

SYNTHESIS OF SOME BICYCLO HETEROCYCLIC SYSTEMS INCLUDING AN ISOXAZOLIDINE RING

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Abstract: *Some bicyclo and spiro isoxazoline derivatives were obtained from 1,3-dipolar cycloadditions of nitrones to reactive dipolarophiles and their stereochemical structures were determined by NMR and X-Ray data.*

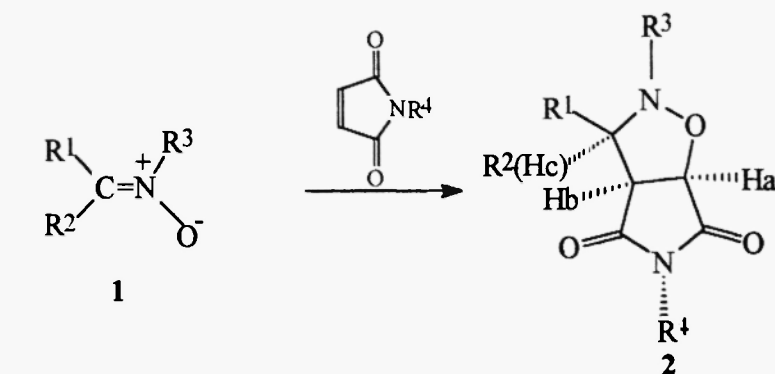
Introduction

1,3-Dipolar cycloaddition of nitrones to different unsaturated systems have been the subject of extensive investigations during the last two decades. Among the products there are indolizine, quinolizine, isoquinoline and indole alkaloids which have significant biological activities¹⁻⁹. The literature search revealed that less examples have appeared for the cycloadditions of nitrones to reactive dipolarophiles such as N-methyl and N-phenyl maleimides. In this study, we would like to report here cycloaddition chemistry of some aromatic and exocyclic nitrones to N-methyl and N-phenyl maleimide to give corresponding isoxazole derivatives.

Results and Discussion

Heating nitrones **1 a-e** in benzene (80°C) in the presence of N-methyl maleimide resulted to afford only one cycloadduct as endo products which was reasoned from ¹H NMR spectra of the reaction mixtures. Thus, the coupling constants of the protons H_a ranging 7.2-7.55 Hz for cycloadducts **2 a-f**, respectively and those of the protons H_b 8.0-8.6 Hz, and for H_c ranging 7.16-8.97 Hz shows that these protons have a cis stereochemistry. On the other hand, cycloaddition of exocyclic nitrone **1 f** to N-methyl maleimide and N-phenyl maleimide gave the cycloadducts **2 g** and **2 h**. The protons H_a and H_b in **2 g,h** also have cis stereochemistry and this was confirmed by X-ray crystallographic data. Measurement of

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	R ¹	R ²	R ³		R ¹	R ²	R ³	R ⁴
1a	p-NMe ₂ -C ₆ H ₄	H	Ph	2a	p-NMe ₂ -C ₆ H ₄	H	Ph	Me
1b	3,4(OH) ₂ -C ₆ H ₄	H	Ph	2b	3,4(OH) ₂ -C ₆ H ₄	H	Ph	Me
1c	p-MeS-C ₆ H ₄	H	Ph	2c	p-MeS-C ₆ H ₄	H	Ph	Me
1d	p-MeO-C ₆ H ₄	H	Ph	2d	p-MeO-C ₆ H ₄	H	Ph	Me
1e	2-Naphthyl	H	Ph	2e	2-Naphthyl	H	Ph	Me
1f	-(CH ₂) ₅ -		Ph	2f	2-Naphthyl	H	Ph	Ph
				2g	-(CH ₂) ₅ -		Me	Me
				2h	-(CH ₂) ₅ -		Me	Ph

