Intramolecular Nitrone–Quinone Cycloaddition. Formation of Isomeric Isoxazolidines by Kinetic and Thermodynamic Control

Arthur G. Schultz* and Wayne G. McMahon

Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12180-3590

Rudolph K. Kullnig

Sterling-Winthrop Research Institute, Rensselaer, New York 12144

Received April 7, 1987

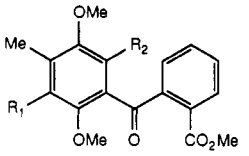
Cyclization of nitrone **5a** occurs at 25 °C to give isoxazolidine **6a**; **6a** is unstable at higher reaction temperatures and rearranges to isoxazolidine **7a** presumably via a 1,3-dipolar cycloreversion to regenerate **5a**. Structural assignments for **6a** and **7a** were made by X-ray diffraction analyses. Only the linearly fused isoxazolidine **7b** was obtained by cyclization of nitrone **5b**. Isoxazolidine **7b** is stable in refluxing benzene but in refluxing methanol undergoes elimination of *N*-methylhydroxylamine to give the anthraquinone **8**. The intermolecular cycloaddition of *C*-phenyl-*N*-methylnitrone (**10**) to benzoquinone (**9a**) or 2,6-dimethylbenzoquinone (**9b**) in the temperature range 25–170 °C could not be detected.

The inter- and intramolecular nitrone to olefin cycloaddition represents a versatile method for preparation of the isoxazolidine ring system.[1] While charge-transfer complexes between certain heterocyclic nitrones and tetrachlorobenzoquinone and tetracyanobenzoquinone are known,[2] cycloadditions of nitrones to 1,4-benzoquinones have not been reported. In this paper, we present the first study of the inter- and intramolecular reactivity of *N*-methylnitrones with 1,4-benzoquinones.[3]

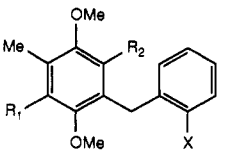
Results and Discussion

Preparation of Substrates for Cyclization Studies. Quinone aldehydes **3a** and **3b** were prepared via the Friedel–Crafts acylation[4] of 1,4-dimethoxy-2,6-dimethylbenzene[5] and 1,4-dimethoxy-2,3-dimethylbenzene[5] with monomethyl phthalate[6] in refluxing trifluoroacetic anhydride.[7] Reduction of keto ester **1a** with zinc dust and cupric sulfate in aqueous sodium hydroxide solution[4a] gave the benzoic acid derivative **2a** in 80% yield. Analogous reduction of **1b** provided lactone **4** and only trace amounts of the desired **2d**. However, hydrogenolysis of the benzylic C–O bond of **4** occurred smoothly with palladium on carbon catalysis to give **2d** in 74% yield.

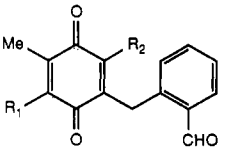
Reduction of **2a** and **2d** with lithium aluminum hydride gave **2b** and **2e**, respectively, and these alcohols were oxidized to aldehydes **2c** and **2f** with pyridinium chlorochromate (PCC).[8] Finally, ceric ammonium nitrate oxidations[9] of **2c** and **2f** provided the bright yellow crystalline quinone aldehydes **3a** and **3b** in excellent yields.



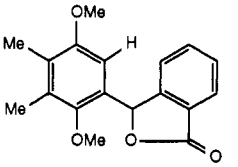
1a, R_1 = H; R_2 = Me
b, R_1 = Me; R_2 = H



2a, R_1 = H; R_2 = Me; X = CO_2H
b, R_1 = H; R_2 = Me; X = CH_2OH
c, R_1 = H; R_2 = Me; X = CHO
d, R_1 = Me; R_2 = H; X = CO_2H
e, R_1 = Me; R_2 = H; X = CH_2OH
f, R_1 = Me; R_2 = H; X = CHO



3a, R_1 = H; R_2 = Me
b, R_1 = Me; R_2 = H



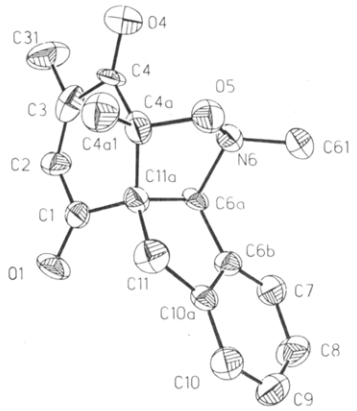
4

Nitrone–Quinone Cycloaddition Studies. Reaction of *N*-methylhydroxylamine with quinone aldehyde **3a** in tetrahydrofuran solution in the presence of anhydrous magnesium sulfate occurred at room temperature to give a yellow crystalline compound (mp 123–125 °C dec) in 65% isolated yield. This material was unstable at higher reaction temperatures and rearranged to an isomeric yellow crystalline compound (mp 159–160 °C) in refluxing methanol (14 h; 81% yield) or refluxing benzene solution (8 h; quantitative yield). Both products gave chemical ionization mass spectra, ^1H and ^{13}C NMR spectra, and combustion analyses that were compatible with isoxazolidine structures **6a** and **7a** (Scheme I). Unique assignments of structure could only be made by X-ray diffraction analyses; the molecular structures of the product of kinetic control, **6a**, and the isomerization product, **7a**, are shown in Figures 1 and 2, respectively.

A sealed-tube NMR experiment was carried out in an attempt to observe nitrone **5a**, the presumed intermediate in the conversion of **3a** to **6a** and **7a**. Quinone aldehyde **3a** in benzene-d_6 was heated to 75 °C and periodically monitored by ^1H NMR (200 MHz) spectroscopy. Only the gradual accumulation of **6a** at the expense of **3a** was observed, with no detectable intermediates (31% conversion after 90 min).

