Tetrahedron Letters No. 50, pp 4445 - 4448, 1975. Pergamon Press. Printed in Great Britain.

# MECHANISMS OF 1,3-DIPOLAR CYCLOADDITIONS TO HIGHLY ELECTRON-DEFICIENT DIPOLAROPHILES

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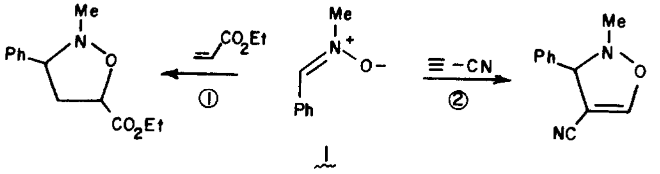
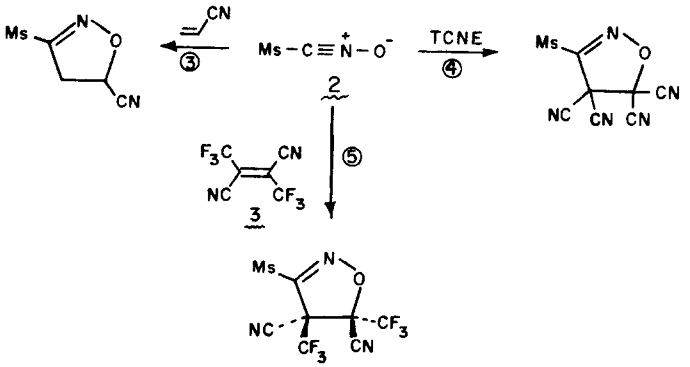
(Received in USA 22 September 1975; received in UK for publication 4 November 1975)

Cycloaddition mechanisms can be separated phenomenologically into three classes· (1) concerted, (2) stepwise--diradical intermediate, and (3) stepwise--zwitterionic intermediate. Generally, Woodward-Hoffmann forbidden cycloadditions occur by diradical or zwitterionic mechanisms,[2] depending on the mutual polarity of the addends, but allowed reactions may occur by any of the three mechanistic types. All of the 1,3-dipolar cycloadditions which have been subjected to mechanistic scrutiny follow concerted pathways as measured by the criteria of stereochemistry, solvent effects, and isotope effects.[3] However, Firestone has postulated that many 1,3-dipolar cycloadditions occur by stepwise-diradical intermediate mechanisms.[4] If authentic stepwise 1,3-dipolar cycloadditions could be found and characterized by low stereospecificity, significant solvent effects on rate, and so forth, those reactions in which these phenomena were not observed would be more convincingly proved to be concerted For theoretical reasons, we have chosen to search for stepwise mechanisms in reactions of addends of very dissimilar polarity, or of nearly identical polarity Our preliminary studies of the first kind are reported here.

As we predicted earlier,[5] and have confirmed experimentally,[6] the reactions of very electron-deficient dipolarophiles with nitrones and nitrile oxides give 4-substituted isoxazoles, isoxazolines, or isoxazolidines. In order to verify that a mechanistic change was not involved in this "reversal" of regioselectivity, the stereochemistry of a reaction of this type and the effect of solvent polarity on reaction rate were studied.

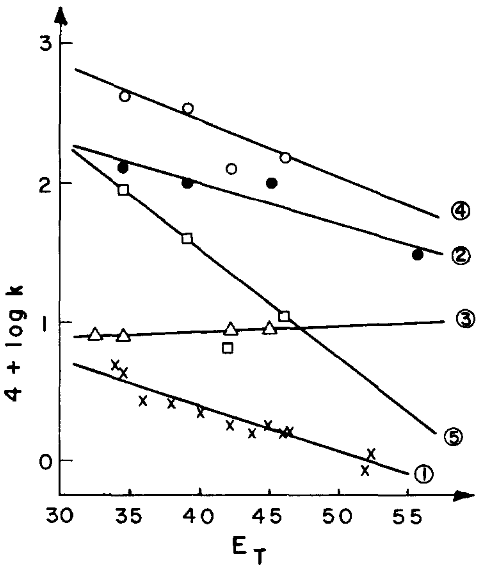
Huisgen and coworkers have found that the reaction of nitrone, **1**, with ethyl acrylate, gives the 4-carboethoxy adduct (reaction number ①).[7] By contrast, the more electron-deficient dipolarophile, cyanoacetylene, reacts with **1** to give only the 5-cyano adduct, ②,[6] In the nitrile oxide series, the slightly electron-deficient acrylonitrile reacts with mesitylnitrile oxide to give the 5-substituted adduct, ③,[8] along with slower formation of a 2:1 adduct involving cycloaddition of the nitrile oxide to the adduct cyano group.[9] Mesitylnitrile oxide reacts rapidly with tetracyanoethylene to give a single adduct, ④,[10] which undergoes slower decomposition, as well as further additions of the nitrile oxide to adduct cyano groups. Finally, 1,2-*bis*-(trifluoromethyl)fumaronitrile, **3**, reacts with mesitylnitrile oxide to give a single adduct, shown by $^{19}$F nmr to be the *trans* adduct ⑤. Thus, two sharp trifluoromethyl resonances are observed at 9.24 and 19.89 ppm (relative to $CFCl_3$). In cyclobutanes with vicinal *trans*-trifluoromethyls, the flourine resonances appear as singlets, whereas the corresponding *cis* compounds show large (J=12Hz) couplings between nonequivalent fluorines.[11]





