Tetrahedron Letters,Vol.24,No.5,pp 435-438,1983 0040-4039/83/050435-04$03.00/0
Printed in Great Britain

THE SYNTHESIS AND CYCLOADDITIONS OF C-CYCLOPROPYL NITRONES[1]

Alexander Z. Bimanand and K. N. Houk*

Departments of Chemistry

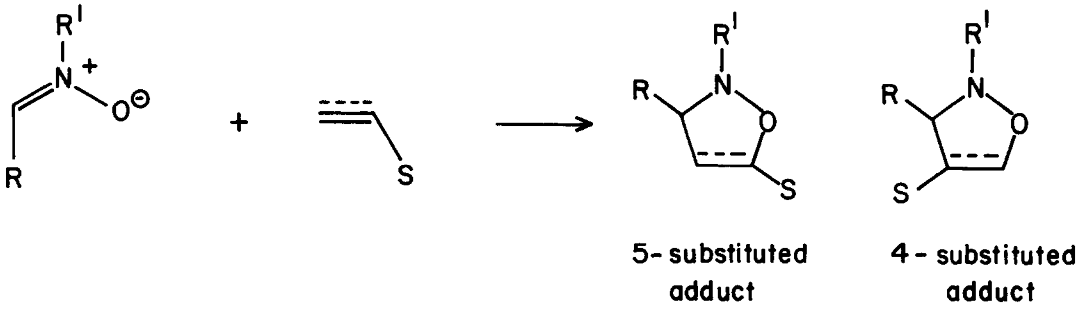
Louisiana State University
Baton Rouge, Louisiana 70803

and

University of Pittsburgh
Pittsburgh, Pennsylvania 15260

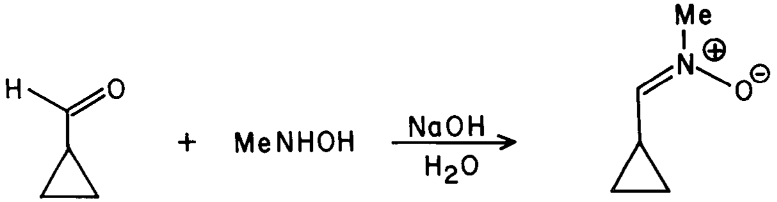
Summary: C-Cyclopropyl-N-methyl nitrone and C,C-dicyclopropyl-N-methyl nitrone have been synthesized, and the cycloadditions of these species to electron-deficient dipolarophiles have been studied.

Prior to 1973, nitrones were believed to add to monosubstituted dipolarophiles in a unidirectional fashion, giving 5-substituted adducts exclusively, regardless of the nature of the alkene substituent.[2] Huisgen discovered several exceptions with electron-deficient acetylenes: a 58:42 mixture of 4- and 5-substituted isoxazolines, respectively, was obtained in the reaction of methyl propiolate with C-phenyl-N-methyl nitrones, and only the 4-substituted isomer was obtained with 3,4-dihydroisoquinoline N-oxide.[3]

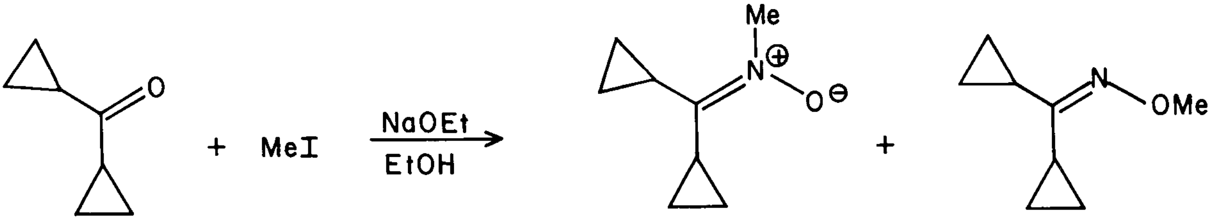


We reported a rationalization of these results, based on the idea that the nitrone LUMO controls regioselectivity, until the dipolarophile becomes very electron-deficient, or the nitrone becomes very electron-rich.[5] Indeed, we reported in 1973 that very electron-deficient dipolarophiles give significant amounts of, or even predominant, 4-substituted isoxazolidines or isoxazolines, in accord with predictions.[6] We have shown that there is a general tendency for the amount of 4-substituted adduct to increase as the ionization potential of the nitrone decreases or as the electron affinity of the dipolarophile increases.[7] This corresponds to an increase in nitrone HOMO energy or decrease in dipolarophile LUMO energy, respectively.

Here we wish to report the synthesis of two electron-rich nitrones, containing the electron donor cyclopropyl substituent. These electron-rich nitrones give significant amounts of 4-substituted adducts with electron-deficient dipolarophiles. C-cyclopropyl-N-methyl nitrone, **1**,[8] was synthesized by the reaction of cyclopropanecarboxaldehyde with N-methylhydroxylamine hydrochloride (2N NaOH, 5 minutes, then chloroform extraction) in 90% yield. The compound is a colorless oil which hydrolyzes readily to starting materials. A similar procedure gives C-cyclopropyl-N-*tert*-butyl nitrone. Dicyclopropyl ketone, like other ketones,[9] does not react with N-methylhydroxylamine, but the nitrone, **2**,[8] could be prepared by methylation of dicyclopropylketone oxime (MeI, NaOEt, EtOH).[7-9] The O-methyl ether, **3**,[6] is also formed. Both **2** and **3** are oils, and are formed in a 2:3 ratio under these conditions.