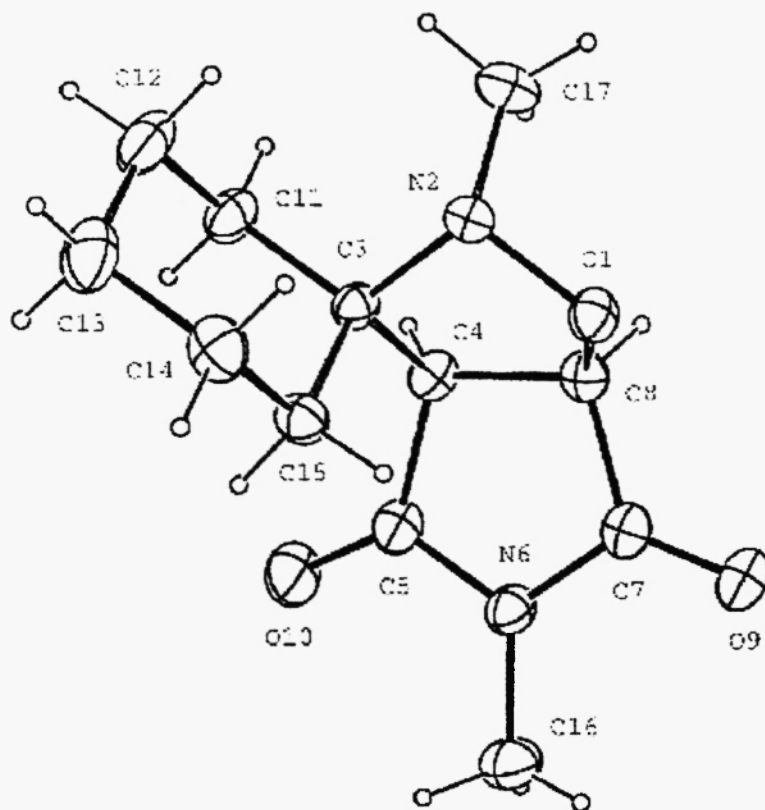
Scheme

proton NMR of the reaction mixtures indicated that the only *cis* stereoisomers formed with high stereoselectivity. These structures agree also with the previous studies on the cycloaddition of N-methyl and N-phenyl maleimide to the similar systems¹⁰⁻¹².

As a typical example, X-Ray structure of the cycloadduct **2g** was shown below.

Experimental

Melting points were determined with a Büchi 510 apparatus and uncorrected. IR spectra were recorded on a Shimadzu 8201 spectrometer. ¹H NMR spectra were recorded on a Philips (300 MHz) and Bruker (200 and 400 MHz) spectrometers with the solvents noted. Chemical shifts are reported in the δ scale in ppm relative to TMS as internal standard.

X-Ray crystallographic structure of **2g**

Mass spectra were obtained on a VG high resolution mass spectrometer. Merck Silica Gels (230-400 Mesh) for flash column and HF254 for thin layer chromatography. Nitrones **1 a-f** were synthesized according to the procedures described in literature^{7,8,14} and characterized by IR, NMR and MS data.

General procedure for the synthesis of cycloadducts **2 a-h**

3,7-Diaza-3-methyl-7-phenyl-8-(4-N,N-dimethylaminophenyl)-6-oxabicyclo[3.3.0]octane-2,4-dione **2a.** A solution of **1a** (0.120 g, 0.5 mmol) and N-methylmaleimide (0.059 g, 0.525 mmol) in benzene (2 mL) was heated at 70-75°C for 2h. After evaporation of the solvent recrystallization of the crude product from benzene-n-hexane gave **2a** (0.142 g, 87 %), mp: 152-153°C. IR (KBr), 1705 (C=O) cm⁻¹. NMR (CDCl₃) 7.29- 6.62 (m, 9H, ArH), 5.00 (d, J=7.2 Hz, H_a), 4.60 (d, J= 8.96 Hz, H_c), 3.80 (t, J=8.6 Hz, H_b), 2.93 (s, 6H, NMe₂), 2.67 (s, 3 H, NMe). MS (FAB) m/z : 351 (M⁺, 100), 240 (36), 231 (19), 224 (17), 174 (6), 149 (23). Anal. Calcd. for C₂₀H₂₁N₃O₃: C, 66.03; H, 6.46; N, 12.83. Found. C, 66.30; H, 6.22; N, 12.76.

