1,3-Dipolar Cycloaddition of Nitrile Oxides to Carvone and Related Compounds

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1,3-Dipolar cycloaddition of nitrile oxides to unsaturated systems is a convenient method of preparing isoxazoline derivatives.[1] The mechanism and orientation in such cycloadditions have been studied.[2,3] The available data suggest that the orientation in such cycloadditions leads to products in which the oxygen of nitrile oxide is bonded to the more substituted carbon atom of the dissymmetric double bond. A few exceptions to this rule have been reported.[4]

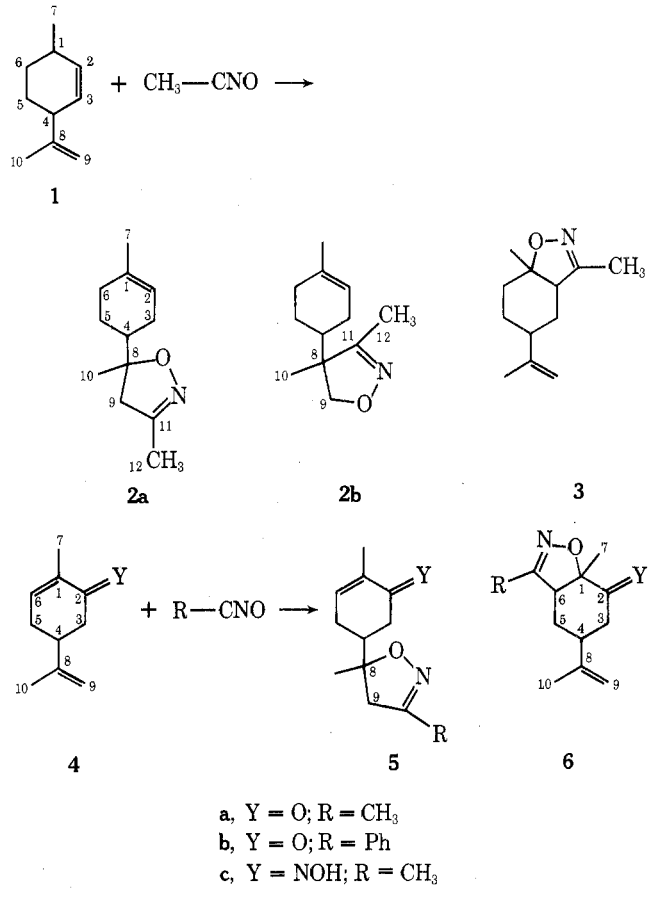
The reactivity of the dipolarophile in such additions is strongly dependent on the substituents. In general, all substituents in the dipolarophile (relative to H) strongly accelerate 1,3-dipolar cycloadditions. α,β-Unsaturated carbonyl compounds are highly reactive dipolarophiles, but the orientation of the cycloaddition does not seem to be uniform in all cases. For example, 1-acetylcyclopentene is reported to add acetonitrile oxide to give mainly the bicyclic 5-acetyl-Δ^2-isoxazoline[5] and several steroidal isoxazolines have been synthesized by cycloaddition of nitrile oxides to the Δ^{16} double bond, reportedly with conflicting orientations.[4,6-8]

Although the relative rates for the reaction of benzonitrile oxide with various dipolarophiles have been reported,[9] a direct comparison of the reactivity of an olefinic double bond with an endocyclic double bond and an isolated double bond with a conjugated double bond are not available. In continuation of our interest in synthesizing substituted isoxazolines,[10] we have studied the reactions of dipentene, carvone, and carvone oxime with nitrile oxides.

Acetonitrile oxide adds to dipentene (1) at the double bond at C-8 to give the Δ^2-isoxazoline **2** without any isomer **3** as detected by GLC. Acetonitrile oxide adds to carvone (**4a**) at both C-8 and C-1 to give a mixture of Δ^2-isoxazolines **5a** and **6a** in a ratio of 1.7:1 (Scheme I). Benzonitrile oxide, however, gave the analogous carvone derivatives **5b** and **5c**, respectively, without contamination of the isomers, **6b** or **6c**.

