. The relative energy differences of the transition states were estimated by calculating transition state total energy. The program is parameterized for transition state carbon (C\$,C#,C*) as well as transition state oxygen. Transition-state bond orders of 0.3 were used.
- 15. NMR 9c δ 4.94 (d, 1H, J=12.0 Hz), 5.02 (d, 1H, J=12.0 Hz), 6.10 (s, 1H), 7.2-7.6 (m, 5H) and 8.05 (s, 1H).
- 16. NMR 11 (R₁=Ph, R₂=H, X=O) δ 3.15 (m, 1H), 3.60 (m, 2H), 3.96 (m, 2H), 4.40 (t, 1H, J=9.0 Hz), 4.50 (d, 1H, J=6.1 Hz), 5.22 (m, 1H) and 7.2-7.6 (m, 5H).
- 17. R. Grigg, M. Jordan, A. Taugthongkum, F.W.B. Einstein and T. Jones J. Chem. Soc. Perkin Trans. I 47 (1984).
- 18. R. Grigg and S. Thianpantangul J. Chem. Soc. Perkin Trans. I 653 (1984)
- 19. R. Grigg Chem. Soc. Rev. 16, 89 (1987).

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