

INTRAMOLECULAR DIPOLAR CYCLOADDITION REACTIONS OF C-ARYL OXAZIRIDINES

Albert Padwa* and Konrad F. Koehler

Department of Chemistry, Emory University, Atlanta, Georgia 30322, U.S.A.

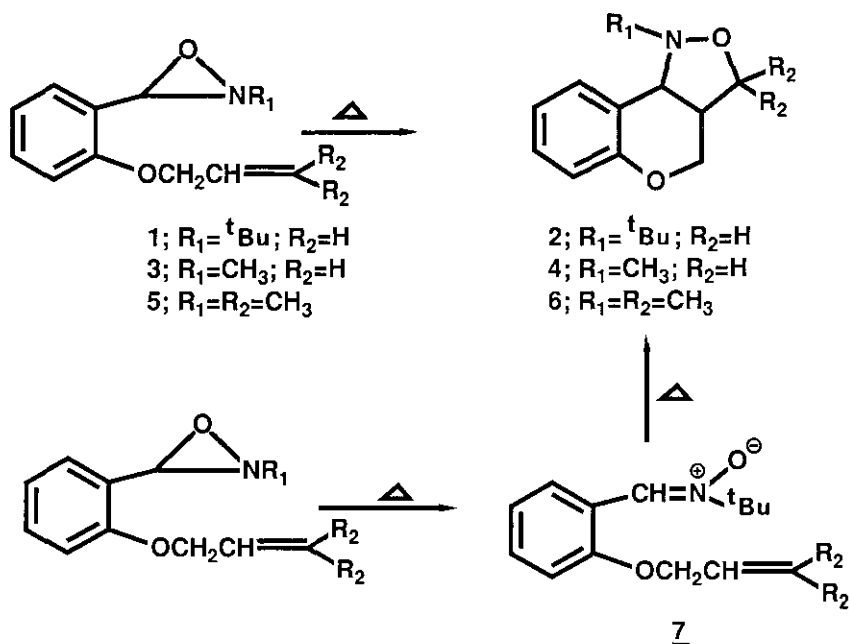
Abstract - Thermolysis of several C-aryl oxaziridines containing π -unsaturation in close proximity to the three-membered ring results in the formation of intramolecular dipolar cycloadducts derived from transient nitronone intermediates.

Condensation of carbonyl compounds with N-substituted hydroxylamines and oxidation of N,N-disubstituted hydroxylamines represent the most common methods for the synthesis of nitrones.¹ While nitrones are versatile synthetic intermediates especially useful for 1,3-dipolar cycloaddition reactions,² they are prone to undergo numerous side reactions. The thermal cycloreversion of isoxazolidines represents an effective method that has been successfully utilized for nitronone protection.³ In certain cases, however, drastic conditions are required for the fragmentation to proceed.⁴ More recently, we have found that cyano-O-silyl-substituted hydroxylamines can be used as nitronone blocking groups.⁵ In this paper we wish to describe the use of aryl oxaziridines as nitronone equivalents.

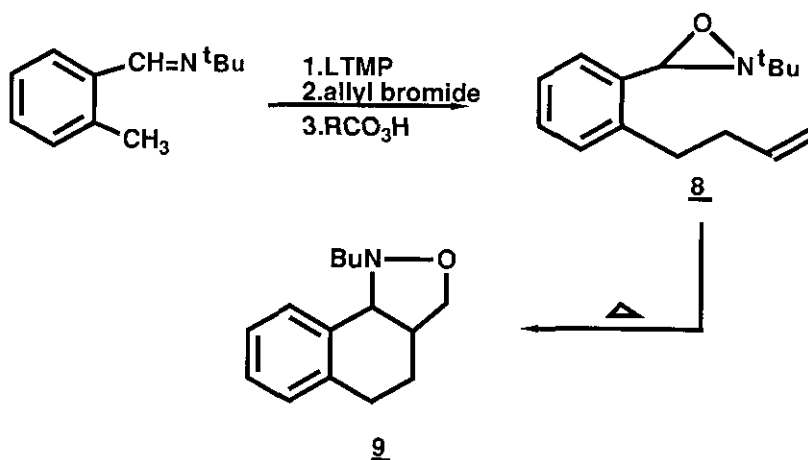
Oxaziridines, in general, are highly reactive molecules that display novel and unusual chemistry.⁶ A particularly effective method to synthesize these three-membered heterocycles involves the peracid oxidation of imines.⁷ Isolable oxaziridines can also be photochemically formed from nitrones⁸ and then thermally isomerize either back to nitrones or to other products such as amides.^{9,10} Nitrones readily undergo 1,3-dipolar cycloaddition reactions with multiply bonded dipolarophiles to yield synthetically useful heterocyclic derivatives.² The intramolecular reactions of nitrones with alkenes lead stereospecifically to isoxazolidines¹¹ which can be reduced to β -amino alcohols.¹² This approach has been employed to advantage in total syntheses of members of several alkaloid classes.¹³ As part of a program directed toward a study of intramolecular 1,3-dipolar cycloaddition reactions¹⁴ we had the occasion to prepare several aryl oxaziridines containing π -unsaturation in close proximity to the three-membered heterocyclic ring. The studies described herein were initiated to assess whether these oxaziridinyl systems will undergo internal dipolar cycloadditions analogous to the corresponding nitrones.