The structures of the Δ^2-isoxazolines **2a, 5a, 6a, 5b,** and **5c** were identified by spectroscopic data and elemental analysis. Compound **2a** has three methyl singlets at δ 1.23, 1.67, and 1.93, a vinyl proton (C-2) at δ 5.5, and two protons at δ 2.67 (C-9) whereas **3** would require an integration for two vinyl protons at C-9, upfield from δ 5.5, and **2b** would require a downfield shift for the C-9 protons.[10] Further evidence for structure **2a** as opposed to **2b** for this compound was obtained from its ^{13}C NMR spectrum. Assignments of carbon-13 chemical shifts are given in Table I. The ^{13}C resonance near 88 ppm is almost certainly that of a quaternary carbon (C-8 in **2a**, Scheme I) attached to the electronegative oxygen of the isoxazoline ring as shown by off-resonance decoupling and the absence of a nuclear Overhauser effect. Assignment of carbons 1–7 was made by analogy with the published[11a] spectrum of dipentene. Carbons 9 and 12, adjacent to the isoxazoline nitrogen, experience large downfield and upfield shifts, respectively, compared to the corresponding carbons in the oxime of 2-butanone,[11b] which seems to be the closest available analogue of the isoxazoline ring. C-1 and C-3 of the oxime stereoisomer with the OH anti to the methyl group have chemical shifts of 19.0 and 23.3 ppm, respectively. The corresponding shifts of 13.5 and 47 ppm for **2a** probably reflect the addition of C-4 and C-10 in the latter compound as well as the addition of oxygen at C-8.

Scheme I



As an interesting side issue, the ^{13}C NMR spectrum clearly shows the presence of two disastereoisomers in **2a;** double peaks (see Table I) are identifiable for C-1, C-3, C-4, C-8, C-9, C-10, and C-11 as numbered in Scheme I. The two diastereoisomers arise from approach of the acetonitrile oxide to the $\Delta^{8,9}$ double bond of the chiral dipentene molecules from bottomside or topside. The properties of the diastereoisomers were not sufficiently different to allow for separation by distillation nor even detection by GLC.

The carbonyl absorption in carvone (**4a**) at 1670 cm^{-1} (conjugated) was shifted to 1710 cm^{-1} in **6a** but remained unchanged in **5a** (1670 cm^{-1}). The NMR spectra of **5a** and **6a** verify that the isoxazoline rings are in the designated positions (Scheme I). In **5a** protons in the three methyl groups appear as singlets at δ 1.33, 1.70, and 1.91 and two protons for C-9 absorb at δ 2.67 while the vinyl proton at C-6 appears at δ 6.6. The corresponding protons in **5a, 5b,** and **5c** have chemical shifts close enough to those in **2a** to warrant the same assignment of the oxygen atom attachment to the quaternary carbon (C-8) as the ^{13}C NMR spectrum showed for **2a.** If structures for **5a, 5b,** and **5c** were analogous to **2b,** then a considerable downfield shift of protons in the $-OCH_2-$ group

Table I. Carbon-13 Chemical Shifts in 2a

Carbon	δ, ppm[a]	Carbon	δ, ppm[a]
1	134.0, 133.9[b] (s)	7	23.9[c]
2	120.1 (d)	8	88.5, 88.1 (s)
3	27.0, 26.7 (t)	9	47.4, 46.4 (t)
4	42.4, 42.3 (d)	10	24.1, 23.0[c,d]
5	23.4[c]	11	154.6, 154.4 (s)
6	30.5 (t)	12	13.5[d] (q)

