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REGIOSELECTIVE CYCLOADDITION OF A C-ALKOXY-NITRONE

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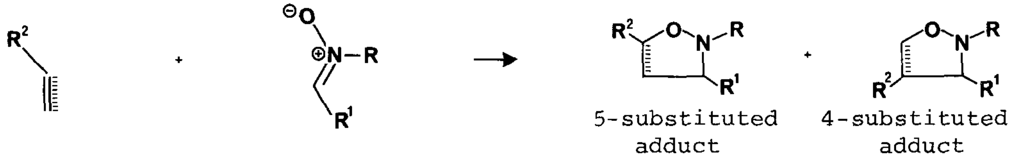
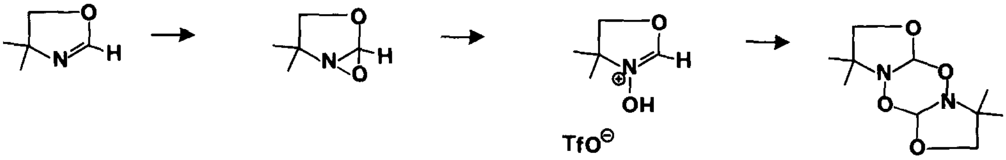
Summary: The first cycloaddition of a C-alkoxy-nitrone is reported and is regiospecific, yielding only the 4-substituted adduct with methyl propiolate as predicted by frontier orbital theory.

Nitrones have long been known to undergo cycloaddition with alkenes to produce isoxazolidines.[1] When this reaction is carried out on mono-substituted olefins or acetylenes the usual result is a 5-substituted adduct in which the oxygen terminus is linked to the substituted olefinic carbon. Huisgen found exception to this generalization in the reaction of nitrones with electron deficient acetylenes, in which case 4-substituted isoxazolines predominated.[2]



Houk used frontier molecular orbital theory to rationalize these results by seeing the nitrone LUMO - dipolarophile HOMO as the predominant interaction until the dipolarophile becomes sufficiently electron deficient to allow for the nitrone HOMO - dipolarophile LUMO interaction to take over.[3] When this happens, orbital coefficients dictate that the regiochemistry of addition be reversed. We envisioned that another way to decrease the energy difference between the nitrone HOMO, dipolarophile LUMO would be to place an electron donating heteroatom on the carbon terminus of the dipole. During the course of our work, Houk reported the reactions of C-cyclopropyl nitrones with dipolarophiles to produce 4-substituted cycloadducts due to the electron-donating nature of the cyclopropyl rings.[4]

C-alkoxy nitrones had been previously synthesized by silica-induced rearrangement of oxaziridines but no cycloadditions were attempted with these compounds.[5] Attempting to reproduce this scheme, we reacted 4,4-dimethyl-2-isoxazoline with 1 equivalent m-chloroperbenzoic acid (-20°, Et_2O, 48 hrs.) to produce oxaziridine 1 [^1H-NMR ($CDCl_3$): δ 5.93, s, 1H; 3.60, d (J=8 hz), 1H ; 3.39, d (J=8 hz), 1H; 1.40, s, 3H; 1.16, s, 3H].