As our first model we chose to investigate the intramolecular dipolar cycloaddition reaction of o-

allyloxy oxaziridine 1. Examination of molecular models of the nitron derived from 1 shows that the side chain is of sufficient length to allow the dipole and dipolarophile units to approach each other in parallel planes. Thermolysis of a solution of 1 in benzene afforded *cis* N-*t*-butyl-1,3a,4,9b-tetrahydro-3H[1]-benzopyrano[4,3-*c*]isoxazole 2 in 86% yield [NMR (CDCl₃, 360 MHz) δ 1.22 (s, 9H), 3.07 (tdt, 1H, J=8.6, 8.6 and 2.6 Hz), 3.99 (dd, 1H, J=8.8 and 7.5 Hz), 4.19 (dd, 1H, J=11.6 and 2.6 Hz), 4.21 (dd, 1H, J=11.6 and 2.6 Hz), 4.30 (dd, 1H, J=8.8 and 7.5 Hz), 4.48 (d, 1H, J=8.6 Hz), 6.77 (dd, 1H, J=8.2 and 1.2 Hz), 6.95 (ddd, 1H, J=7.7, 7.4 and 1.2 Hz), 7.11 (ddd, 1H,

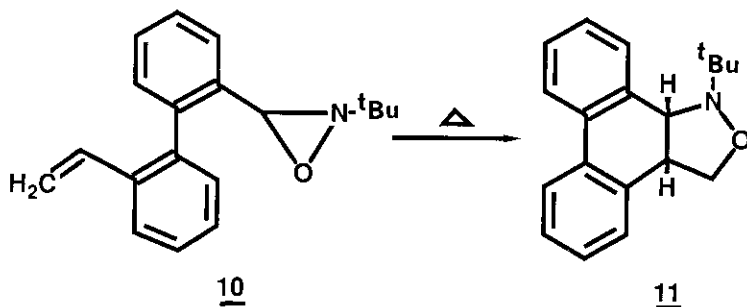


J=8.2, 7.4 and 1.2 Hz) and 7.34 (dd, 1H, J=7.7 and 1.2 Hz)]. This same product was also formed in high yield when a sample of nitron 7 was heated in benzene. This observation strongly suggests