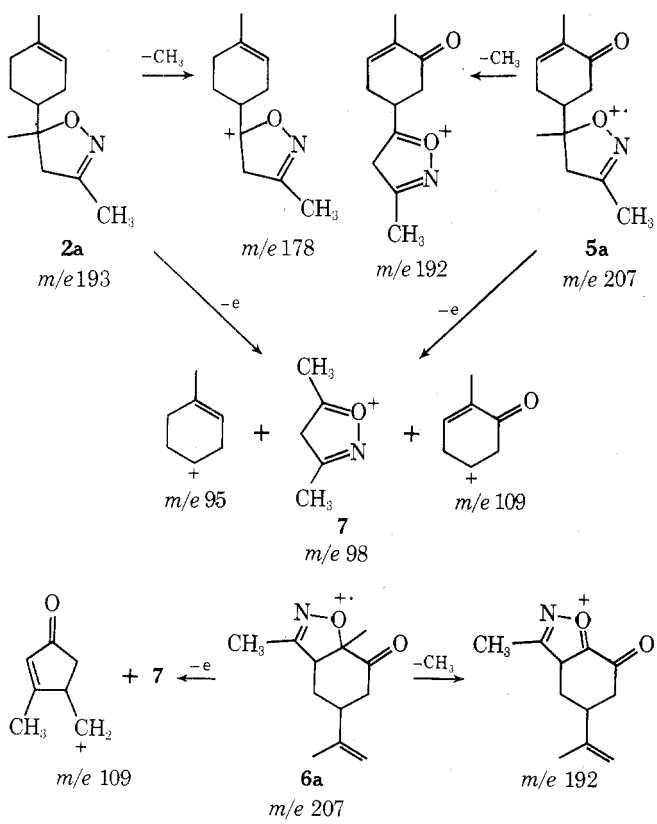
[a] Relative to Me_4Si; letters in parentheses refer to multiplicities of lines in off-resonance decoupled spectra. [b] Lines doubled owing to presence of nearly equal amounts of diastereomers. [c] Lines too badly overlapped in off-resonance decoupled spectra to determine multiplicities. [d] Tentative assignment based on the assumption that the carbon closest to the asymmetric center would exhibit different chemical shifts in the two diastereomers.

of the isoxazoline (at C-9) would be expected[10] but was not observed (Experimental Section).

The NMR spectrum of **6a** has the three corresponding singlets of methyl groups at δ 1.20, 1.70, and 1.97, a proton for C-6 at δ 3.1, and of necessity two vinyl protons for C-9 at δ 4.7. If oxygen were attached at C-6 rather than at C-1 (Scheme I) the chemical shift of the C-6 proton would have been expected[10] at no less than δ 4.7, downfield from δ 3.1.

The orientation of addition of nitrile oxides to form compounds **2a, 5a,** and **6a** as determined by ^{13}C NMR spectra for **2a** is consistent with the decomposition patterns of these compounds in the mass spectrometer. The relative abundances of the mass peaks due to $M - CH_3$ and $M - C_5H_8NO$ are more reasonable from the mechanism shown in Scheme II than they would be from **2b** and the analogous structures for **5** and **6.**

Scheme II



The relative reactivity of the two isolated double bonds in dipentene depends on the reagent. Nitrosyl chloride[12] and peroxy acids[12] add at C-1,2 but hydrogen chloride[12] adds at C-8,9. The 1,3-dipolar cycloaddition of acetonitrile oxide to dipentene occurs only at C-8,9 to give compound **2a.** In view of Firestone's work[2] it cannot be argued that this result obtains because of steric requirements, although Huisgen[3] invoked steric considerations in similar cases.

Since carvone oxime reacts with phenyl isocyanate to give a phenylcarbamate, phenyl isocyanate cannot be used in the generation of nitrile oxides from primary nitroalkanes by the Mukaiyama and Hoshino method[13] for the preparation of **5c.**

Results of the present work indicate that orientation in the addition of nitrile oxides to dipentene, carvone, and carvone oxime follows the general rule—oxygen becomes bonded to the more substituted carbon atom of an unsymmetrical double bond. Acetonitrile oxide adds to the external double bond in dipentene and to both the isolated and conjugated double bond in carvone but the less reactive benzonitrile oxide adds only to the isolated double bond in carvone and carvone oxime.