1



2 3

The cyclopropyl nitrones have considerably lower ionization potentials than C-phenyl nitrones,[7,10] due to the potent electron-donor ability of the cyclopropyl group.[12] C-phenyl-N-methyl nitrone has π ionization potentials of 8.01 and 9.91 eV. The first IP involves an orbital only about 50% localized on the nitrone moiety. C-Cyclopropyl-N-methyl and C, C-dicyclopropyl-N-methyl nitrones have π IP's of 8.30 and 7.89 eV, respectively, and computations indicate that the corresponding HOMO's are heavily localized on the nitrone moiety. We expected, therefore, that these relatively electron-rich nitrones should react rapidly with electron-deficient dipolarophiles, and more of the 4-substituted adducts should be formed than are found for less electron-rich nitrones.

The Table shows the ratios of adducts formed from a variety of dipolarophiles. The adduct structures were assigned from nmr spectra of the separated adducts, while ratios were determined by nmr integration of the crude reaction mixtures.[1a,8]

Table. Ratios of 4-Substituted: 5-Substituted 1, 3-Dipolar Cycloadducts.[a]

Dipolarophile	Nitrone 1[b]	 2
Styrene	only 5-	only 5-
Methyl acrylate	1:4	1:1
Acrylonitrile	1:2	3:1
Phenyl vinyl sulfone	1.6:1	only 4-
Ethyl propiolate	4:1	only 4-

a) All reactions were carried out in chloroform at 63°.
b) Each regioisomer was formed as a mixture of cis and trans stereoisomers.

Both nitrones produce the expected 5-substituted adduct with the conjugated, relatively electron-rich, styrene, but with electron-deficient dipolarophiles, the amount of 4-substituted adduct increases roughly as the electron-deficiency of the dipolarophile increases. In general, the more electron-rich C, C-dicyclopropyl-N-methyl nitrone gives more of the 4-substituted adducts than are formed from the monocyclopropyl compound. In fact, C, C-dicyclopropyl-N-methyl nitrone shows complete "reversal of regioselectivity" in cycloadditions to the very electron-deficient phenyl vinyl sulfone and methyl propiolate. Because of the high-lying HOMO and LUMO of C, C-dicyclopropyl-N-methylnitrone, the dipole HOMO-dipolarophile LUMO interaction becomes so much more important than the dipolarophile HOMO-dipole LUMO interaction that the former completely dominates the reactions and leads to the formation of only the 4-substituted adducts.

In all reactions with dipolarophiles, C-cyclopropyl-N-methyl nitrone is more reactive than C,C-dicyclopropyl-N-methyl nitrone. The reverse is expected on the basis of electronic factors only, but the approach of 2 to the dipolarophile is more sterically hindered than the approach of 1. This steric effect does not prevent formation of the more hindered adduct, however.

The results of this work suggest that when the dipole is made sufficiently electron-rich and the dipolarophile sufficiently electron-deficient, the regioselectivity of nitrone cycloadditions is controlled mainly by electronic considerations rather than steric factors.

Acknowledgement. We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this research and to Nelson G. Rondan for helpful discussions.

References and Notes

(*1*) (*a*) Taken in part from Ph.D. Dissertation of A. Z. B., Louisiana State University, Baton Rouge, 1980; (*b*) Address correspondence to the University of Pittsburgh.

(*2*) R. Huisgen, R. Grashey, and J. Sauer, in "The Chemistry of Alkenes", S. Patai, ed., Interscience, London, 1964, pp 806-878.

(*3*) H. Seidl, R. Huisgen, R. Knorr, Chem. Ber., 102, 904 (1969).

(*4*) R. Huisgen, H. Seidl, and J. Wulff, Chem. Ber., 102, 915 (1969).

(*5*) (*a*) K. N. Houk, J. Sims, R. E. Duke, Jr., R. W. Strozier, and J. K. George, J. Am. Chem. Soc., 95, 7287 (1973); (*b*) K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, J. Am. Chem. Soc., 95, 7301 (1973).

(*6*) J. Sims and K. N. Houk, J. Am. Chem. Soc., 95, 5798 (1973).

(*7*) K. N. Houk, A. Bimanand, D. Mukherjee, J. Sims, Y. M. Chang, D. C. Kaufman, L. N. Domelsmith, Heterocycles, 7, 293 (1977).

(*8*) All new compounds gave spectral data and elemental analysis or accurate masses in accord with the assigned structures. Salient spectral data: 1; nmr, 0.52-1.27 δ(4H, cyclopropyl) 1.97-2.54 δ(1H, cyclopropyl methine), 3.66 δ(3H, CH_3), 6.32 δ (1H, d, J=8.3 Hz); ir, 1622, 1202 cm^{-1}. 2: nmr, 0.63-2.54 δ(10H, cyclopropyl), 3.92 δ (3H, CH_3); ir, 1565, 1200 cm^{-1}.

(*9*) J. Hamer and A. Macaluso, Chem. Rev., 64, 473 (1964).

(*10*) D. Mukherjee, L. N. Domelsmith, and K. N. Houk, J. Am. Chem. Soc., 100, 1954 (1978).

(*11*) (*a*) P. A. S. Smith and J. E. Robertson, J. Am. Chem. Soc., 84, 1197 (1962); (*b*) E. Buchler, J. Org. Chem., 32, 261 (1976).

(*12*) A. de Meijere, Angew. Chem. Int. Ed. Engl., 18, 809 (1979).

(Received in USA 9 September 1982)