SYNTHESIS OF ISOMERIC CAGE-FUNCTIONALIZED DIACYLFUROXANS AND THEIR SUBSEQUENT THERMOLYTIC FISSION TO AN ACYL NITRILE OXIDE[†]

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Abstract- A three step synthesis of a mixture of isomeric cage-functionalized furoxans (**4**) is described. When heated in the presence of ethyl propiolate, furoxans (**4**) undergo cycloreversion to afford two equivalents of the corresponding acyl nitrile oxide (**5**) which is trapped *in situ* by ethyl propiolate. The trapping reaction proceeds *via* a highly regioselective [3 + 2] cycloaddition to produce **6** (61% yield), whose structure was established unequivocally *via* application of X-Ray crystallographic methods. The observed regioselectivity of the [3 + 2] cycloaddition process is rationalized *via* frontier molecular orbital analysis by using semiempirical MO calculations (AM1 Hamiltonian) and at the HF/3-21G* level of theory.

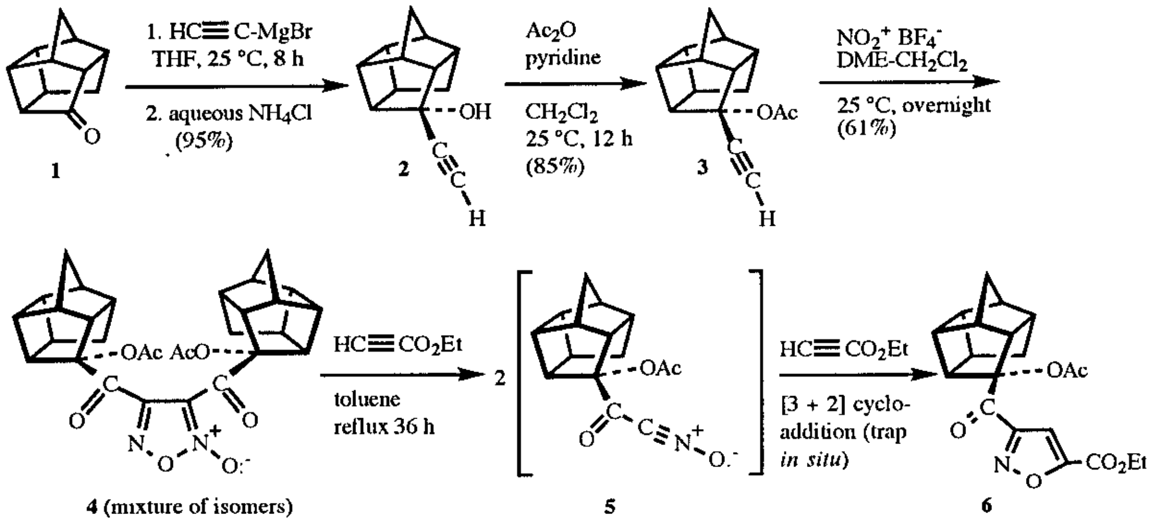
1,2,5-Oxadiazole-2-oxides (furoxans) constitute an important class of heterocyclic compounds that has received considerable attention in recent years as intermediates in the synthesis of biologically active compounds (e. g., medicinal and/or pharmacological agents and pesticides).[1] Nitro-functionalized furoxans and 1,2,5-oxadiazoles (furazans) derived therefrom are of interest as high density, relatively insensitive energetic materials.[2] As part of continuing programs that are concerned with (i) the synthesis and chemistry of polycyclic cage compounds[3] and (ii) the synthesis and explosive performance properties of novel, high density energetic materials,[4] we now report the synthesis of unusual, cage-functionalized diacylfuroxans of the type (**4**) along with the results of a study of their chemical behavior during thermolysis.

Our synthesis of the mixture of isomeric furoxans (**4**) is shown in Scheme 1. Addition of ethynylmagnesium bromide to pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one (**1**)[5] afforded *exo*-8-ethynylpentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-*endo*-8-ol (**2**) in excellent yield. Subsequent reaction of **2** with Ac_2O produced the corresponding *O*-acetyl derivative (**3**) (85% yield). Finally, reaction of **3** with NO_2^+ BF_4^- afforded the corresponding furoxans (**4**) (mixture of isomers, 61%).[6] The presence of a strong IR band at 1610 cm^{-1} and the observed UV λ_{max} (EtOH) 275 nm (log ε 3.45) confirm the presence of a furoxan ring in **4**.[6] The fact that **4** was obtained as a mixture of two isomers is confirmed by the fact that its integrated, gated-decoupled and proton noise-decoupled ^{13}C NMR spectrum in benzene-d_6 solvent contains resonance signals that correspond to 60 nonequivalent carbon atoms.

