1,3-DIPOLAR CYCLOADDITION REACTIONS OF N-METHYL-C-SUBSTITUTED-PHENYLNITRONES WITH N-METHYLMALEIMIDE

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Abstract: 1,3-Dipolar cycloaddition reactions of N-methyl-C-substituted phenylnitrones with N-methylmaleimide were studied. The reaction of p-dimethylamino and 4-benzyloxy-3-methoxy substituted phenylnitrones with N-methyl maleimide gave only cis cycloadducts. Contrarily, the reaction of p-nitro and p-chloro substituted phenylnitrones with N-methylmaleimide gave cis and trans cycloadducts.The substituent effects on the stereochemistry of N-methyl-C-substituted phenylnitrone cycloaddition reactions are discussed.

Introduction

Nitrones are among the most useful 1,3-dipoles used in organic synthesis, due to the good yields, mild reaction conditions, high stereoselectivities and predictabilities encountered (1). The 1,3-dipolar cycloaddition of nitrones to a wide variety of dipolarophiles has been formulated as single-step, concerted four-centered reactions which proceed under both thermal and high-pressure conditions (2). Numerous isoxazolines, which are especially attractive heterocycles for the synthesis of the β-lactam ring, have been prepared from nitrones (3).

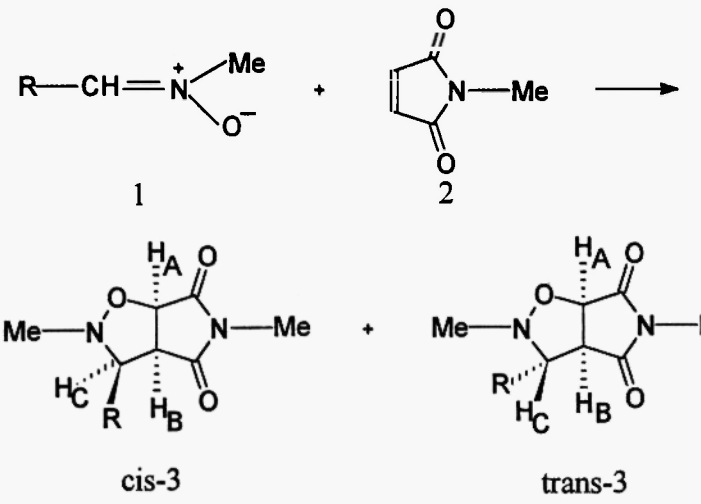
Although the regiochemical and stereochemical outcomes of the cycloaddition reactions of N-alkyl-C-phenylnitrones with alkenes have been studied (4-6), to our knowledge substituent effects on the stereochemistry of N-alkyl-C-substituted phenylnitrone cycloaddition reactions have not been reported.

Results and Discussion

In this work, we have investigated the cycloaddition behavior of N-methyl-C-substituted phenylnitrones with N-methylmaleimide (Scheme 1).

The reaction of N-methyl-C-(p-dimethylaminophenyl)nitrone with N-methylmaleimide gave 2,6-dimethyl-3-(p-dimethylaminophenyl)-1-oxa-2,6-diazabicyclo[3.3.0]octane-5,7-dione, cis-3a. The stereochemical assignment of cis-3a is made on the basis of the magnitude of the H_B-H_C coupling constant (J=8.5 Hz). Nmr experiments reveal that the cis-isomer gives rise to a larger H_B-H_C coupling constant (J≈6-8 Hz) than is observed for the trans-isomer (J≈2-5 Hz) (6-8).The reaction of N-methyl-C-(4-benzyloxy-3-methoxyphenyl)nitrone with N-methylmaleimide also gave only the cis-isomer (cis-3b, H_B-H_C coupling constant J=5.5 Hz).

N-Methyl-C-(p-nitrophenyl)nitrone and N-methyl-C-(p-chlorophenyl) nitrone were reacted with N-methylmaleimide respectively, and cis-isomers (cis-3c, J=8.2) were obtained along with trans-isomers (trans-3c, J=4.3 Hz and trans-3d, J=3.8 Hz).



