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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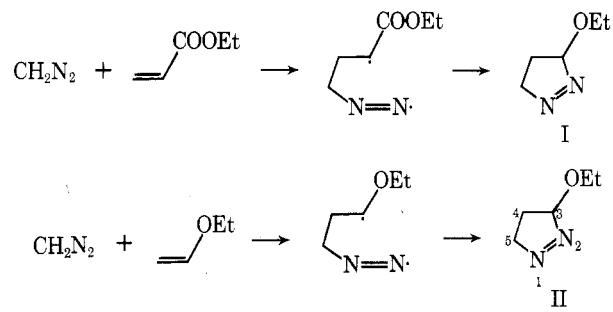
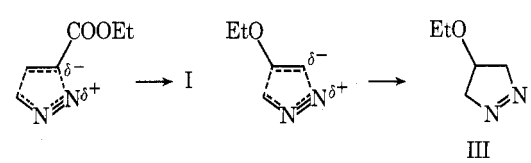
Orientation in 1,3-dipolar cycloadditions has been a major area of discussion in the controversy over stepwise-diradical vs. concerted mechanisms.[1,2] According to the diradical mechanism, each 1,3 dipole should be unidirectional in its cycloadditions with both electron-rich and electron-poor olefins, 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-

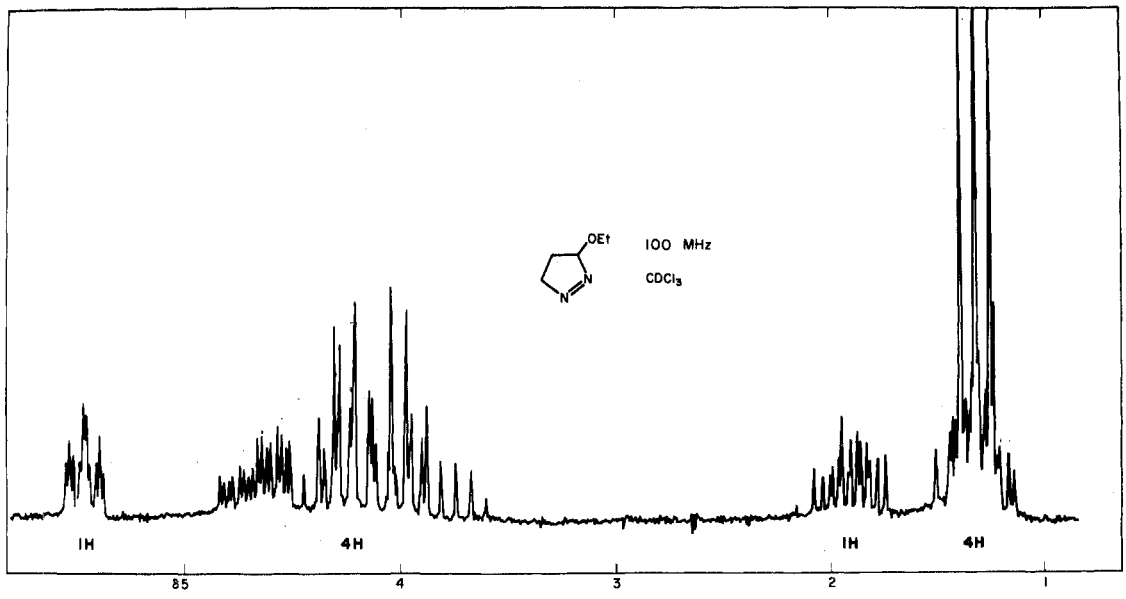


Figure 1.

tions. All MO calculations, assuming a concerted cycloaddition, predict that the product will be III and not II.[7,8] In contrast, the diradical theory predicts that II and not III should be the product.[3]

It was reported in 1947 that diazomethane and butyl vinyl ether give 4-butoxypyrazoline,[12] corresponding to III in orientation. Butyl vinyl ether (and also ethoxyacetylene)[13] thus exhibits exceptional behavior with diazomethane, which otherwise gives 3-substituted 1-pyrazolines with both electron-rich and electron-poor olefins.[3] However, the paucity of experimental data and the vigor of the cycloaddition conditions[12] prompted a reexamination of this reaction.

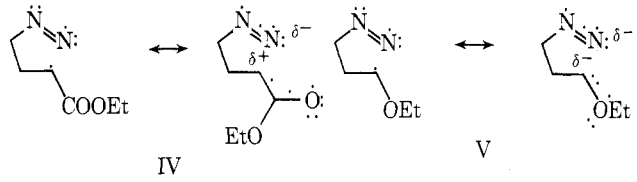
We now report that the sole product of cycloaddition of diazomethane with ethyl vinyl ether is not III but II. Diazomethane was prepared from nitrosomethylurea and allowed to react with excess ethyl vinyl ether in diethyl ether for 38 days at room temperature in the dark. The reaction is very slow (vide infra), and when worked up the yellow color was not noticeably faded. Nevertheless, 24% of II was obtained based on NMU, and since the yield of diazomethane from NMU is usually about 50% in our hands, the yield of II is probably closer to 50%, not allowing for unreacted diazomethane. The crude reaction mixture showed nothing by GLC but solvent and II. The total residue on careful evaporation of solvent was identical with pure II by ir and NMR.