Additional verification of the proposed furoxan structure for **4** was obtained *via* its thermal cracking to the corresponding acyl nitrile oxide (**5**, Scheme 1), which was trapped *in situ via* highly regioselective [3 + 2] cycloaddition to ethyl propiolate, thereby producing the corresponding, substituted isoxazole (**6**) (61% yield). The structure of **6** was established unambiguously *via* application of X-Ray crystallographic methods (see the Experimental Section).

[†] Dedicated to Professor Koji Nakanishi on the occasion of his 75th birthday.

Scheme 1



The observed regioselective formation of the 5-substituted isoxazole (with virtually complete exclusion of for-mation of the corresponding 4-substituted oxazole) *via in situ* trapping of **5** by ethyl propiolate is remark-able. Precedent for this observation is provided by the corresponding results reported by Britelli and Boswell[7] for a series of acyl nitrile oxides that were generated *via* thermolysis of diacylfuroxans and subsequently were trapped *in situ* by a variety of dipolarophiles.

Britelli and Boswell[7] accounted for their observations by performing extended Hückel and CNDO/2 frontier molecular orbital calculations. The HOMO$_{\text{(acyl nitrile oxide)}}$ - LUMO$_{\text{(dipolarophile)}}$ interaction directs 4-substituted isoxazole formation, while the HOMO$_{\text{(dipolarophile)}}$ - LUMO$_{\text{(acyl nitrile oxide)}}$ interaction controls formation of the 5-substituted oxazole.[8] The results of the calculations performed by Britelli and Boswell[7] suggest that the regiochemistry of cycloaddition of acyl nitrile oxides of the type RC(O)CNO to electron-poor acetylenic dipolarophiles is controlled by the HOMO$_{\text{(dipolarophile)}}$ - LUMO$_{\text{(acyl nitrile oxide)}}$ interaction, thereby accounting for the observed preference for formation of 5-substituted isoxazoles *via* their trapping experiments.

In the present study, frontier molecular orbital energies for **5** and for ethyl propiolate were calculated at the semiempirical level (AM1 Hamiltonian)[9] and at the HF/3-21G* level of theory. The results thereby obtained are shown in Figures 1 and 2. Inspection of the data in Figure 1 reveals that, at both the semiempirical and *ab initio* levels of theory, HOMO$_{\text{(dipolarophile)}}$ - LUMO$_{\text{(acyl nitrile oxide)}}$ is the favorable, and, hence, regiochemically controlling frontier orbital interaction. This conclusion is confirmed *via* inspection of the relevant calculated orbital coefficients (Figure 2). Our prediction, which is in accord with experiment and with computational conclusions reached previously by Britelli and Boswell,[7] is most pronounced at the highest level of theory employed in either study. Furthermore, this result confirms their previous conclusion that, according to Sustman's[10] classification scheme, acyl nitrile oxides are "Type III" dipoles.

EXPERIMENTAL

Melting points are uncorrected. Elemental microanalytical data was obtained by personnel at M-H-W Laboratories, Phoenix, AZ.