3,7-Diaza-3-methyl-7-phenyl-8-(3,4-dihydroxyphenyl)-6-oxabicyclo[3.3.0] octane-2,4-dione 2b. Reaction time, 3h, benzene-n-hexane 0.124 g, 73 %, mp: 190°C (dec.). IR (KBr) 1699 (C=O) cm^{-1} . NMR (CDCl_3) 9.40 (s, 2 H, 2 OH), 7.80-6.80 (m, 8H, ArH), 5.05 (d, 1H, $J=7.2$ Hz, H_a), 4.90 (d, 1H, $J=7.16$ Hz, H_c), 4.10 (t, 1H, $J=8$ Hz, H_b), 2.65 (s, 3H, NMe). MS (FAB) m/z (%): 340 ($M+H$, 32), 230 (42), 213 (7), 101 (100). Anal. Calcd. for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_5$: C, 63.52; H, 4.73; N, 8.23. Found. C, 63.65, H, 5.05; N, 7.90

3,7-Diaza-3-methyl-7-phenyl-8-(4-methylthiophenyl)-6-oxabicyclo [3.3.0] octane-2,4-dione 2c. Reaction time, 2h, benzene-petroleum ether, 0.145 g, 91 %, mp: 165-166°C. IR (KBr) 1705 (C=O) cm^{-1} . NMR (CDCl_3) 7.41- 6.91 (m, 9H, ArH), 5.06 (d, 1 H, $J=7.39$ Hz, H_a), 4.66 (d, 1H, $J=8.84$ Hz, H_c), 3.85 (t, 1 H, $J=8.4$ Hz, H_b), 2.95 (s, 3H, NMe), 2.70 (s, 3H, SMe). MS (FAB) m/z (%) 354 ($M+H$, 100), 241 (11), 228 (27), 226 (6). Anal. Calcd. for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$. C, 64.38; H, 5.11; N, 7.90. Found. C, 64.25; H, 5.20; N, 8.05.

3,7-Diaza-3-methyl-7-phenyl-8-(4-methoxyphenyl)-6-oxabicyclo[3.3.0] octane-2,4-dione 2d. Reaction time, 4h, benzene-n-hexane 0.165 g, 67 %, mp: 139-140°C. IR (KBr) 1716 (C=O) cm^{-1} . NMR (CDCl_3) 7.36-6.85 (m, 9H, ArH), 5.09 (d, 1H, $J=7.55$ Hz, H_a), 4.66 (d, 1H, $J=8.97$ Hz, H_c), 3.85 (t, 1H, $J=8.06$ Hz, H_b), 3.80 (s, 3H, OMe), 2.99 (s, 3H, NMe). MS (FAB) m/z (%) 338 (M^+ , 100), 228 (13), 226 (5), 210 (11), 161 (5), 104 (6). Anal. Calcd. for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_4$. C, 67.44; H, 5.36; N, 8.27. Found. C, 67.55; H, 5.15; N, 7.85.

3,7-Diaza-3-methyl-7-phenyl-8-(2-naphthyl)-6-oxabicyclo[3.3.0] octane-2,4-dione 2e. Reaction time, 2h, benzene-n-hexane 0.140 g, 78 %, mp. 167-169°C. IR (KBr) 1708 (C=O) cm^{-1} . NMR (CDCl_3) 7.97-6.90 (m, 12H, ArH), 5.00 (d, 1H, $J=7.23$ Hz, H_a), 4.70 (d, 1 H, $J=7.16$ Hz, H_c), 4.01 (t, 1 H, $J=8$ Hz, H_b), 2.70 (s, 3H, NMe). MS (FAB) m/z (%) 358 (M^+ , 100), 248 (12), 232 (11), 181 (5), 104 (6). Anal. Calcd. for $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_3 \cdot 0.25 \text{H}_2\text{O}$. C, 72.81; H, 5.13; N, 7.71. Found. C, 72.85; H, 5.25; N, 8.05.