The orientation observed in the reactions of unsymmetrical dipolarophiles, the stereospecificity observed in reaction ⑤, and the rates of these reactions in benzene (k② : k① = 5200:1 at 85°, k⑤ . k④ : k③ = 11.55·1) can also be explained by concerted mechanisms.[5,6] However, the orientation observed in reaction ② and the stereospecificity of reaction ⑤ could be rationalized equally well by stepwise mechanisms involving zwitterionic intermediates, because **3** has been found to react stereospecifically with electron-rich alkenes.[11]

However, the solvent effects measured here rule out such intermediates. The graph shows the logs of the relative rates of cycloadditions ①-⑤ in various solvents plotted against the solvent polarity parameter, $E_T$.[12] The data for reaction ① were reported by Huisgen and coworkers.[7]



**Rate Constants ($x10^5$) in Different Solvents**

| Solvent | | $CCl_4$ | $C_6D_6$ | $CDCl_3$ | $(CD_3)_2CO$ | DMSO-$d_6$ | $CD_3CN$ | $CD_3OD$ |
|---|---|---|---|---|---|---|---|---|
| $E_T$[12] | | 32 5 | 34 5 | 39 1 | 42 2 | 45 0 | 46 0 | 55 5 |
| Reaction # (°C) | | | | | | | | |
| ①[7,14] | (85) | — | 0 23 | — | 0 188 | 0 182 | 0 163 | — |
| ② | (25) | — | 19 | — | 14 | 15 | — | 3 4 |
| ③ | (35) | 79 | 78 | — | 87 | 89 | — | — |
| ④ | (25) | — | 4400 | 3500 | 1300 | — | 1500 | — |
| ⑤ | (35) | — | 900 | 410 | 64 | — | 107 | — |

The two nitrone reactions show very similar rate decelerations by solvents of increasing polarity, regardless of the adduct orientation. The slopes of these lines ($\frac{\Delta \log k}{\Delta E_T}$ = -0.03) are not only much smaller in magnitude, but opposite in sign to that (+0.29) for the cycloaddition of butyl vinyl ether to TCNE, a reaction involving a zwitterionic intermediate.[13] The reactions of $\underset{\sim}{2}$ vary in sensitivity, but the slopes (+.005, -0.04, and -0.08 for ③, ④, and ⑤, respectively) are all well within the range expected for concerted reactions. By contrast, enormous accelerations of the $\left[2 + 2\right]$ cycloadditions of $\underset{\sim}{3}$ are caused by polar solvents.[11] The large anomalous deceleration cause by acetone-$d_6$ ($E_T$=42.2) is doubtless due to the presence of water ($E_T$=63.1) in the solvent.

Finally, we should note that reactions ④ and ⑤ may not follow simple second order kinetics, since charge transfer complexes are visually apparent as soon as the reagents are mixed, and we have found that mesitylnitrile oxide adducts form charge transfer complexes with TCNE, undoubtedly involving the electron-rich mesityl group, where the highest HOMO electron density is located.

Acknowledgment. Financial support from the National Science Foundation and the National Institutes of Health, and a generous gift of **3** from Drs. H. E. Simmons, W. J. Middelton and S. Proskow of E. I. du Pont de Nemours, are gratefully acknowledged.

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(8) Ring proton nmr ($CCl_4$) ABX pattern, $\delta_A = 3.24$, $\delta_B = 3.57$ ($CH_2$), $\delta_X = 5.28$ (CHCN); $J_{AX} = 6.2$ Hz, $J_{BX} = 9.0$ Hz, $J_{AB} = 17.0$ Hz.

(9) Ring proton nmr ($CCl_4$): ABX pattern; $\delta_A = 3.55$; $\delta_B = 3.81$ ($CH_2$); $\delta_X = 5.92$ (CHAr); $J_{AX} = 9.5$ Hz, $J_{BX} = 7.4$ Hz; $J_{AB} = 16.0$ Hz.

(10) The ortho and para methyl resonances in **2** appear at 2.42$\delta$ and 2.33$\delta$, respectively, in $CDCl_3$, and shift to 2.24$\delta$ and 2.35$\delta$ in the adduct.

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