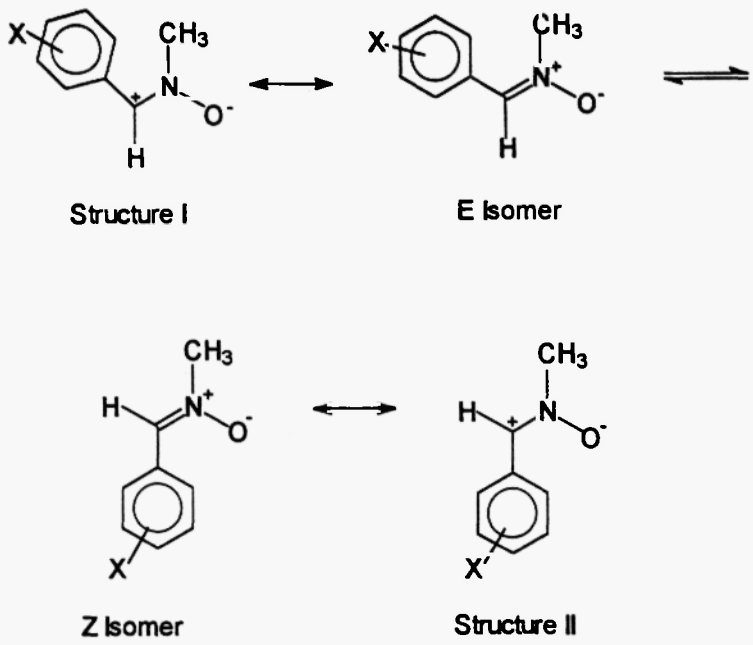
R	Cycloadduct
p-$Me_2NC_6H_4$	cis-3a
4-$PhCH_2O$-3-$MeOC_6H_3$	cis-3b
p-$NO_2C_6H_4$	cis-3c
p-$NO_2C_6H_4$	trans-3c
p-ClC_6H_4	cis-3d
p-ClC_6H_4	trans-3d

Scheme 1

For each experiment, the cycloaddition products were checked by tlc for each experiment and nitrones with electron-releasing substituents always gave one spot, while nitrones with electron-withdrawing substituents gave two spots.

The H_C protons of the cis-isomers were observed as multiplets in their nmr spectra together with H_B protons at about 3.7 ppm. Contrarily, the H_C protons of the trans-isomers appeared as doublets at about 4 ppm.

It was suggested previously (4), that the E isomer of N-methyl-C-phenylnitrone was present in solution in significant quantities (~10% at room temperature) and that this underwent dipolar cycloaddition at a faster rate than the Z isomer for steric reasons (9, 10). E isomers of N-methyl-C-substituted phenylnitrones can even be more stabilized by electron-releasing substituents than unsubstituted one (Scheme 2, Structure I).



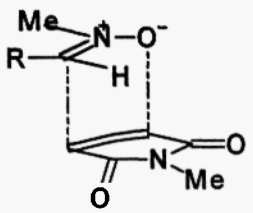
Scheme 2

Therefore, it is possible that E isomers of N-methyl-C-(p-dimethylamino phenyl)nitrone, 1a and N-methyl-C-(4-benzyloxy-3-methoxyphenyl) nitrone, 1b should be present in solution sufficient amounts. We assume that cis-3a and cis-3b cycloadducts were derived from the E isomers of the nitrones 1a and 1b. In these cases, the secondary orbital interaction through an endo transition state is effective (11) and this leads to cis-3a and cis-3b cycloadducts (endo approach of E isomer, Scheme 3). When electron-withdrawing substituents are present on the phenyl group of N-methyl-C-substituted phenylnitrones, E isomers should be destabilized by these substituents (Structure 1, Scheme 2), and only the Z isomers should exist in solution. With this system, the endo and exo transition states leading to the trans and cis cycloadducts are of comparable energies (4) (exo and endo approach of Z isomer,Scheme 3).

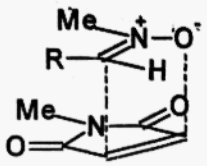
Therefore, a mixture of cis-3c and trans-3c stereoisomers was formed from the reaction of the Z isomer of nitrone, 1c with N-methylmaleimide. Similarly, a mixture of cis-3d and trans-3d stereoisomers were obtained from the reaction of the Z-isomer of nitrone 1d with N-methylmaleimide.