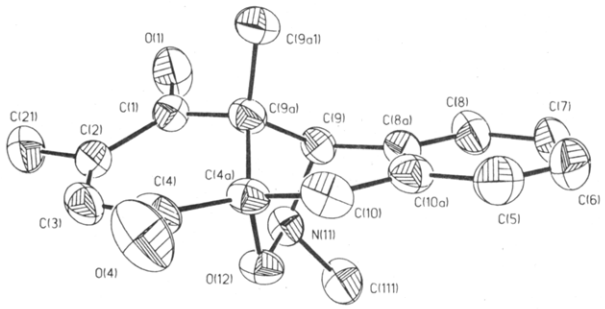
(1) (a) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*, Vol. 2; Padwa, A., Ed.; Wiley: New York, 1984; pp 83–168. (b) For a recent application of the intramolecular nitrone cycloaddition, see: LeBel, N. A.; Caprathe, B. W. *J. Org. Chem.* **1985**, *50*, 3938.
(2) Nour-el-Din, A. M.; Mourad, A. E. *Monatsh. Chem.* **1983**, *114*, 211 and references cited therein.
(3) For rearrangements of 2-(azidoalkyl)-1,4-benzoquinones, see: Schultz, A. G.; McMahon, W. G. *J. Org. Chem.* **1984**, *49*, 1676.
(4) For related examples, see (a) Fieser, L. F.; Hershberg, F. B. *J. Am. Chem. Soc.* **1940**, *62*, 49. (b) Fieser, L. F.; Gates, M. D., Jr.; Kilmer, G. W. *J. Am. Chem. Soc.* **1940**, *62*, 2966.
(5) (a) Birkinshaw, J. H.; Raistrick, H. *Biochem. J.* **1932**, *26*, 441. (b) Smith, L. I.; Austin, F. L. *J. Am. Chem. Soc.* **1942**, *64*, 528.
(6) (a) Eliel, E. L.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1949**, *71*, 2251. (b) Höfle, G.; Steglich, W. *Synthesis* **1972**, 619.
(7) (a) Marsh, J. P., Jr.; Iwamoto, R. H.; Goodman, L. *J. Chem. Soc. D* **1968**, 589. (b) Wong, C. M.; Popien, D.; Schwenk, R.; Te Raa, J. *Can. J. Chem.* **1971**, *49*, 2712.
(8) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(9) Jacob, P., III; Callery, P. S.; Shulgin, A. T.; Castagnoli, N., Jr. *J. Org. Chem.* **1976**, *41*, 3627.

0022-3263/87/1952-3905$01.50/0



C(1)-O(1)	1.204(8)	C(1)-C(2)	1.480(9)
C(1)-C(11a)	1.520(8)	C(2)-C(3)	1.313(8)
C(3)-C(31)	1.528(11)	C(3)-C(4)	1.510(11)
C(4)-O(4)	1.192(8)	C(4)-C(4a)	1.563(10)
C(4a)-C(4a1)	1.530(7)	C(4a)-O(5)	1.425(7)
C(4a)-C(11a)	1.530(6)	O(5)-N(6)	1.483(5)
N(6)-C(61)	1.457(8)	N(6)-C(6a)	1.494(7)
C(6a)-C(6b)	1.526(7)	C(6a)-C(11a)	1.571(5)
C(6b)-C(7)	1.377(6)	C(6b)-C(10a)	1.391(7)
C(7)-C(8)	1.384(8)	C(8)-C(9)	1.387(7)
C(9)-C(10)	1.382(7)	C(10)-C(10a)	1.371(8)
C(10a)-C(11)	1.509(7)	C(11)-C(11a)	1.557(6) Å

Figure 1. Molecular structure and bond lengths of **6a**.



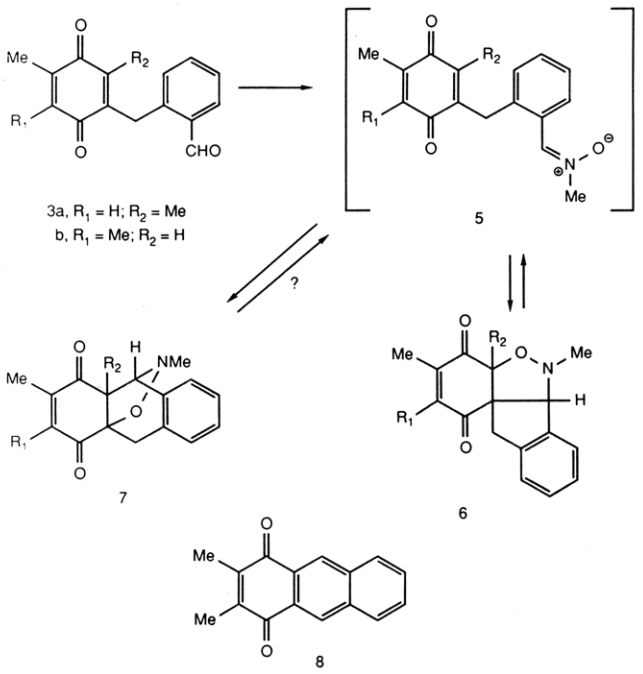
C(1)-O(1)	1.208(2)	C(1)-C(2)	1.491(3)
C(1)-C(9a)	1.533(3)	C(2)-C(21)	1.503(3)
C(2)-C(3)	1.330(3)	C(3)-C(4)	1.476(3)
C(4)-O(4)	1.201(2)	C(4)-C(4a)	1.519(3)
C(4a)-C(9a)	1.545(2)	C(4a)-C(10)	1.513(3)
C(4a)-O(12)	1.443(2)	C(5)-C(6)	1.381(3)
C(5)-C(10a)	1.388(3)	C(6)-C(7)	1.375(3)
C(7)-C(8)	1.394(3)	C(8)-C(8a)	1.384(3)
C(8a)-C(9)	1.509(3)	C(8a)-C(10a)	1.405(2)
C(9)-C(9a)	1.531(2)	C(9)-N(11)	1.480(2)
C(9a)-C(9a1)	1.529(3)	C(10)-C(10a)	1.512(3)
N(11)-C(111)	1.452(2)	N(11)-O(12)	1.492(2) Å

Figure 2. Molecular structure and bond lengths of **7a**.