Experimental Section

Infrared spectra were measured on a Beckman IR 8 spectrophotometer and ultraviolet spectra were measured in cyclohexane using a Perkin-Elmer 402 spectrophotometer. Mass spectra were taken in a Hitachi RMU-6E double focusing mass spectrophotometer using 70 eV ionizing energy with the inlet system at 200 °C. The NMR spectra were taken on a Varian A-60A spectrometer in deuteriochloroform or carbon tetrachloride with Me_4Si as an internal standard. The ^{13}C NMR spectrum was taken on a Bruker WP-60 15.08-MHz spectrometer in 2 M $CDCl_3$ solution, reported with Me_4Si as standard. GLC analyses and preparative separations of the reaction mixtures were carried out on an F & M Model 810 gas chromatograph using a 10 ft × 0.375 in. 15% SE-30 column heated at 90 °C for 8 min and then programmed at 2 °C/min to 250 °C. Melting points are uncorrected.

3,5-Dimethyl-5-[4′-(1′-methyl-1′-cyclohexenyl)]-Δ²-isoxazoline (2a). To a 200-ml three-necked round-bottomed flask, 5.44 g (0.04 mol) of dipentene, 3.1 g (0.04 mol) of nitroethane, and 9.8 g (0.08 mol) of phenyl isocyanate[13] in 80 ml of benzene was added. The solution was cooled in an ice–water bath and stirred while a few drops of triethylamine in 20 ml of benzene were added dropwise over a period of 5 min. The reaction mixture was stirred at room temperature for 1 h and then refluxed for 24 h. The reaction mixture was cooled and diphenylurea (8.0 g) was removed. The precipitate was washed with 50 ml of benzene and the washing was added to the filtrate. The combined filtrate was washed twice with 100 ml of water to remove traces of dimethylfuroxan and dried over anhydrous sodium sulfate. The benzene was removed and the remaining oil (6.6 g) showed two peaks in GLC with retention times of 5 and 31 min which were identified as starting material and product, respectively. The oil was distilled at reduced pressure: yield 3.8 g, 49%, of compound **2a,** bp 108–110 °C (1.4 mm). Dipentene (2.4 g, 44%) was also recovered: ir (neat) 1601 w (C=C), 1650 cm^{-1} m (C=N); uv λ_{max} 211, 255 nm; ^1H NMR ($CDCl_3$) δ 1.23 (s, 3), 1.67 (s, 3), 1.93 (s, 3), 2.67 (q, J = 16 Hz, 2), 5.5 (s, 1); mass spectrum m/e (rel intensity) 193 (10), 178 (12.5), 98 (100), 95 (3.3). The ^{13}C NMR chemical shifts and assignments are given in Table I.

Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.68; H, 9.70; N, 7.16.

Addition of Acetonitrile Oxide to Carvone. To a round-bottomed flask, 6.0 g (0.04 mol) of carvone, 3.1 g (0.04 mol) of nitroethane, and 9.8 g (9.08 mol) of phenyl isocyanate[13] in 90 ml of benzene were added. The solution was cooled in an ice–water bath and stirred while a few drops of triethylamine in 10 ml of benzene were added dropwise. The reaction mixture was stirred at room temperature overnight and then refluxed for 2 h. The reaction mixture was cooled and diphenylurea (8.8 g) was removed. The precipitate was washed with 100 ml of benzene. The filtrate was washed twice with 100 ml of water and dried over anhydrous sodium sulfate. The benzene was removed and the remaining oil (5.7 g) showed three peaks with retention times of 13, 31, and 43 min which were identified as unreacted carvone, **5a,** and **6a,** respectively. The ratio of carvone to **5a** and to **6a** was 60:25:15. The ratio of **5a** to **6a** was 1.7:1. Compound **5a** was obtained in pure form for analysis but **6a** was contaminated with **5a** and was identified by ir, NMR, and mass spectral analyses.