3,7-Diaza-3,7-diphenyl-8-(2-naphthyl)-6-oxabicyclo[3.3.0] octane-2,4-dione 2f. Reaction time, 5h, benzene-n-hexane 0.210 g, 50 %, mp 184°C (dec.). IR (KBr) 1714 (C=O) cm^{-1} . NMR (CDCl_3) 8.04-7.02 (m, 17H, Ar H), 5.13 (d, 1H, $J=7.36$ Hz, H_a), 4.72 (d,

1H, J=7.00 Hz, H_c), 4.20 (t, 1H, J=8.05 Hz, H_b). MS (FAB) m/z (%): 420 (M+H, 100), 248 (22), 232 (15), 101 (6). Anal.Calcd. for C₂₇H₂₀N₂O₃. 2.25 H₂O. C, 70.34; H, 5.35; N, 6.07. Found. 70.05; H, 4.7; N, 6.07.

3,7-Diaza-3,7-dimethyl-6-oxaspiro[bicyclo[3.3.0]octane-8,1'-cyclohexane]-2,4-dione 2g.

Reaction time, 4h. benzene-n-hexane after chromatography (EtOAc-petroleum ether; 1:1), 0.420 g, 34 %. mp: 127-128°C. IR (KBr) 1701 (C=O) cm⁻¹. NMR (CDCl₃) 4.67 (d, 1H, J= 7.50 Hz, H_a), 3.45 (d, 1H; J=7.50 Hz, H_b), 3.01 (s, 3H, NMe), 2.58 (s, 3H, NMe), 2.0-1.20 (m, 10H, -(CH₂)₅-). MS (EI) m/z (%) : 238 (M⁺, 46), 195 (100), 182 (26), 110 (22), 78 (21), 62 (22). Anal.Calcd. for C₁₂H₁₈N₂O₃. C, 60.48; H, 7.61; N, 11.75. Found. C, 60.22; ; H, 7.82; N, 11.82.

3,7-Diaza-3-methyl-7-phenyl-6-oxaspiro[bicyclo[3.3.0]octane-8,1'-cyclohexane]-2,4-

dione 2_h. Reaction time, 4h. benzene-petroleum ether, 0.221 g, 40 %, mp 70-72°C. IR (KBr) 1708 (C=O) cm⁻¹. NMR (CDCl₃) 7.50-7.20 (m, 5H, ArH), 4.85 (d, 1H, J=7.70 Hz, H_a), 3.60 (d, 1H, J= 7.70 Hz, H_b), 2.65 (s, 3H, NMe), 2.0-1.2 (m, 10H, -(CH₂)₅-). MS (EI) m/z (%) 300 (M⁺, 66), 257 (100), 173 (57), 110 (60), 68 (34). Anal.Calcd. for C₁₇H₂₀N₂O₃. C, 67.98; H, 6.71; N, 9.32. Found. C, 68.12; H, 6.77; N, 9.07.

Single Crystal X-ray analysis of 2_g. The crystallographic data were obtained with a Enraf-Nonius CAD-4-diffractometer at 297 K using Cu Kα X-radiation (λ = 1.54184 Å). 22<θ<44 °. C₁₂ H₁₈ N₂ O₃, 0.38X0.28X0.10 mm, M_r=232.24 orthorhombic, plate, colorless, space group, P2₁2₁2₁, a=6.2430(5) Å, b=7.8671 (6) Å, c=24.142(2) Å, α=90, β=90, γ=90, V=1185.7(2) Å³, Z=4, D_x =1.300 Mg m⁻³, μ =0.751 mm⁻¹, R_{int}=0.03628, θ_{max}=75.0°, h=0→7, k=-9→0, l=-30→0, T_{min}=0.9007, T_{max} = 0.9989.

Acknowledgement

We are grateful for the financial support of Kocaeli University Research Fund. Dr. F.Fronczek (Department of Chemistry, Louisiana State University, U.S.A) is gratefully acknowledged for obtaining X-ray data of the compounds.

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Received on November 9, 1998