The isomerization of **6a** to **7a** most likely occurs by a 1,3-dipolar cycloreversion[10] to regenerate **5a**. Retrograde reactions previously have been observed for both intermolecular[11a] and intramolecular[11b] nitrone–olefin cycloadditions. Furthermore, LeBel and co-workers have provided an explanation of the variable distribution of isomeric isoxazolidines resulting from nitrone cycloadditions.[11c] The rationale is based on a consideration of transition states resulting from both syn and anti configurations of the intermediate nitrone.

Only the linearly fused isoxazolidine **7b** (73% yield) together with anthraquinone **8** (4%)[12] was obtained from cyclization of nitrone **5b** at room temperature. Isoxazolidine **7b** was stable in refluxing benzene solution for at least 12 h but in refluxing methanol solution (20 h) underwent elimination of the elements of *N*-methylhydroxylamine to give **8** in quantitative yield.[13]

Scheme I



The assignment of structure for **7b** rests primarily on the chemical shift of δ 3.32 for the proton at C(9a), which is typical for a methine proton adjacent to a carbonyl group. This resonance is ~1.5 ppm upfield from that expected of a methine proton adjacent to both a carbonyl group and an oxygen atom as would be required for the proton at C(4a) in **6b**. Protons at C(9) and C(9a) in **7b** appear as singlets because of the dihedral angle of ~80° for H–C(9)–C(9a)–H estimated from a consideration of molecular models of **7b**.

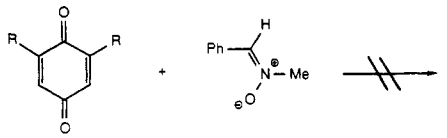
Chemical reactivity data are consistent with the assignment of structure **7b** to the substance obtained from cyclization of **5b**. Isoxazolidine **6a** rearranged to **7a** in refluxing benzene, but **7b** remained unchanged in refluxing benzene. The elimination of HONHMe from **7b** in refluxing methanol presumably occurs via β-elimination of the protonated N(11); elimination of HONHMe from **6b** would require a skeletal rearrangement.

The dramatic effect of the C(3) methyl substituent (R_2 = Me) on the rate of cyclization to isoxazolidines of type **7** presumably is of steric origin. Molecular models indicate the existence of steric crowding between the C(3) methyl substituent and the nitrone aryl group in the transition state for the conversion of **5a** to **7a**. No serious steric interactions are encountered in the transition state leading to **6a**.

The ease with which nitrones **5a** and **5b** underwent intramolecular cycloaddition suggested that intermolecular cycloaddition of nitrones with benzoquinones might be possible. However, attempted reaction of nitrone **10**[14,15] with an equivalent amount of benzoquinone (**9a**) or 2,6-dimethylbenzoquinone (**9b**) failed in the temperature range 25–140 °C; only hydrocarbon solvents were investigated (1 M, benzene, toluene, and xylene) and only unreacted starting materials were observed by ^{1}H NMR spectroscopy or by analysis of the reaction mixtures by thin layer

(10) Bianchi, G.; De Micheli, C.; Gandolfi, R. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 721.
(11) (a) Delpierre, G. R.; Lamchen, M. *J. Chem. Soc.* **1963**, 4693. (b) LeBel, N. A.; Lajiness, T. A. *Tetrahedron Lett.* **1966**, 2173. (c) LeBel, N. A.; Post, M. E.; Whang, J. J. *J. Am. Chem. Soc.* **1964**, *86*, 3759.
(12) Serpaud, B.; LePage, Y. *Bull. Soc. Chim. Fr.* **1977**, 539.
(13) For a related elimination, see: Winterfeldt, E.; Krohn, W.; Stracke, H.-U. *Chem. Ber.* **1969**, *102*, 2346.
(14) Buehler, E.; Brown, G. B. *J. Org. Chem.* **1967**, *32*, 265.
(15) *C*-Phenyl-*N*-methylnitrone (**10**) was obtained as a colorless solid: mp 82–83 °C (lit.[14] mp 82–83 °C).

chromatography. Furthermore, cycloaddition was not observed even when quinone **9a** or **9b** was heated in a melt with an equimolar amount of **10** in a sealed tube at 170 °C.



9a, R = H
b, R = Me

10

The failure to detect products of intermolecular cycloaddition between nitrone **10** and benzoquinones is interesting in light of reports of cycloaddition of phenyl azide to quinones in benzene solution.[16] It is possible that an unfavorable equilibrium exists between nitrone **10** and cycloadduct, which precludes detection by ^{1}H NMR spectroscopy. Such is the case for triphenylnitrone, which does not give a cycloaddition product with dimethyl fumarate because of a favored cycloreversion.[17]

Experimental Section

^{1}H NMR spectra were recorded on either a Varian XL-200 (200 MHz) or Hitachi-Perkin Elmer R-600 (60 MHz) instrument ($CDCl_3$ solvent, Me_4Si internal standard). ^{13}C NMR spectra were recorded on either the Varian XL-200 or an IBM WP-100 instrument. Infrared spectra were recorded on either Perkin-Elmer 198 or 137 spectrometers (polystyrene standard). Mass spectra were recorded on either a Hewlett-Packard HP-5987A mass spectrometer (chemical ionization, electron impact) or a Hitachi-Perkin Elmer RMU-6E mass spectrometer (electron impact). Ultraviolet spectra were recorded on a Perkin-Elmer UV–vis 552 spectrophotometer. Melting points were measured on a Thomas Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by either Spang Microanalytical Laboratories, Eagle Harbor, MI, or Galbraith Laboratories, Knoxville, TN. X-ray diffraction data were obtained on a Nicolet P3F single-crystal diffractometer, using Cu Kα (λ = 1.5418 Å) radiation.