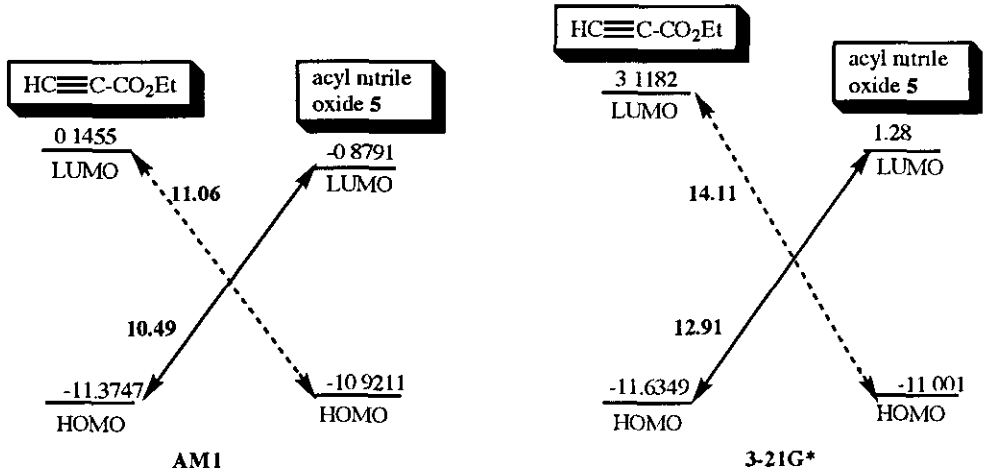


Figure 1. Frontier molecular orbital energies at the semiempirical (AM1)[9] level and at the HF/3-21G* level of theory for [3 + 2] cycloaddition of ethyl propiolate to acyl nitrile oxide (5).

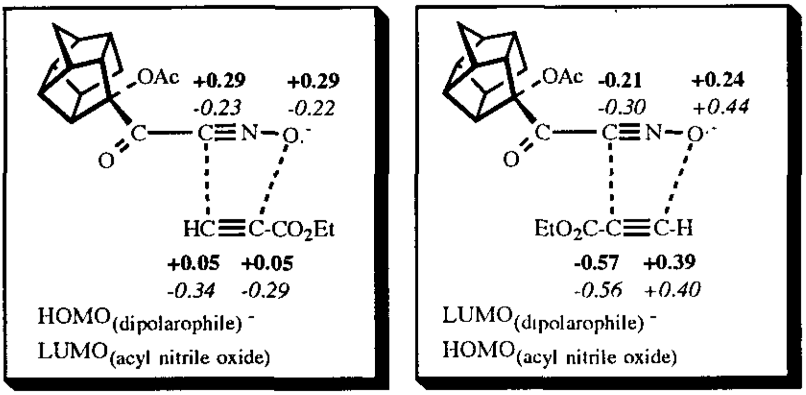


Figure 2. Calculated HOMO and LUMO orbital coefficients for ethyl propiolate and acyl nitrile oxide (5). The results obtained *via* semiempirical (AM1)[9] calculations are shown in boldface; the corresponding results calculated at the HF/3-21G* level of theory are shown in italics.

***exo*-8-Ethynylpentacyclo[$5.4.0.0^{2,6}.0^{3,10}.0^{5,9}$]undecan-*endo*-8-ol (2).** To a stirred solution of ethynylmagnesium bromide in THF (150 mL of a 0.5 M solution in THF, 75 mmol) a solution of ketone (**1**)[5] (8.0 g, 50 mmol) in THF (25 mL) was added dropwise with stirring, and the resulting solution was stirred at ambient temperature for 8 h. Saturated aqueous NH_4Cl (30 mL) was added to quench the reaction, and the resulting aqueous suspension was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with water (2 x 30 mL), dried (Na_2SO_4), and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified *via* column chromatography on silica gel by eluting with 1:6 EtOAc-hexane). Pure **2** (8.8 g, 95%) was thereby obtained as a colorless microcrystalline solid: mp 90-91°C (lit.,[11] mp 90-91 °C). The infrared, ^1H NMR, and ^{13}C NMR spectra of this material were essentially identical with the corresponding spectral data that has been published previously for **2**.[11]

***exo*-8-Ethynylpentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-*endo*-8-acetate (3).** A solution of **2** (5.0 g, 27 mmol) and pyridine (13 mL, 161 mmol) in CH_2Cl_2 (80 mL) was cooled to 0 °C *via* application of an external ice-water bath. To this cooled solution was added dropwise with stirring Ac_2O (7.5 mL, 80 mmol). The external cold bath was removed, and the reaction mixture was stirred at ambient temperature for 12 h. Methylene chloride (50 mL) was added, and the resulting mixture was washed sequentially with water (2 x 50 mL), 10% aqueous HCl (2 x 50 mL), and water (2 x 50 mL). The organic layer was dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. Compound (**3**) (5.2 g, 85%) was thereby obtained as a colorless, viscous oil, which was further purified *via* column chromatography on silica gel by eluting with 20% EtOAc-hexane. Application of this procedure afforded pure **3** as a colorless, viscous oil; IR ($CHCl_3$): 3296 (s), 2962 (vs), 2877 (s), 1745 (vs), 1375 (s), 1244 (vs), 1128 (m), 1047 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 0.98 (br d, J = 13.6 Hz, 1 H), 1.15 (d, J = 13.6 Hz, 1 H), 1.65 (*A*B, J_{AB} =13.0, 1 H), 1.84 (A*B*, J_{AB} =13.0, 1 H), 2.00 (s, 3 H), 2.12- 2.80 (m, 8 H), 3.10 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.2 (q), 29.1 (t), 34.8 (t), 36.5 (d), 39.7 (d), 41.8 (d), 42.7 (d), 43.6 (d), 46.4 (d), 47.5 (d), 49.6 (d), 72.7 (d), 79.6 (s), 84.9 (s). Anal. Calcd for $C_{15}H_{16}O$: C, 78.92; H, 7.06. Found: C, 79.11; H, 6.89.