Experimental

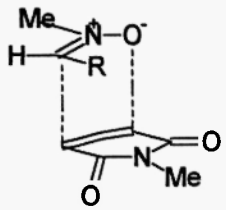
Melting points were determined on a Buchi apparatus and are uncorrected. ir spectra were recorded on a Simadzu FTIR-821PC Fourier Transform ir spectrometer and are reported in



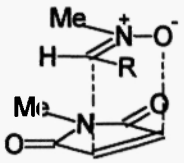
Exo approach of E-isomer



Endo approach of E-isomer



Exo approach of Z-isomer



Endo approach of Z-isomer

R: p-dimethylaminophenyl 4-benzyloxy-3-methoxyphenyl, p-nitrophenyl, p-chlorophenyl.

Scheme 3

wavenumbers(cm^{-1}). ^1H nmr spectra were recorded on a Bruker AC 200-L(200 MHz) spectrometer using deuteriated chloroform with Me_4Si as an internal standard. E.I. mass spectral data were obtained from a VCZAPSPEC instrument operating at 70 eV. Preparative t.l.c. plates were prepared using silica gel HF_{254}(Merck).Petroleum ether refers to the fraction with b.p. 40-60^{0}C. N-Methyl-C-substituted phenylnitrones were prepared by the literature method (12).

2,6-Dimethyl-3-(p-dimethylaminophenyl)-1-oxa-2,6-diazabicyclo[3.3.0] octane-5,7-dione, cis-3a

A mixture of N-methyl-C-(p-dimethylamino phenyl)nitrone (1.18 mmol, 0.208g) and N-methylmaleimide (1.28 mmol, 0.142g) in benzene (25ml) was refluxed for 4h. The benzene was then evaporated under reduced pressure. The residue was recrystallized from ethyl acetate-petroleum ether (1:1) to give cis-3a (0.235g, 70%); m.p. 162-164^{0}C; ir (potassium bromide): 1680cm^{-1} (C=O); ^1H nmr (deuteriated chloroform) : δ 2.59(s, 3H ,CH_3), 2.95(s, 3H, CH_3), 3.02(s, 3H, CH_3), 3.66(m, 2H, H_B and H_C, J=8.51 and 8.61 Hz), 4.84(d, 1H, H_A, J=6.81 Hz), 6.64-7.03(m, 4 aromatic H); ms (EI, 70 eV) : m/z 291(M^+). *Anal.* Calcd. for $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.62; N, 14.52. Found: C, 62.85; H, 7.13; N, 14.50.

2,6-Dimethyl-3-(4-benzyloxy-3-methoxyphenyl)-1-oxa-2,6-diazabicyclo [3.3.0]octane-5,7-dione, cis-3b

A mixture of N-methyl-C-(4-benzyloxy-3-methoxyphenyl)nitrone (0.849 mmol, 0.230g) and N-methylmaleimide (0.937 mmol, 0.104g) in benzene (25ml) were refluxed for 4h. The benzene was then evaporated under reduced pressure. The residue was crystallized from benzene-

petroleum ether (1:3) to give cis-3b (0.127g, 39%); m.p. 162-164°C; ir (potassium bromide) :.1708cm^{-1} (C=O); ^{1}H nmr (deuteriated chloroform) : δ 2.62(s, 3H, CH_3), 3.01(s, 3H, CH_3), 3.74(m, 2H, H_B and H_C, J=5.47 Hz), 3.83(s, 3H, CH_3), 4.87(d, 1H, H_A, J=6.57 Hz), 5.14(s, 2H, CH_2), 6.83(m, 3 aromatic H), 7.26(m, 5 aromatic H); ms (EI, 70 eV) : m/z 382(M^+).

2,6-Dimethyl-3-(p-nitrophenyl)-1-oxa-2,6-diazabicyclo[3.3.0]octane-5,7-dione, cis-3c and trans-3c

N-Methyl-C-(p-nitrophenyl)nitrone (0.83 mmol, 0.150g) and N-methylmaleimide (0.93 mmol, 0.103g) in benzene (25) were refluxed for 6h. The benzene was then evaporated. The residue was subjected to thin layer chromatography (eluant, Methanol:Chloroform:Petroleum Ether, 1:3:2) to yield cis-3c (92mg, 38%, Rf=0.72) and trans-3c (57mg, 24%, Rf=0.56).