Tetrahydrofuran was dried by distillation in the presence of potassium metal, under a nitrogen atmosphere, using benzophenone ketyl as the indicator. Dimethylformamide was distilled under reduced pressure from calcium hydride and stored over 4-Å molecular sieves (activated at 110 °C for 12 h). Benzene, toluene, and xylenes were dried over calcium hydride and distilled at atmospheric pressure.

With the exception of oxidations, all reactions were carried out in vessels that were flame-dried and blanketed with a positive pressure of dry nitrogen. All thermolyses were conducted in the dark. Flash column chromatography followed the procedure described by Still.[18] Preparative high performance liquid chromatography (HPLC) was performed on a Waters Prep-500 chromatograph with PrepPAK-500 silica gel cartridges.

2-[2-(Methoxycarbonyl)benzoyl]-1,4-dimethoxy-3,5-dimethylbenzene (1a). A solution of 1,4-dimethoxy-2,6-dimethylbenzene[5] (7.42 g, 44.6 mmol) and monomethyl phthalate (1.1 equiv) in trifluoroacetic anhydride was refluxed for 10 h. Evaporation and preparative HPLC (hexane–ethyl acetate, 5:1) gave **1a** (colorless oil, 9.87 g, 67%): ^{1}H NMR ($CDCl_3$) δ 2.21 (s, 3 H), 2.35 (s, 3 H), 3.55 (s, 3 H), 3.70 (s, 3 H), 3.79 (s, 3 H), 6.59 (s, 1 H), 7.3–7.7 (overlapping multiplets, 4 H); IR (film) 2950, 2850, 1728, 1665 cm^{-1}; chemical ionization mass spectrum, m/z 329 (M^+ + 1).

Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.49; H, 6.15. Found: C, 69.37; H, 6.14.

2-[2-(Methoxycarbonyl)benzoyl]-1,4-dimethoxy-5,6-dimethylbenzene (1b). 1,4-Dimethoxy-2,3-dimethylbenzene[5] (22-h reaction time) afforded **1b** (82%): ^{1}H NMR ($CDCl_3$) δ 2.18 (s, 3 H), 2.20 (s, 3 H), 3.32 (s, 3 H), 3.71 (s, 3 H), 3.82 (s, 3 H), 7.13 (s, 1 H), 7.4–7.7 (overlapping multiplets, 3 H), 7.89 (m, 1 H); IR (film) 3060, 2995, 2950, 2850, 1720, 1650, 1595 cm^{-1}; electron impact mass spectrum, m/z 328 (M^+).

Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.49; H, 6.15. Found: C, 69.57; H, 6.30.

Preparation of 2a and 2d by Reduction–Saponification of Keto Esters. General Procedure.[4a] To a stirred mixture of the keto ester in water (~0.1 M) was added sodium hydroxide (5 equiv), zinc dust (3 equiv), and cupric sulfate (0.1 equiv), after which the mixture was heated to reflux for 18 h. The crude mixture was filtered, acidified with 6 N hydrochloric acid, and extracted with dichloromethane (3×). The combined extracts were dried ($MgSO_4$) and concentrated to give the crude product.

2-(2-Carboxybenzyl)-1,4-dimethoxy-3,5-dimethylbenzene (2a). Keto ester **1a** (3.90 g, 11.9 mmol) gave a tan solid, which was washed with hexane to afford a colorless solid (2.85 g, 80%; mp 157–159 °C, with sublimation): ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 3 H), 2.34 (s, 3 H), 3.68 (s, 3 H), 3.71 (s, 3 H), 4.48 (s, 2 H), 6.62 (s, 1 H), 6.82 (m, 1 H), 7.27 (m, 2 H), 8.08 (m, 1 H), acid proton not observed; IR (KBr pellet) 2950 (br), 1675, 1595, 1570 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 301 (M^+ + 1, 6.14), 300 (M^+ – H, 11.8), 283 (M^+ – 17).

Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.97; H, 6.72. Found: C, 71.80; H, 6.65.

Attempted Reduction–Saponification of Keto Ester 1b. Preparation of 2-(3-Phthalidyl)-1,4-dimethoxy-5,6-dimethylbenzene (4). Keto ester **1b** (867 mg, 2.67 mmol) gave a tan solid. Washing with hexane afforded a colorless solid (678 mg, 87%; mp 142–142.5 °C): ^{1}H NMR ($CDCl_3$) δ 2.14 (s, 3 H), 2.26 (s, 3 H), 3.62 (s, 3 H), 3.79 (s, 3 H), 6.24 (s, 1 H), 6.79 (s, 1 H), 7.4–8.1 (overlapping multiplets, 4 H); IR (KBr pellet) 2950, 2930, 2850, 1760, 1595 cm^{-1}; chemical ionization mass spectrum, m/z 299 (M^+ + 1).

Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.46; H, 6.09. Found: C, 72.52; H, 6.18.