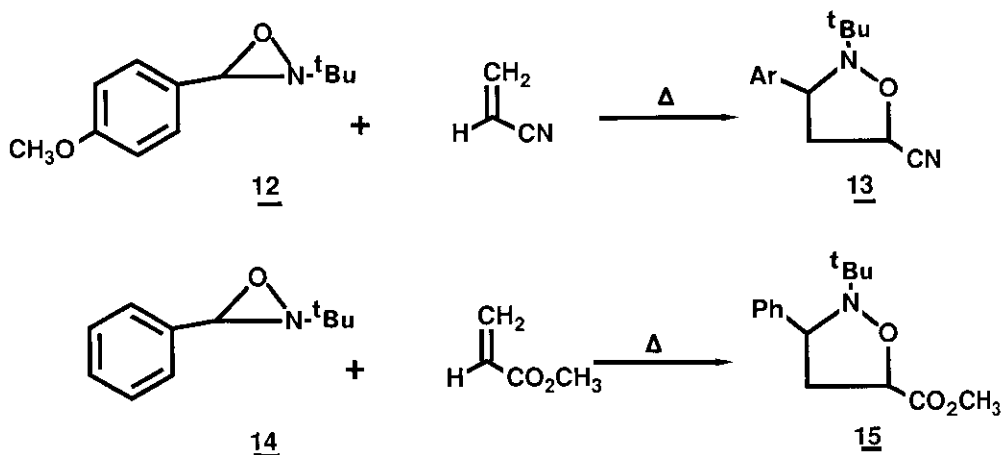


that 7 is initially formed from 1 and then undergoes a subsequent internal cycloaddition reaction. Related cycloadducts were also obtained from the thermolysis of *N*-methyloxaziridines 3 and 5.¹⁵ An additional system that was also studied corresponded to oxaziridine 8. This material was conveniently prepared by treating *N*-*t*-butyl-*o*-toluylaldehyde imine with lithio 2,2,6,6-tetramethylpiperidine (LTMP) followed by reaction with allyl bromide. The resulting imine was subjected to oxidation using *m*-chloroperbenzoic acid to give 8. Heating a sample of 8 in benzene afforded cycloadduct 9 in 78% isolated yield.¹⁶

Another case where a *C*-aryl oxaziridine was found to undergo intramolecular dipolar cycloaddition was encountered with compound 10. Thermolysis of 10 in benzene afforded 1-phenylphenanthro[9,10-*c*]-isoxazole 11 in 62% isolated yield as the only detectable product.¹⁷ The exclusive formation of 11 is especially interesting in light of Huisgen's work dealing with the bimolecular reaction of *N*-phenylbenzalnitron with styrene.¹⁸ Huisgen's group was able to show that the cycloaddition of *N*-phenylbenzalnitron with aryl conjugated olefins give 5-substituted isoxazolidines. Thus, the



regioselectivity observed in the intramolecular reaction of 10 is directly opposite to the earlier results reported by Huisgen. The preferential formation of 11 is probably a consequence of steric factors rather than HOMO-LUMO interactions, which generally control the regioselectivity in bimolecular cycloaddition reactions.¹⁹⁻²¹



Having verified that aryl oxaziridines containing π -unsaturation undergo smooth intramolecular dipolar-cycloaddition, we turned our attention to the bimolecular reaction of a representative aryl oxaziridine. The regioselectivity for nitronc cycloadditions onto monosubstituted ethylenes was originally believed to proceed in a unidirectional fashion, giving 5-substituted adducts regardless of the alkene substituent.²² More recent work suggests that those ethylenes bearing electron-withdrawing groups show an increasing tendency to afford the corresponding 4-substituted isoxazolidine as the electron withdrawing ability of the attached substituent increases.²³⁻²⁵ The ability to utilize nitronc cycloadditions in organic synthesis depends heavily on understanding the factors which determine the regiochemistry of the reaction. Our interest in using oxaziridine cycloadditions for the synthesis of several alkaloids has focused our attention on the regioselectivity of the reaction of oxaziridine 12 with acrylonitrile. We found that heating a sample of 12 with acrylonitrile afforded the expected 5-substituted isoxazolidine 13 in 80% yield. Similar results were obtained when oxaziridine 14 was heated in the presence of methyl acrylate. These results are in general accord with the earlier observations that most electron-deficient dipolarophiles undergo cycloaddition with nitrones to give 5-substituted isoxazolidines.²³ Thus, aryl oxaziridines may prove to be of some value as nitronc blocking groups. Further studies dealing with the use of oxaziridines in alkaloid synthesis will be reported at a later date.

ACKNOWLEDGEMENT

We gratefully acknowledge support of this work by the National Institutes of Health.

REFERENCES AND NOTES

- *Alexander von Humboldt Senior Scientist, 1985; University of Wurzburg.
1. For reviews of nitronc synthesis see (a) G. Tennant, "Comprehensive Organic Chemistry", D. H. R. Barton and W. D. Ollis, Ed., Pergamon Press, New York, Vol 2, part 8, 1979 (b) J. Hamer and A. Macaluso, Chem. Rev., 64, 473 (1964).
2. J. J. Tufariello, "1,3-Dipolar Cycloaddition Chemistry", A. Padwa, Ed., Chapt' 9, John Wiley Inc., New York, 1984.
3. J. J. Tufariello, G. B. Mullen, J. J. Tegler, E. J. Trybulski, S. C. Wong and S. A. Ali, J. Am. Chem. Soc., 101, 2435 (1985).
4. G. Bianchi and R. Gandolfi, "1,3-Dipolar Cycloaddition Chemistry", Vol 2, Chapter 14, 1984, John Wiley Inc., 1984.
5. A. Padwa and K. F. Koehler, manuscript in press.
6. E. Schmitz, Adv. Heterocycl. Chem., 24, 63 (1979).
7. W. D. Emmons, J. Am. Chem. Soc., 79, 5739 (1957).
8. C. G. Spence, E. C. Taylor and O. Buckardt, Chem. Rev., 70, 231 (1970).

