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REACTIONS OF NITRONES BEARING AN OLEFINIC DIPOLAROPHILE WITH DIMETHYL ACETYLENEDICARBOXYLATE. INTER- AND INTRAMOLECULAR DOUBLE 1,3-DIPOLAR CYCLOADDITIONS

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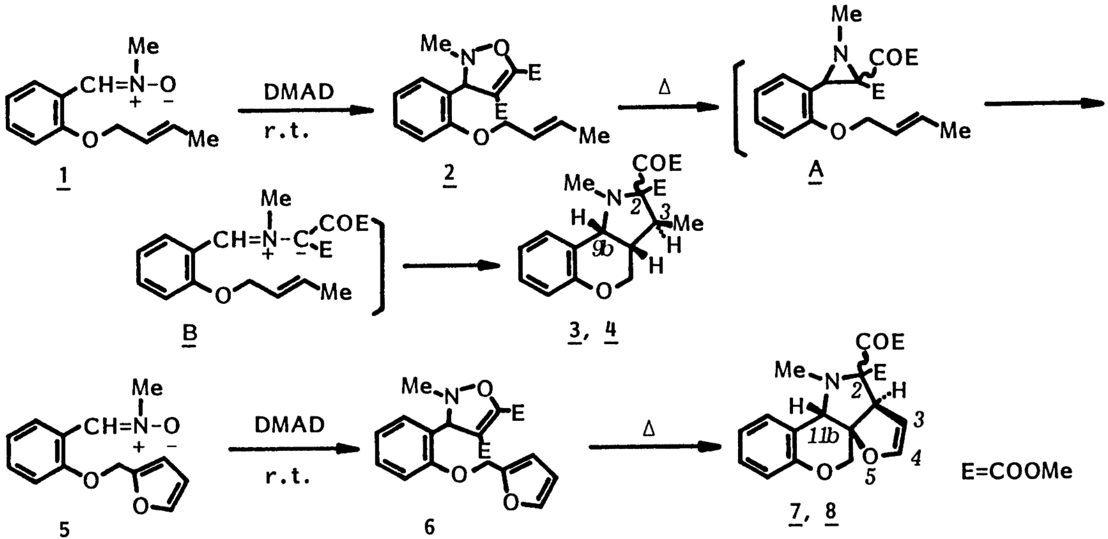
The reaction of nitrones, derived from benzaldehydes having an olefinic dipolarophile at the o-position, with DMAD provides the first example for the inter- and intramolecular double 1,3-dipolar cycloaddition.

Intramolecular 1,3-dipolar cycloadditions represent a general scheme for the synthesis of novel fused heterocycles.[1)] In contrast to many studies of the bimolecular 1,3-dipolar cycloadditions of azomethine ylides, there are only few examples for intramolecular ones of the ylides.[2-4)] 1,3-Dipolar cycloadditions of azomethine ylides, generated from the thermal and photochemical cleavage of aziridines, to dipolarophiles are well known.[5)] To our knowledge, however, the study of intramolecular cycloadditions using properly functionalized aziridines has not been extended beyond that reported by Padwa and Ku.[4)] On the other hand, 4-isoxazolines formed from the cycloaddition of nitrones to alkynes are generally unstable and thermally rearrange into acylaziridines which more often change to stable compounds via an azomethine ylide;[6)] stable azomethine ylides have actually been isolated in some cases.[7)] It is thus expected that 4-isoxazolines can be used as precursors of azomethine ylides in the 1,3-dipolar cycloaddition. However, the investigation from such a standpoint has not so far been reported.

As a part of our program directed toward a study of intramolecular cycloadditions of 1,3-dipolar systems where dipolarophiles are properly connected through an aromatic ring,[3a-3d,8)] we planned to investigate the possibility of intramolecular cycloaddition of azomethine ylides generated from 3-aryl-4-isoxazolines bearing a dipolarophile. In this communication we report the reaction of nitrones having an olefinic dipolarophile with dimethyl acetylenedicarboxylate (DMAD): This provides the first example for the 1,3-dipolar cycloaddition using an azomethine ylide generated from a 4-isoxazoline.

We have first investigated the reaction of α-(o-crotyloxy)phenyl-N-methylnitrone 1[9)] with DMAD. Oppolzer and Weber[10)] reported that the reaction of o-crotyloxybenzaldehyde with methylhydroxylamine in toluene under reflux gave an intramolecular cycloadduct of 1 formed in situ. At room temperature, however, 1 reacted with an equivalent of DMAD to give the expected isoxazoline 2 (mp 44-44.5 °C) in 85% yield.[11)] When a solution of 2 in toluene was refluxed for 3 h, two isomers, 3 (mp 136-137 °C) and 4 (mp 75-76 °C), were obtained in 35 and 15% yields, respectively. Based on spectral data showing the presence of three methines, a quaternary carbon and three carbonyl carbons,12) 3 and 4 were assigned as stereoisomeric cis-hexahydro[1]benzopyrano[4,3-b]pyrroles. Thus it is evident that the reaction proceeds via an intramolecular cycloaddition of an azomethine ylide B generated from a ring cleavage of an intermediary aziridine A (Scheme 1). In the cycloadducts 3 and 4, however, the stereochemistry at 2-positions come from geometry of azomethine ylide moiety could not be solved.