Hydrogenolysis of Phthalide 4. Preparation of 2-(2-Carboxybenzyl)-1,4-dimethoxy-5,6-dimethylbenzene (2d). To a stirred solution of phthalide **4** (355 mg, 1.19 mmol) in ethyl acetate (10 mL) and glacial acetic acid (10 mL) was added 5% palladium on carbon (120 mg) and 70% perchloric acid (10 drops), after which the mixture was hydrogenated at 1 atm for 25 h. The mixture was filtered through Celite, combined with hexane (100 mL), and concentrated to afford a colorless solid (264 mg, 74%; mp 125–126 °C): ^{1}H NMR ($CDCl_3$) δ 2.13 (s, 3 H), 2.22 (s, 3 H), 3.60 (s, 3 H), 3.67 (s, 3 H), 4.45 (s, 2 H), 6.40 (s, 1 H), 7.1–7.6 (overlapping multiplets, 3 H), 8.03 (m, 1 H), acid proton not observed; IR (KBr pellet) 2930 (br), 1675 (br) cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 301 (M^+ + 1, 6.71), 300 (M^+, 21.7), 283 (M^+ – 17, 100).

Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.97; H, 6.72. Found: C, 71.77; H, 6.78.

Preparation of 2b and 2e by Reduction of Carboxylic Acids. General Procedure. To a stirred solution of the acid in tetrahydrofuran (~0.25 M) was carefully added $LiAlH_4$ (2.2 equiv) at room temperature. After evolution of hydrogen was complete, the mixture was heated to reflux for 6 h. Excess hydride was destroyed with saturated sodium sulfate solution at room temperature. The mixture was extracted with ether (3×). After drying ($MgSO_4$) the combined extracts were concentrated to give the crude product.

2-[2-(Hydroxymethyl)benzyl]-1,4-dimethoxy-3,5-dimethylbenzene (2b). Carboxylic acid **2a** (2.73 g, 9.09 mmol) gave a pale yellow semisolid, which on washing with hexane afforded a colorless solid (2.03 g, 78%; mp 91–92 °C): ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3 H), 2.33 (s, 3 H), 3.68 (s, 3 H), 3.69 (s, 3 H), 4.06 (s, 2 H), 3.74 (br s, 1 H), 4.85 (s, 2 H), 6.61 (s, 1 H), 6.75 (m, 1 H), 7.16 (m, 2 H), 7.37 (m, 1 H); IR (KBr pellet) 3380 (br), 2920 (br), 2830, 1605 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 287 (M^+ + 1, 2.79), 286 (M^+, 13.9), 269 (M^+ – 17, 100).

Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.48; H, 7.76. Found: C, 75.29; H, 7.81.

2-[2-(Hydroxymethyl)benzyl]-1,4-dimethoxy-5,6-dimethylbenzene. Carboxylic acid **2d** (138 mg, 0.459 mmol) gave a yellow oil; flash column chromatography (hexane–ethyl acetate, 5:1) afforded a colorless oil (113 mg, 86%): ^{1}H NMR ($CDCl_3$)

(16) (a) Wolff, L. *Liebigs Ann. Chem.* **1912**, *394*, 68, 86. (b) Wolff, L. *Liebigs Ann. Chem.* **1913**, *399*, 274.

(17) However, triphenylnitrone does give the corresponding isoxazolidine with dimethyl maleate: Huisgen, R.; Hauck, H.; Grashey, R.; Siedl, H. *Chem. Ber.* **1969**, *102*, 736.

(18) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

δ 2.12 (s, 3 H), 2.15 (br s, 1 H), 2.22 (s, 3 H), 3.48 (s, 3 H), 3.66 (s, 3 H), 4.09 (s, 2 H), 4.72 (br s, 2 H), 6.40 (s, 1 H), 7.1–7.3 (overlapping multiplets, 4 H); IR (film) 3405 (br), 2940, 2840 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 287 ($M^+ + 1$, 2.39), 286 (M^+, 11.7), 369 ($M^+ - 17$, 100).

Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.48; H, 7.76. Found: C, 75.60; H, 8.02.

Preparation of 2c and 2f by Pyridinium Chlorochromate (PCC) Oxidations of Primary Alcohols. General Procedure. To a stirred suspension of pyridinium chlorochromate[8] in dichloromethane (~1.5 M) was added a solution of the alcohol (0.45 equiv) in dichloromethane (0.75 M) at room temperature. After 1.0 h, an equal volume of ether was added and the supernatant liquid was decanted. The black residue was washed with ether (3×), after which the combined extracts were filtered through Florisil and concentrated to give the crude product.

2-(2-Formylbenzyl)-1,4-dimethoxy-3,5-dimethylbenzene (2c). Alcohol **2b** (772 mg, 2.70 mmol) gave a colorless solid (738 mg, 96%; mp 70.5–71 °C): ^1H NMR ($CDCl_3$) δ 2.09 (s, 3 H), 2.32 (s, 3 H), 3.66 (s, 3 H), 3.68 (s, 3 H), 4.47 (s, 2 H), 6.60 (s, 1 H), 6.84 (m, 1 H), 7.34 (m, 2 H), 7.88 (m, 1 H), 10.44 (s, 1 H); IR (KBr) pellet 2935, 2835, 2740, 1690, 1598 cm^{-1}; chemical ionization mass spectrum, m/z 285 ($M^+ + 1$).

Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.02; H, 7.10. Found: C, 76.08; H, 7.17.

2-(2-Formylbenzyl)-1,4-dimethoxy-5,6-dimethylbenzene (2f). Alcohol **2e** (113 mg, 0.395 mmol) gave a yellow oil. Flash column chromatography (hexane–ethyl acetate, 7.5:1) afforded a colorless oil (83 mg, 74%): ^1H NMR ($CDCl_3$) δ 2.12 (s, 3 H), 2.23 (s, 3 H), 3.65 (overlapping singlets, 6 H), 4.46 (s, 2 H), 6.32 (s, 1 H), 7.2–8.2 (overlapping multiplets, 4 H), 10.34 (s, 1 H); IR (film) 2930, 2830, 1690 cm^{-1}; electron impact mass spectrum, m/z 284 (M^+).

Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.02; H, 7.10. Found: C, 76.27; H, 7.26.

Preparation of 3a and 3b by Ceric Ammonium Nitrate (CAN) Oxidations[9] of 2c and 2f. General Procedure. To a stirred solution of the 1,4-dimethoxybenzene in acetonitrile (~0.1 M solution) was added a solution of ceric ammonium nitrate (2.2 equiv) in water (0.5 M solution), over several minutes, at room temperature. After 1 h, the mixture was combined with an equal volume of water and extracted with dichloromethane (3×). The combined extracts were dried ($MgSO_4$) and concentrated to give the crude product.

2-(2-Formylbenzyl)-3,5-dimethyl-1,4-benzoquinone (3a). Dimethoxybenzene **2c** (688 mg, 2.42 mmol) gave a bright yellow solid (611 mg, 100%; mp 136–137 °C): ^1H NMR ($CDCl_3$) δ 1.99 (s, 3 H), 2.09 (d, 3 H, J = 1.6 Hz), 4.38 (s, 2 H), 6.63 (d, 1 H, J = 1.6 Hz), 7.00 (m, 1 H), 7.44 (overlapping multiplets, 2 H), 7.83 (overlapping multiplets, 1 H), 10.31 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 12.5, 15.8, 28.2, 126.7, 128.6, 133.0, 133.6, 133.7, 133.9, 139.9, 142.1, 142.9, 145.6, 186.8, 187.8, 192.9; IR (KBr pellet) 2838, 2740, 1692, 1649, 1622, 1600, 1570 cm^{-1}; chemical ionization mass spectrum, m/z 255 ($M^+ + 1$); UV (MeOH) λ_{max} (nm) 252 (ε 14 000), 210 (ε 9100).

Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.56; H, 5.56. Found: C, 75.34; H, 5.65.

2-(2-Formylbenzyl)-5,6-dimethyl-1,4-benzoquinone (3b). Dimethoxybenzene **2f** (83 mg, 0.29 mmol) gave an orange solid. Flash column chromatography (hexane–ethyl acetate, 5:1) afforded a bright yellow solid (67 mg, 91%; mp 63–64 °C): ^1H NMR ($CDCl_3$) δ 1.99 (d, 3 H, J = 1.2 Hz), 2.07 (d, 3 H, J = 1.2 Hz), 4.18 (d, 2 H, J = 1.8 Hz), 5.99 (t, 1 H, J = 1.8 Hz), 7.30 (m, 1 H), 7.56 (overlapping multiplets, 2 H), 7.86 (m, 1 H), 10.09 (s, 1 H); IR (KBr pellet) 2940, 2850, 1690, 1635 (br), 1600 cm^{-1}; chemical ionization mass spectrum, m/z 255 ($M^+ + 1$).

Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.56; H, 5.56. Found: C, 75.46; H, 5.64.

Preparation of 6a,11-Dihydro-3,4a,6-trimethyl-1*H*,6*H*-benzo[*d*]indeno[1,2-*c*]isoxazole-1,4(4a*H*)-dione (6a). To a stirred solution of quinone aldehyde **3a** (311 mg, 1.22 mmol) in tetrahydrofuran (2.0 mL) were added *N*-methylhydroxylamine (120 mg, 2.55 mmol) and magnesium sulfate (200 mg), after which the mixture was stirred at room temperature. Periodic monitoring of the reaction by TLC (SiO_2; hexane–ethyl acetate, 3:2) indicated the formation of one new product. After 2.0 h, additional *N*-methylhydroxylamine (120 mg) was added, after which the mixture was stirred for an additional 1.0 h. The reaction mixture was concentrated to give an orange semisolid. Flash column chromatography (hexane–ethyl acetate, 10:1) gave a bright yellow solid (224 mg, 65%; mp 123–125 °C, with decomposition): ^1H NMR ($CDCl_3$) δ 1.39 (s, 3 H), 2.11 (d, 3 H, J = 1.6 Hz), 2.56 (s, 3 H), 3.25 (d, 1 H, J = 16.6 Hz), 3.66 (d, 1 H, J = 16.6 Hz), 4.82 (s, 1 H), 6.77 (d, 1 H, J = 1.6 Hz), 7.1–7.4 (overlapping multiplets, 4 H); ^1H NMR (C_6D_6) δ 1.12 (s, 3 H), 1.66 (d, 3 H, J = 1.4 Hz), 2.35 (s, 3 H), 2.96 (d, 1 H, J = 16.8 Hz), 3.69 (d, 1 H, J = 16.8 Hz), 4.52 (s, 1 H), 6.30 (d, 1 H, J = 1.4 Hz), 6.9–7.2 (overlapping multiplets, 4 H); ^{13}C NMR ($CDCl_3$) δ 16.4, 18.4, 35.6, 41.7, 72.9, 81.0, 86.2, 124.4, 126.2, 126.6, 129.3, 135.7, 137.3, 144.0, 148.9, 196.3, 199.7; IR (KBr pellet) 2955, 2920, 2890, 1675 (br), 1645 cm^{-1}; chemical ionization mass spectrum, m/z 284 ($M^+ + 1$); UV (MeOH) λ_{max} (nm) 240 (ε 6700).

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.06; N, 4.94. Found: C, 71.93; H, 6.03; N, 4.81.