Assignment of structure rests on elemental analysis and ir, Raman, ^{1}H NMR, ^{13}C NMR, and mass spectra. Of particular significance are the following observations. The ^{1}H NMR spectrum has two high-field protons, assigned to 4-CH_2; no such protons exist in isomer III. The ^{13}C NMR spectrum has this CH_2 at 23.9 ppm, typical for CH_2 flanked only by carbon atoms[14] and outside the range for O- or N-substituted CH_2.[15] In addition, the 3-CH is at 113.4 ppm, J = 156 Hz, characteristic for carbon attached to two heteroatoms.[16] Neither chemical shift is possible for any carbon atoms in III. The N=N stretch is visible in the ir and Raman spectra at 1552 cm^{-1}; cf. pyrazoline itself, 1548 cm^{-1}.[17] Further details are given in the Experimental Section.

How much of isomer III could possibly be present? The ^{13}C NMR spectrum is clean, and shows II only; the most unfavorable interpretation permits no more than 6% of III to be present, and probably less. The GC–MS shows >99% of the nonsolvent volatiles in a single homogeneous peak; thus >1% of III could be present only if its retention time were identical with that of II. At present, then, lacking an authentic sample of III, we can assign the minimum figure of 97 ± 3% to the purity of II.

A qualitative experiment, based on comparing the rate of fading of the yellow color, showed no difference in the reaction rate in ether vs. 1:1 ether–acetonitrile; neither lost much color over several weeks. Thus a change in mechanism from the normal nonpolar one is unlikely.

A final point for discussion is the slow rate of this reaction. It is frequently observed with the most studied 1,3 dipoles such as benzonitrile oxide, diphenylnitrilimine, diazomethane, diphenyldiazomethane, phenyl azide, and *C*-phenyl-*N*-methylnitrone, that 1,3 dipoles add faster to electron-poor olefins than to electron-rich ones.[18–20] This phenomenon is a result of the partial formal charges[3] of the diradical intermediates. Once again, diazomethane stands as an example.



IV V

In diradical IV, the two radical sites have opposite partial formal charges, but in V the partial charges are of the same sign. Thus IV prefers the cyclo form while V prefers the extended one, in which repulsion between the like charges is reduced. Since in the diradicals, the radical site arising from all 1,3-dipoles bears a partial negative charge on its terminus, this phenomenon should be a general one.

Exactly the same explanation was used to account for the effect of substituents in arylacetylenes on the partitioning of diradicals, formed from nitrile oxides or nitrile imines, between hydrogen transfer and cyclization.[3]

The question of ethoxyacetylene, which with diazomethane gives 4-ethoxypyrazole,[13] will be deferred to a later time.

Experimental Section

The GC–mass spectra were performed by Mr. Jack L. Smith. Microanalysis was by Mrs. Florence N. Antes. The Raman spectrum was obtained by Dr. Alan Rein. NMR spectra were run and interpreted by Dr. Byron H. Arison.

Cycloaddition of Diazomethane and Ethyl Vinyl Ether. Diazomethane was made from 15 g (0.145 mol) of nitrosomethylurea by shaking with 43 ml of 40% KOH and 200 ml of ether. The ether layer

was separated and dried with KOH pellets. To this solution was added 50 ml (0.52 mol) of ethyl vinyl ether, and the mixture was kept in the dark at room temperature. A small sample was withdrawn after 27 days and submitted for GC–MS. Conditions were 3% OV-101, 3 mm i.d. by 8 ft, column and injector block at 60 °C. Only two sharp, well-separated peaks were seen, solvent and product, with <1% of anything else. The MS of early, middle, and late portions of the product peak were all identical with that of pure II; thus the peak was homogeneous.

After 38 days, the yellow color was still strong. The reaction mixture was concentrated to a small volume by slowly distilling through a 5-in. helix-packed column, heating with a water bath at 40–44 °C, overhead temperature 34 °C. The initial distillate was very yellow; the final distillate and pot residue were colorless. The residue was further slowly concentrated to constant weight, 4.82 g (29% based on NMU) at <25 °C, 130 mm pressure. The ir and NMR spectra of the crude product were identical with those of pure II.