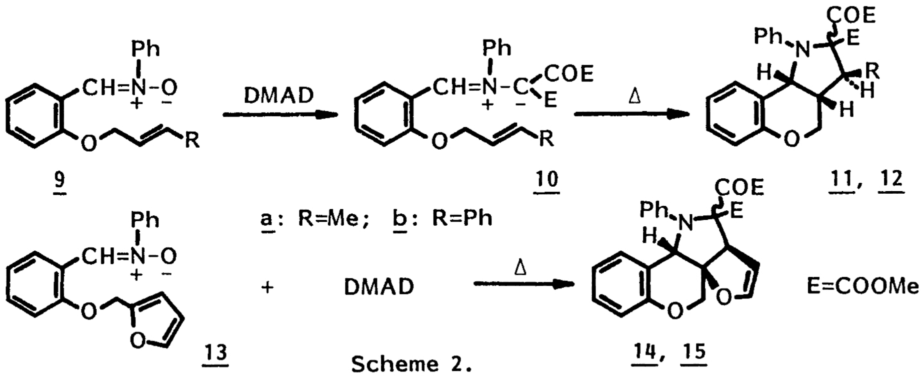
Scheme 1.

We have recently found that 1,3-dipolar systems derived from o-(2-furylmethyloxy)benzaldehyde undergo an intramolecular cycloaddition to the furan ring.3d) However, the nitrone 5 reacted with DMAD in benzene at room temperature to give the 4-isoxazoline 6 (colorless oil) in a quantitative yield.13) On heating in benzene under reflux for 10 h 6 gave again two stereoisomeric hexahydrofuro[2,3-c][1]benzopyrano[4,3-b]pyrroles, 7 (mp 136-137 °C) and 8 (mp 104-105 °C), in 34 and 6% yields, respectively. Spectral data supported the assigned structures.14)

The reaction of N-phenylnitrones with DMAD was next investigated. When the nitrone 9a was heated with an equivalent of DMAD in toluene under reflux, the solution turned to red over a period of ca. 10 min,15) and then gradually faded with time into pale yellow. After heating for 6 h, two stereoisomeric intramolecular cycloadducts, 11a (mp 187-188 °C) and 12a (mp 169-170 °C), like 3 and 4 were obtained in 21 and 16% yields, respectively.16)

It has been reported that 2-aryl-4-isoxazolines are generally less stable than 2-alkyl derivatives,17) and that stable colored azomethine ylides were formed in some reactions of nitrones with alkynes.7) Thus, a red-colored intermediate formed in an initial stage of the above reaction was assumed as an azomethine ylide. In fact, the formation of the azomethine ylide 10a (red oil) was confirmed in the reaction at room temperature for 6 h in chloroform.18)

Similarly, the reaction of DMAD with the nitrone 9b (reflux in toluene, 20 h) or with the nitrone 13 (reflux in benzene, 6 h) proceeded via a reddish azomethine



Scheme 2.

ylide to give the intramolecular cycloadducts, 11b (mp 190-191 °C) and 12b (mp 178-179 °C), or 14 (mp 179-180 °C) and 15 (mp 178-179 °C), in 52 and 8% yields, or 15 and 25% yields, respectively (Scheme 2).

Structural elucidation of the cycloadducts, 11, 12, 14, and 15, was again accomplished on the basis of spectral data.

Thus, it can be concluded that the reaction reported here proceeds via an initial intermolecular 1,3-dipolar cycloaddition of the nitrone moiety to DMAD, followed by an intramolecular one of azomethine ylide, generated from an acylaziridine through an initially formed 4-isoxazoline moiety, to the dipolarophile.

References

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4) A. Padwa and H. Ku, J. Org. Chem., 44, 255 (1979).
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8) O. Tsuge, K. Ueno, and A. Inaba, Heterocycles, 4, 1 (1976).
9) Nitrones, 1 (mp 69-70 °C), 5 (mp 106-107 °C), 9a (mp 90-91 °C), 9b (mp 90-91 °C) and $13^{3d)}$ (mp 89-90 °C), were prepared by the reaction of the corresponding benzaldehyde with the hydroxylamine, respectively. All new compounds re-

ported herein gave satisfactory elemental analyses. The NMR spectra were all measured in $CDCl_3$.

10) W. Oppolzer and H. P. Weber, Tetrahedron Lett., 1970, 1121.

11) 2: ^{1}H NMR δ 1.73 (3H, d, $C\underline{H}_3$, J=5.0 Hz), 2.96 (3H, s, $NC\underline{H}_3$), 3.59, 3.87 (each 3H, s, $OC\underline{H}_3$), 4.45 (2H, m, $C\underline{H}_2$), 5.50 (1H, s, $C\underline{H}$), 5.72 (2H, m, $=C\underline{H}$), 6.75-7.26 (4H, m, $Ar\underline{H}$); MS m/e 347 (M^+).