Thermal Isomerization of 6a. Preparation of 9,10-Dihydro-2,9a,11-trimethyl-4*H*-4a,9-(epoxyimino)anthracene-1,4(9a*H*)-dione (7a). A stirred solution of isoxazolidine **6a** (75 mg, 0.26 mmol) in methanol (25 mL) was heated to reflux temperature for 14 h. Periodic monitoring of the reaction mixture by TLC (SiO_2; hexane–ethyl acetate, 3:2) indicated the formation of a new product of R_f higher than **6a**. ^1H NMR analysis of the concentrated reaction mixture indicated the presence of **7a** (93%), together with **6a** (7%). Flash column chromatography (hexane–ethyl acetate, 10:1) gave a bright yellow solid (61 mg, 81%; mp 159–160 °C): ^1H NMR ($CDCl_3$) δ 1.14 (s, 3 H), 2.13 (d, 3 H, J = 1.6 Hz), 2.27 (s, 3 H), 3.15 (d, 1 H, J = 20 Hz), 3.31 (d, 1 H, J = 20 Hz), 4.57 (s, 1 H), 6.76 (d, 1 H, J = 1.6 Hz), 7.1–7.5 (overlapping multiplets, 4 H); ^1H NMR (C_6D_6) δ 0.87 (s, 3 H), 1.75 (d, 3 H, J = 1.4 Hz), 2.12 (s, 3 H), 3.07 (d, 1 H, J = 18 Hz), 3.37 (d, 1 H, J = 18 Hz), 4.50 (s, 1 H), 6.42 (s, 1 H, J = 1.4 Hz), 6.7–7.2 (overlapping multiplets, 4 H); ^{13}C NMR ($CDCl_3$) δ 15.3, 16.6, 34.5, 41.0, 60.5, 72.0, 83.7, 126.4, 129.0, 129.4, 130.2, 131.0, 133.6, 135.9, 147.7, 193.6, 199.0; IR (KBr pellet) 3023, 2995, 2965, 2925, 2885, 1670 (br), 1640 cm^{-1}; chemical ionization mass spectrum, m/z 284 ($M^+ + 1$); UV (MeOH) λ_{max} (nm) 242 (ε 2200), 212 (ε 1900).

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.06; N, 4.94. Found: C, 71.91; H, 6.16; N, 4.84.

Thermal Isomerization of 6a in Benzene. A stirred solution of **6a** (2 mg) in benzene (10 mL) was heated to reflux for 8 h. ^1H NMR analysis of the crude concentrated reaction mixture indicated quantitative conversion to **7a**.

Thermal Isomerization of 6a at 75 °C in Hexadeuteriobenzene. A solution of **6a** (5 mg) in a sealed NMR tube, containing benzene-d_6 (1.0 mL), was heated to 75 °C, while in the XL-200 NMR probe. After 90 min, 31% conversion to **7a** had occurred; no intermediates were observed.

Attempted Thermal Isomerization of 7a in Methanol. A stirred solution of **7a** (5 mg) in methanol (20 mL) was heated to reflux for 18 h. ^1H NMR analysis of the crude concentrated reaction mixture indicated no isomerization.

Generation of 7b and 8. To a stirred solution of **3b** (16 mg, 0.063 mmol) in tetrahydrofuran (0.25 mL) were added *N*-methylhydroxylamine (6.5 mg, 0.14 mmol) and magnesium sulfate (10 mg), after which the mixture was stirred at room temperature. Periodic monitoring of the reaction mixture by TLC (SiO_2; hexane–ethyl acetate, 3:2) indicated the formation of two new products of R_f lower and higher than **3b**. The mixture was concentrated to give an orange semisolid. Flash column chromatography (hexane–ethyl acetate, 5:1) afforded two fractions. The first fraction contained **7b** a bright yellow solid (13 mg, 73%; mp 160–165 °C, with decomposition); the second fraction contained 8, a bright yellow solid (6 mg, 4%; mp 217–219 °C; lit.[12] mp 218 °C, with sublimation).

9,10-Dihydro-2,3,11-trimethyl-4*H*-4a,9-(epoxyimino)-anthracene-1,4(9a*H*)-dione (7b): ^1H NMR ($CDCl_3$) δ 2.11 (d, 3 H, J = 1.0 Hz), 2.13 (d, 3 H, J = 1.0 Hz), 2.32 (s, 3 H), 3.17 (d, 1 H, J = 18 Hz), 3.32 (s, 1 H), 3.48 (d, 1 H, J = 18 Hz), 4.75 (s, 1 H), 7.1–7.4 (overlapping multiplets, 4 H); ^{13}C NMR ($CDCl_3$) δ 13.0, 13.9, 37.7, 37.8, 40.8, 58.7, 68.7, 79.0, 126.1, 129.0, 129.7, 133.6, 144.9, 145.6, 193.0, 203.4; IR (KBr pellet) 2985, 2925, 2880, 2850, 1660 (br), 1615 cm^{-1}; chemical ionization mass spectrum, m/z 284 ($M^+ + 1$).

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.06; N, 4.94. Found: C, 71.87; H, 6.22; N, 4.77.

2,3-Dimethyl-1,4-anthraquinone (8): ^1H NMR ($CDCl_3$) δ 2.25 (overlapping singlets, 6 H), 7.69 (m, 2 H), 8.04 (m, 2 H), 8.63 (s, 2 H); IR (KBr pellet) 1655, 1610, 1590 cm^{-1}; chemical ionization mass spectrum, m/z 237 ($M^+ + 1$).

Conversion of 7b to 8. A stirred solution of **7b** (6 mg) in methanol (10 mL) was heated to reflux for 20 h. ^1H NMR analysis of the crude concentrated reaction mixture indicated quantitative conversion to **8**. **7b** was stable in refluxing benzene solution for 12 h.