Samples were distilled at 120 °C (130 mm) and 27 °C (0.2 mm), giving pure II in both cases in >81% yield from crude. Thus the overall yield from NMU to pure II was >24%. Anal. Calcd: C, 52.6; H, 8.77; N, 24.6. Found: C, 52.6; H, 8.56; N, 24.9. ^{1}H NMR ($CDCl_3$) δ 1.31 t, J = 7 Hz, CH_3; 1.30 m, 1.90 m, 4-CH_2; 4.1 m, CH_2O; 4.0 m, 5-CH_a; 4.65 m, J = 17.5, 9.1, 4.0, 1.7 Hz,[21] 5-CH_b; 5.47 m, J = 7.8, 6.3, 1.5 Hz,[21] 3-CH. Integrals (mm, from a T-60 spectrum): CH_3 and 4-CH_a, 39; 4-CH_b, 12; CH_2O and 5-CH_2, 42; 3-CH, 9. The ^{1}H NMR spectrum is provided (Figure 1), as it is complex; further scan to δ 11.6 shows nothing more. ^{13}C NMR ($CDCl_3$) 113.4 d, J = 156 Hz, C-3; 75.0 t, J = 144 Hz, C-5; 66.4 t, J = 141 Hz, and 15.5 q, J = 127 Hz, ethyl group; 23.9 ppm t, J = 134 Hz, C-4. The ir has a weak band and the Raman a strong one at 1552 cm^{-1}, N=N stretch; other peaks are in accord with II. MS m/e 114 weak, 86 strong, 57, 58 very strong.

In another experiment, ca. 0.3 g (7.13 mmol) of diazomethane was prepared from 2.15 g of Diazald with 0.5 g of KOH in 0.8 ml of H_2O and 2.5 ml of EtOH, distilling with 24 ml of ether. To the distillate was added 6.8 ml (71.3 mmol) of ethyl vinyl ether, total volume 27.5 ml. Half of this was diluted to 25 ml with ether, and the other half to 25 ml with acetonitrile. Both solutions were kept in the dark at room temperature for 2 weeks. Over this period there was no noticeable difference between them in color.

Acknowledgment. Although much invaluable assistance was received from several of Merck's analytical experts, a special debt is owed to Dr. Byron H. Arison for his definitive interpretation of the ^{1}H NMR and ^{13}C NMR spectra.

Registry No.—II, 58832-35-2; ethyl vinyl ether, 109-92-9; diazomethane, 334-88-3.

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(20) Exceptions are found with highly electrophilic 1,3 dipoles such as ozone, carbonyl oxides, and *p*-nitrophenyl azide. With regard to the latter, see ref 3, p 2188.
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Stereospecific Reductive Alkylation of Acetylenes by Successive Hydralumination and Carbodemetalation[1]

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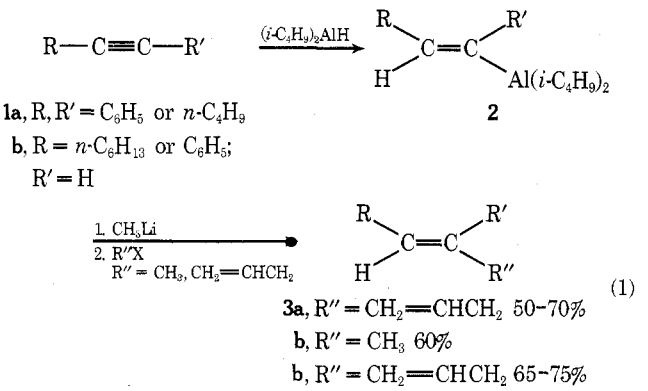
The widespread natural occurrence of substituted olefinic groups having a preferred geometrical configuration, such as those in terpenes, antibiotics, and pheromones, has stimulated the search for stereospecific olefin syntheses.[2] We wish to present here a potentially general and flexible method that is based on the stereospecific cis hydralumination of acetylenes[3] and the alkylation of the aluminate complexes[4] of the resulting vinylalanes (eq 1).[5]



The direct hydralumination of mono- or disubstituted acetylenes (eq 1) provides a convenient and direct route to stereoregular di- and trisubstituted olefins, respectively. Drawbacks lie in (1) the slow rate with which certain disubstituted acetylenes hydraluminate;[7] (2) the regioisomeric mixtures resulting when R ≠ R′;[3a,6b,7] and (3) the contamination of **2** with small amounts of R—C≡C—AlR_2' formed from the metalation of terminal alkynes by aluminum alkyls.[8] This method appears feasible, however, for symmetrical or terminal acetylenes and for reactive alkylating agents, such as methyl iodide and allylic or benzylic halides.

Since the trimethylsilyl derivatives of monosubstituted acetylenes can be hydraluminated selectively in a cis or trans manner (by conducting the addition in the presence or absence of a Lewis base[6]), this same alkylation method can lead to the stereospecific synthesis of either the *Z* or the *E* alkenylsilane[5] (eq 2).