2,6-Dimethyl-3-(p-nitrophenyl)-1-oxa-2,6-diazabicyclo[3.3.0]octane-5,7-dione, cis-3c

M.p. 210-212°C; ir(potassium bromide) : 1720cm^{-1} (C=O); ^{1}H nmr (deuteriated chloroform) : δ 2.66(s, 3H, CH_3), 3.85(m, 2H, H_B and H_C, J=8.2 Hz), 4.92(d, 1H, H_A, J=7.2 Hz), 7.38-8.2(m, 4 aromatic H); ms (EI, 70 eV) : m/z 291(M^+). *Anal.* Calcd. for $C_{13}H_{13}N_2O_5$: C, 53.61; H, 4.50; N, 14.43. Found: C, 54.13; H, 4.87; N, 13.88.

2,6-Dimethyl-3-(p-nitrophenyl)-1-oxa-2,6-diazabicyclo[3.3.0]octane-5,7-dione, trans-3c

M.p. 180-182°C; ir(potassium bromide) : 1704cm^{-1} (C=O);^{1}H nmr (deuteriated chloroform) : δ 2.55(s, 3H, CH_3), 3.07(s, 3H, CH_3), 3.63(dd, 1H, H_B, J=4.27 Hz), 4.15(broad d, 1H, H_C, J=4.03 Hz), 4.92(d, 1H, H_A, J=7.36 Hz), 7.53-8.24(m, 4 aromatic H); ms (EI, 70 eV) : m/z 291(M^+).

2,6-Dimethyl-3-(p-chlorophenyl)-1-oxa-2,6-diazabicyclo[3.3.0]octane-5,7-dione, cis-3d and trans-3d

N-methyl-C-(p-chlorophenyl)nitrone (1.1 mmol, 0.186g) and N-methylmaleimide (1.2 mmol, 0.132g) in benzene (25 ml) were refluxed for 5h. The benzene was then evaporated under reduced pressure. The residue was extracted with petroleum ether. The petroleum ether extract was evaporated and the residual oil was crystallized from petroleum ether to give trans-3d (48mg, 16%). After the extraction, the remaining solid was crystallized from benzene-petroleum ether (1:3) to give cis-3d (63mg, 20%).

2,6-Dimethyl-3-(p-chlorophenyl)-1-oxa-2,6-diazabicyclo[3.3.0]octane-5,7-dione, trans-3d

M.p. 131-133°C; ir(potassium bromide) : 1705cm^{-1} (C=O); ^{1}H nmr (deuteriated chloroform) : δ 2.49(s, 3H, CH_3), 3.05(s, 3H, CH_3), 3.62(dd, 1H, H_B, J=3.83 Hz), 4.02(broad d, 1H, H_C), 4.88(d, 1H, H_A, J=7.35 Hz), 7.30(m, 4 aromatic H); ms (EI, 70 eV) : m/z 280(M^+). *Anal.* Calcd. for $C_{13}H_{13}ClN_2O_3$: C, 55.62; H, 4.67; N, 9.98. Found: C, 56.00; H, 4.96; N, 9.60.

2,6-Dimethyl-3-(p-chlorophenyl)-1-oxa-2,6-diazabicyclo[3.3.0]octane-5,7- dione, cis-3d

M.p. 181-183°C; ir (potassium bromide) : 1710cm^{-1} (C=O); ^{1}H nmr (deuteriated chloroform) : δ 2.63(s, 3H, CH_3), 2.99(s, 3H, CH_3), 3.74(m, 2H, H_B and H_C, J=8.23 Hz), 4.88(d, 1H, H_A, J=6.97 Hz), 7.10-7.30(m, 4 aromatic H); ms (EI, 70 eV) : m/z 280(M^+). *Anal.* Calcd. for $C_{13}H_{13}ClN_2O_3$: C, 55.62; H, 4.67; N, 9.98. Found: C, 55.39; H, 4.87; N, 9.64.

Acknowledgements

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