Acknowledgment. This work was supported by the National Institute of General Medical Science (GM 26568). We thank the National Science Foundation and RPI for funds for the purchase of the Nicolet X-ray diffractometer.

Registry No. **1a**, 109243-48-3; **1b**, 109243-49-4; **2a**, 109243-50-7; **2b**, 109243-51-8; **2c**, 109243-52-9; **2d**, 109243-53-0; **2e**, 109243-54-1; **2f**, 109243-55-2; **3a**, 109243-56-3; **3b**, 109243-57-4; **4**, 109243-58-5; **6a**, 109243-59-6; **7a**, 109243-60-9; **7b**, 109243-61-0; **8**, 65869-73-0; **9a**, 106-51-4; **9b**, 527-61-7; **10**, 3376-23-6; 1,4-dimethoxy-2,6-dimethylbenzene, 14538-50-2; 1,4-dimethoxy-2,3-dimethylbenzene, 39021-83-5; monomethyl phthalate, 4376-18-5.

Supplementary Material Available: Tables of crystal structure data, atomic coordinates, bond lengths, bond angles, anisotropic parameters, and hydrogen atom coordinates for **6a** and **7a** (8 pages). Ordering information is given on any current masthead page.

Cycloaddition of Nitrones with Allenes. An Example of Steric Control of Regiochemistry

Albert Padwa,* Donald N. Kline, Konrad F. Koehler, Michael Matzinger, and M. K. Venkatramanan

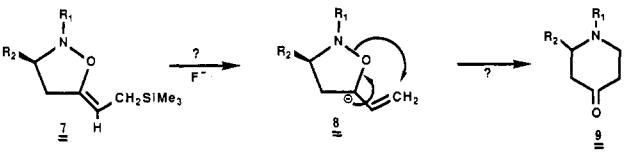
Department of Chemistry, Emory University, Atlanta, Georgia 30322

Received March 9, 1987

A study of the cycloaddition behavior of a series of electron-deficient allenes with *C*-phenyl-*N*-alkylnitrones has been carried out. The 1,3-dipolar cycloaddition proceeds in high yield with complete regiospecificity to produce 5-methylene substituted isoxazolidines. The reactions follow frontier orbital predictions. The orientation has been explained in terms of maximum orbital overlap of the nitrone HOMO-allene LUMO. In certain cases diastereomeric isoxazolidines were formed via different two-plane orientation complexes. The ratio of the diastereomers reflects the free energy difference of the two transition states. This difference comes from repulsive interactions caused by steric hindrance and attractive van der Waal forces associated with maximum π overlap of the substituent groups. The transition state that dominates in a particular case will depend on the nature of the groups attached to the N atom of the nitrone and to the dipolarophile π bond. An unusual regiochemical crossover occurred in the reaction of *N*-*tert*-butyl-*C*-phenylnitrone with methyl 2-methyl-2,3-butadienoate. In this case, the regiochemistry appears to be steric rather than stereoelectronic in origin. This contention was supported by molecular mechanics calculations.

The 1,3-dipolar cycloaddition reaction occupies a position of prominence in the arsenal of the synthetic organic chemist, as a consequence of its good yields, mild reaction conditions, high stereoselectivity, and predictability.[1] Nitrones represent a long-known and thoroughly investigated class of 1,3-dipoles.[2] Through the use of nitrone cycloaddition chemistry, numerous isoxazolidines have been prepared with excellent stereochemical control.[2] The 1,3-dipolar cycloaddition reaction has also attracted considerable attention as a convenient tool for the rapid construction of widely varied classes of natural products.[3-9]

Scheme I



The presence of a nitrogen atom within the isoxazolidine ring has made this heterocycle moiety especially attractive for the synthesis of the β-lactam ring.[10-15] The key feature of this approach generally involves a reductive cleavage of the isoxazolidine ring to give a γ-amino alcohol,[16-20]

(1) *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984.
(2) Tufariello, J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 2.
(3) Black, D. St. C.; Crozier, R. F.; Davis, V. C. *Synthesis* **1975**, *7*, 205.
(4) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396.
(5) Kametani, T.; Huang, S. D.; Nakayama, A.; Hondu, T. *J. Org. Chem.* **1982**, *47*, 2328.
(6) Oppolzer, W.; Grayson, J. I.; Wegmann, H.; Urea, M. *Tetrahedron* **1983**, *39*, 3695.
(7) Wovkulich, P. M.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 3956.
(8) Baggiolini, E. G.; Lee, H. L.; Pizzolato, G.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 6460.
(9) Deshong, P.; Leginus, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 1686.
(10) Tufariello, J. J.; Lee, G. E. *Tetrahedron Lett.* **1979**, 4359.
(11) Kametani, T.; Huang, S. P.; Nakayama, A.; Honda, T. *J. Org. Chem.* **1982**, *47*, 2328.
(12) Stevens, R. V.; Albizati, K. *J. Chem. Soc., Chem. Commun.* **1982**, 104.
(13) Baldwin, J. E.; Chan, M. F.; Gallacher, G.; Monk, P.; Prout, K. *J. Chem. Soc., Chem. Commun.* **1983**, 250.
(14) Dutta, D. K.; Boruah, R. C.; Sandhu, J. S. *Heterocycles* **1986**, *24*, 655.
(15) Baldwin, S. W.; Aube, J. *Tetrahedron Lett.* **1987**, *28*, 179.
(16) LeBel, N. A.; Post, M. E.; Whang, J. J. *J. Am. Chem. Soc.* **1964**, *86*, 3759.
(17) Kozikowski, A. P.; Chen, Y. Y. *J. Org. Chem.* **1981**, *46*, 5248.

0022-3263/87/1952-3909$01.50/0