Isoxazoline **5a:** ir (CCl_4) 1670 (C=O), 1600, 1330 cm^{-1}; uv λ_{max} 225 nm; NMR (CCl_4) δ 1.33 (s, 3), 1.70 (s, 3), 1.90 (s, 3), 2.67 (q, J = 16 Hz, 2), 6.6 (s, 1); mass spectrum m/e (rel intensity) 207 (5.2), 192 (1.3), 109 (12.9), 98 (100).

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.26; N, 6.76. Found: C, 69.34; H, 8.26; N, 6.77.

Isoxazoline **6a:** ir (CCl_4) 1710 cm^{-1} (C=O); NMR (CCl_4) δ 1.20 (s, 3), 1.70 (s, 3), 1.97 (s, 3), 3.10 (br, 1), 4.7 (s, 2); mass spectrum *m/e* (rel intensity) 207 (8.5), 192 (7.5) 98 (100).

Addition of Benzonitrile Oxide to Carvone. A solution of 375 mg (2.5 mmol) of carvone, 390 mg (2.5 mmol) of benzhydroxamoyl chloride,[14] and 260 mg (2.5 mmol) of triethylamine in 30 ml of ether was stirred at room temperature overnight. The precipitated amine hydrochloride was removed by suction filtration. The filtrate was washed with two 20-ml portions of water. The organic layer was dried over anhydrous sodium sulfate. Ether was distilled and the residue was recrystallized from ethanol–water to give 530 mg (83%) of the isoxazoline **5b:** mp 110–112 °C; NMR (Me_2SO-d_6) δ 1.35 (s, 3), 1.67 (s, 3), 3.26 (q, 2), 6.92 (br, 1), 7.5 (m, 5).

Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.29; H, 6.67; N, 5.50. Found: C, 75.26; H, 6.93; N, 5.60.

Addition of Benzonitrile Oxide to Carvone Oxime. A solution of 415 mg (2.5 mmol) of carvone oxime was treated with 2.5 mmol of benzonitrile oxide generated by the procedure just mentioned to give 240 mg (34%) of the isoxazoline **5c:** mp 193–195 °C dec; NMR (Me_2SO-d_6) δ 1.37 (s, 3), 1.80 (s, 3), 3.28 (q, 2), 6.03 (br, 1), 7.5 (m, 5), 10.83 (s, 1). Carvone oxime (55%) was also recovered.

Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.42; H, 7.05; N, 9.46.

Reaction of Carvone Oxime with Phenyl Isocyanate. A solution of 210 mg (1.3 mmol) of carvone oxime, 300 mg (2.5 mmol) of phenyl isocyanate, and few drops of triethylamine in 20 ml of benzene was stirred at room temperature overnight and then refluxed for 1 h. The mixture was cooled to room temperature and filtered by suction. The filtrate was washed with water several times. The organic layer was dried and then evaporated to dryness. The residue was recrystallized from ethanol–water to give 300 mg (81%) of the phenylcarbamate: mp 119–120 °C; NMR (CCl_4) δ 1.93 (s, 3), 4.78 (s, 2), 6.22 (br, 1), 7.3 (m, 5), 8.25 (br, 1).

Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81, H, 7.09; N, 9.85. Found: C, 71.96; H, 7.08; N, 10.19.

Registry No.—1, 5989-27-5; **2a** isomer 1, 58718-55-1; **2a** isomer 2, 58718-56-2; **4a,** 99-49-0; **4c,** 31198-76-2; **4c** phenylcarbamate, 58718-57-3; **5a,** 58718-58-4; **5b,** 58718-59-5; **5c,** 58718-60-8; **6a,** 58718-61-9; phenyl isocyanate, 103-71-9; acetonitrile oxide, 7063-95-8; benzonitrile oxide, 873-67-6.