12) 3: ^{1}H NMR δ 2.30-2.56 (1H, m, 3a-H), 2.91 (1H, quintet, 3-H, J=7.0, 7.0 Hz), 3.92-4.13 (2H, m, $C\underline{H}_2$), 4.10 (1H, d, 9b-H, J=8.0 Hz); ^{13}C NMR δ 42.9 (d, 3-C), 44.3 (d, 3a-C), 60.7 (d, 9b-C), 67.3 (t, 4-C), 80.4 (s, 2-C), 162.5, 170.3, 194.5 (each s, $\underline{C}=O$); MS m/e 347 (M^+). 4: ^{1}H NMR δ 2.40-2.70 (1H, m, 3a-H), 2.88 (1H, quintet, 3-H, J=7.0, 7.0 Hz), 3.92 (2H, m, $C\underline{H}_2$), 4.08 (1H, d, 9b-H, J=8.0 Hz); ^{13}C NMR δ 41.9 (d, 3-C), 44.1 (d, 3a-C), 61.4 (d, 9b-C), 66.2 (t, 4-C), 81.6 (s, 2-C), 164.4, 168.0, 193.0 (each s, $\underline{C}=O$); MS m/e 347 (M^+).

13) 6: ^{1}H NMR δ 2.87 (3H, s, $NC\underline{H}_3$), 3.57, 3.87 (each 3H, s, $OC\underline{H}_3$), 4.96 (2H, s, $C\underline{H}_2$), 5.45 (1H, s, $C\underline{H}$), 6.31 (2H, m, β-H of furan ring), 6.80-7.35 (5H, m, $Ar\underline{H}$ + α-H of furan ring); MS m/e 373 (M^+).

14) 7: ^{1}H NMR δ 4.24 (2H, d, $C\underline{H}_2$, J=4.0 Hz), 4.28 (2H, s (11b-H) and t (2a-H, J=2.0 Hz)), 4.70 (1H, t, 3-H, J=2.0 Hz), 6.23 (1H, t, 4-H, J=2.0 Hz); ^{13}C NMR δ 55.7 (d, 2a-C), 64.2 (d, 11b-C), 67.1 (t, 6-C), 79.1 (s, 2-C), 87.9 (s, 5a-C), 98.8 (d, 3-C), 148.1 (d, 4-C), 160.8, 168.7, 189.2 (each s, $\underline{C}=O$); MS m/e 373 (M^+). 8: ^{1}H NMR δ 4.06 (2H, d, $C\underline{H}_2$, J=4.0 Hz), 4.16 (2H, s (11b-H) and t (2a-H, J=2.0 Hz)), 4.94 (1H, t, 3-H, J=2.0 Hz), 6.32 (1H, t, 4-H, J=2.0 Hz); ^{13}C NMR δ 56.7 (d, 2a-C), 64.4 (d, 11b-C), 68.2 (t, 6-C), 79.5 (s, 2-C), 86.9 (s, 5a-C), 99.4 (d, 3-C), 147.4 (d, 4-C), 162.5, 168.6, 189.0 (each s, $\underline{C}=O$); MS m/e 373 (M^+).

The stereochemical relationship among 2a-, 5a-, and 11b-positions was assumed on the basis of comparison of spectral data of cycloadducts obtained from 1,3-dipolar systems derived from o-(2-furylmethyloxy)benzaldehyde.[3d)]

15) In the reaction at room temperature the solution turned also to red over a period of ca. 40 min.

16) The reaction of N-phenylnitrones, 9 and 13, was accompanied by a small amount of an unidentified isomer showing an NH absorption at 3400 cm^{-1}. A study on the structure of by-product is in progress.

17) J. E. Baldwin, R. G. Pudussery, A. K. Qureshi, and B. J. Sklarz, J. Am. Chem. Soc., 90, 5325 (1968).

18) When 9a was stirred with an equivalent of DMAD in $CDCl_3$ at room temperature, the solution turned to red over a period of ca. 30 min. After stirring for 2 h, no signal of azomethine proton (δ 8.31) in 9a was detected, but instead a new signal appeared at δ 7.00 in the ^{1}H NMR spectrum. After evaporation of the solvent, red oil which is very labile to moisture was obtained: IR (neat) 1740, 1640 cm^{-1}; ^{1}H NMR δ 1.66 (3H, pseudo d, $C\underline{H}_3$), 3.73, 3.76 (each 3H, s, $OC\underline{H}_3$), 4.45 (2H, m, $C\underline{H}_2$), 5.66 (2H, m, $=C\underline{H}$), 6.60-7.63 (9H, m, $Ar\underline{H}$), 7.00 (1H, s, $N=C\underline{H}$); $FeCl_3$-color test, positive.

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