9. J. S. Splitter and M. Calvin, J. Org. Chem., **23**, 651 (1958); ibid., **30**, 3427 (1965).
10. B. Bigot, D. Roux, A. Sevin and A. Devaquet, J. Am. Chem. Soc., **101**, 2560 (1979).
11. N. A. LeBel and D. Hwang, Org. Synth., **58**, 106 (1978).
12. N. A. LeBel, M. E. Post and J. J. Whang, J. Am. Chem. Soc., **86**, 3759 (1964).
13. J. J. Tufariello, Acc. Chem. Res., **12**, 396 (1979).
14. A. Padwa, "1,3-Dipolar Cycloaddition Chemistry", John Wiley and Sons, Chapter 12, N. Y., N. Y., 1984.
15. NMR 4 (CDCl₃, 90 MHz) δ 2.80 (s, 3H), 3.4-3.75 (m, 3H), 4.05-4.35 (m, 3H), 6.7-7.2 (m, 4H);
NMR 5 (CDCl₃, 90 MHz) δ 1.20 (s, 3H), 1.25 (s, 3H), 2.65 (s, 3H), 3.31 (m, 1H), 4.10 (m, 3H)
and 6.7-7.2 (m, 4H).
16. NMR 2 (CDCl₃, 360 MHz) δ 1.20 (s, 9H), 1.56 (ddt, 1H, J=13.6, 7.2 and 5.0 Hz), 2.03 (dddd, 1H,
J=13.6, 8.9, 6.7 and 4.5 Hz), 2.56 (ddd, 1H, J=15.3, 7.2 and 4.4 Hz), 3.06 (dtdd, J=8.9, 7.8,
6.7 and 5.0 Hz), 3.54 (t, 1H, J=7.8 Hz), 4.20 (t, 1H, J=7.8 Hz), 4.22 (d, 1H, J=8.9 Hz), 7.21
(d, 1H, J=7.3 Hz), 7.53 (d, 1H, J=7.3 Hz).
17. NMR 5 (CDCl₃, 100 MHz) δ 3.39-3.88 (m, 2H), 4.50 (dd, 1H, J=16.0 and 12.0 Hz), 5.14 (d, 1H,
J=6.0 Hz), 7.5-7.8 (m, 5H). Addition of Eu (fod)₃ shift reagent to the NMR sample resulted
in the conversion of the multiplet at 3.39-3.88 into a doublet of doublets of doublets (δ
3.68, 1H, J=9.0 and 7.0 Hz). The doublet of doublets at δ 4.50 was slightly compressed [δ
4.28 (dd, 1H, J=9.0 and 6.0 Hz)] and the doublet at δ 5.14 remained unchanged except for a
slight downfield shift (δ 5.20).
18. R. Huisgen, R. Grashey and H. Leittermann, Tetrahedron Lett., **9** (1960).
19. K. N. Houk, R. Duke, J. George, J. Sims and R. Strozier, J. Am. Chem. Soc., **95**, 7287 (1973);
ibid., **95**, 7301 (1973).
20. R. Sustmann, Tetrahedron Lett., 2727 (1971).
21. I. Fleming, "Frontier Orbitals and Organic Chemical Reactions", John Wiley, New York (1976).
22. R. Huisgen, Angew. Chem. Int. Ed. Engl., **2**, 565, 633 (1963).
23. R. Huisgen, "1,3-Dipolar Cycloaddition Chemistry", Chapter 1, John Wiley and Sons, Inc.,
New York, N. Y., 1984.
24. K. N. Houk, A. Bimanand, D. Mukherjee, J. Sims, Y. Chang, D. C. Kaufman and L. N. Domelsmith,
Heterocycles, **7**, 293 (1977).
25. S. A. Ali, P. A. Senaratne, C. R. Illig, H. Meckler and J. J. Tufariello, Tetrahedron Lett.,
4167 (1979).

Received, 31st October, 1985