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Orientation in the 1,3-Dipolar Cycloaddition of Diazomethane and Ethyl Vinyl Ether

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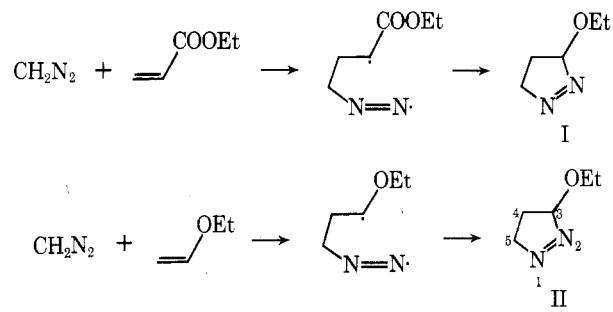
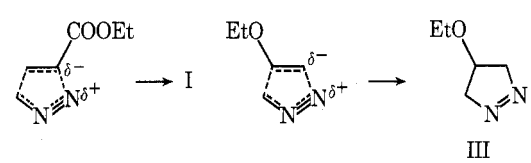
Orientation in 1,3-dipolar cycloadditions has been a major area of discussion in the controversy over stepwise-diradical vs. concerted mechanisms.[1,2] According to the diradical mechanism, each 1,3 dipole should be unidirectional in its cycloadditions with both electron-rich and electron-poor olefins, because the best diradical intermediates will tend to have one radical center located always at the same end of the 1,3 dipole, and the other located always next to the substituent of the dipolarophile, since both electron-releasing and electron-withdrawing substituents stabilize a radical center better than hydrogen does.[1,3] Thus, for example, both calculations and experience show that diazomethane prefers to react with dipolarophiles D first at carbon, giving an intermediate $DCH_2N_2\cdot$ rather than $\cdot CH_2N_2D$.[3] Therefore, both types of olefins, represented by ethyl acrylate and ethyl vinyl ether, should give the preferred diradicals shown, which lead to 3-carbethoxy-1-pyrazoline (I) and 3-ethoxy-1-pyrazoline (II), respectively, rather than the 4-substituted pyrazolines.



The "concerted but not synchronous"[2,4] mechanism, on the other hand, should give rise to opposite orientation for electron-rich vs. electron-poor dipolarophiles[1,3] because, although the preferred partial charge on the 1,3 dipole in the transition state cannot be predicted easily, any given 1,3 dipole should prefer a partial charge of the same sign consistently. This leads to a preference for a partial charge of the opposite sign on the adjacent atom that comes from the dipolarophile, which should then orient one way if its substituent stabilizes this charge, and the opposite way if it does not. The argument is illustrated for diazomethane below. We deduce the preferred



partial charge on diazomethane in its transition states from its orientation with ethyl acrylate, which gives I.[5] With ethyl vinyl ether, then, diazomethane should give the opposite orientation, III rather than II, since ethoxy does not stabilize a partial negative charge as carbethoxy does.

Another reason why the concerted mechanism predicts opposite orientation for the two types of dipolarophiles is based on electrostatically bound prereaction complexes. These are discussed in ref 3 and the argument need not be repeated here.

Needless to say, advocates of the concerted mechanism do not accept this argument. In particular, Huisgen rejects the prediction of obligatory bidirectionality for concerted cycloadditions. Instead, he proposes that MO theory be used to account for orientation, in the absence of overriding steric effects.[6] Many recent applications of MO theory to 1,3-dipolar cycloadditions have been published, all supporting the concerted mechanism.[7–11] Sometimes it predicts bidirectionality, and sometimes not.

A good test case is the reaction of diazomethane with ethyl vinyl ether, where the two theories predict opposite orienta-