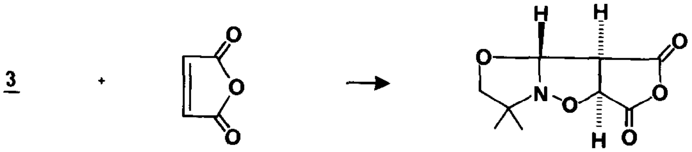


1 2 3

However, a nitrone product could not be isolated on treatment of this compound with silica. Rearrangement of the oxaziridine was effectively carried out using trifluoromethanesulfonic acid to produce 2 [^1H-NMR ($CDCl_3$): δ 13.3, s, 1H; 8.67, s, 1H; 4.88, s, 2H; 1.57, s, 6H, IR (CH_2Cl_2): 1655 cm^{-1}]. When triflate salt 2 was reacted with 1 equivalent of NaH in THF, dimer 3 could be isolated in 95% overall yield as a high-melting white solid [mp=237-38°, ^1H-NMR (C_6D_6): δ 6.16, s, 1H; 3.77, d (J=8 hz), 1H; 3.39, d (J=8 hz), 1H; 1.27, s, 3H; 1.19, s, 3H, ^{13}C-NMR ($CDCl_3$): δ 119.4, 75.8, 62.1, 22.7, 19.3, mass spectrum (m/e): 230 (100%), 115]. It was on this dimer that the initial cycloaddition experiments were carried out.

In an NMR experiment, when allowed to react with 2.2 equivalents of maleic anhydride/23°/$CDCl_3$, the ^1H-NMR resonances corresponding to dimer 3 disappeared after 12 hrs. and new peaks appeared which were indicative of a single adduct, compound 4 [δ 5.35, s, 1H; 5.14, d(J=8 hz), 1H; 4.02, d (J=8 hz), 1H; 3.79, d (J=7 hz), 1H; 3.56, d (J=7 hz), 1H; 1.40, s, 3H; 1.30, s, 3H]. The singlet at δ 5.35 was assigned as the proton on the carbon between the nitrogen and oxygen atoms. When the structure in which this proton is trans to the adjacent anhydride ring proton is subjected to an MM2 minimization procedure,[6] the dihedral angle between these two protons is found to be 92°. This is in accord with the observed lack of coupling in the NMR spectrum.

Demonstrating that the dimer is in equilibrium with the reactive monomer form in solution, reaction with an unsymmetrical dipolarophile was attempted. Thus, when dimer 3 was heated with 2.2 equivalents of methyl propiolate in $CDCl_3$ (sealed tube, 110°, 4 hrs.), compound 6 was produced in 89% yield after chromatography [mp=106-8°, ^{1}H-NMR ($CDCl_3$): δ 10.83, br. s, 1H; 9.80, s, 1H; 4.34, s, 2H; 3.77, s, 3H; 1.50, s, 6H, ^{13}C-NMR ($CDCl_3$): δ 188.6, 188.2, 169.4, 88.2, 80.2, 58.5, 50.8, 27.2, IR ($CDCl_3$): 1687, 1634, 1545 cm^{-1}, mass spectrum (m/e): 199, 167, 140 (100%), 124]. Compound 6 is the result of a thermally allowed [1,5] H-shift in the intermediary adduct 5 as shown. At no time during the monitoring of the reaction by ^{1}H-NMR was intermediate 5 or products resulting from the opposite regiochemical mode of addition seen. It should also be mentioned that cycloaddition products with both maleic anhydride and methyl propiolate could be formed by heating oxaziridine 1 with these dipolarophiles (sealed tube, $CDCl_3$, 110°). However, in both cases, the reaction products formed were not as clean as when the dimer was used.



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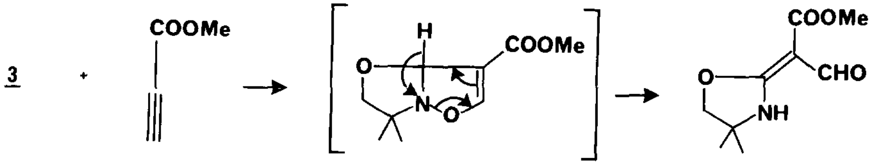

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Unfortunately, the alkoxy-nitrone proved too unreactive for other simple dipolarophiles. No adducts were formed on heating either 1 or 3 with acrylonitrile, methyl acrylate, phenylacetylene, or methyl vinyl ketone up to 150° (the dimer decomposes above 150°). Thus, while alkoxy-nitrones do show a regiochemical preference of addition as predicted by frontier orbital theory, the deactivation incurred by the electron-donating oxygen atom limits the synthetic utility of this reaction.

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