Reaction of 3 with Nitronium Tetrafluoroborate.[6] A solution of NO_2^+ BF_4^- (6.1 g, 46 mmol) in dimethoxyethane (DME, 100 mL) was cooled to 0 °C *via* application of an external ice-water bath. To this cooled solution was added dropwise wish stirring a solution of **3** (3.5 g, 15.4 mmol) in CH_2Cl_2 (80 mL). The external cold bath was removed, and the reaction mixture was allow to stir at ambient temperature overnight. The reaction mixture was washed with water (3 x 50 mL). The organic layer was dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified *via* column chromatography on silica gel by eluting with 1:7 EtOAc-hexane. Compound (**4**) (mixture of isomers, 2.5 g, 61%) was thereby obtained as a colorless, viscous oil which gradually solidified when allowed to stand at ambient temperature for several days. The resulting solid, a mixture of isomers, displayed mp 119-123 °C; IR (KBr): 2962 (s), 2868 (s), 1737 (vs), 1710 (s), 1610 (vs), 1464 (m), 1372 (m), 1251 (s), 1234 (s), 1049 (m), 781 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.19-1.24 (m, 8 H), 1.64-1.70 (*A*B, J_{AB} = 12.8 Hz, 4 H), 2.00-2.05 (m, 12 H), 2.28 (m, 8 H), 2.63-2.78 (m, 24 H), 3.10-3.30 (m, 4 H); ^{13}C NMR (benzene-d_6) δ 20.9-20.0 (4 C, q, number of carbon atoms determined *via* careful integration of the gated decoupled ^{13}C NMR spectrum of **4**), 29.8 (4 C , t), 35.0-35.2 (4 C, t), 36.6 (2 C, d), 36.8 (d), 37.7 (d), 39.0 (d), 39.1 (d), 40.4 (d), 40.6 (d), 41.3 (d), 41.8 (d), 41.9 (d), 42.1 (d), 42.2 (d), 42.4 (2 C, d), 42.5 (2 C, d), 43.3 (d), 44.0 (d), 44.1 (d), 44.2 (4 C, d), 46.1 (d), 46.4 (d), 47.0 (2 C, d), 47.5 (4 C, d), 90.9 (s), 91.1 (s), 92.0 (2 C, s), 112.1 (s), 112.3 (s), 153.0 (s), 153.1 (s), 170.4 (s), 170.7 (s), 171.1 (2 C, s). 186.0 (s), 186.2 (s), 187.6 (2 C, s). This material was used as obtained in the next synthetic step without additional purification or characterization.

Reaction of 4 with Ethyl Propiolate.[7] A mixture of furoxan (**4**) (mixture of isomers, 600 mg, 1.09 mmol) and ethyl propiolate (0.22 mL, 2.1 mmol) in toluene (10 mL) was refluxed for 36 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified *via* column chromatography on silica gel by eluting with 1:9 EtOAc-ligroin. Compound (**6**) (250 mg, 61%) was thereby obtained as a colorless, viscous oil that gradually solidified upon standing at ambient temperature. Recrystallization of the material thereby obtained from EtOAc-*i*-PrOH afforded pure **6** as a colorless microcrystalline solid: mp 110-111 °C; IR ($CHCl_3$): 2966 (vs), 2883 (m), 1734 (vs), 1712 (vs), 1568 (m), 1454 (m), 1363 (s), 1276 (s), 1045 (m), 1010 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 1.15 (d, *J* = 10.0 Hz, 2 H), 1.33 (t, *J* = 9.0 Hz, 3 H), 1.60 (d, *J* = 10.2 Hz, 1 H), 1.93 (br s, 4 H), 2.13 (d, *J* = 13.6 Hz, 1 H), 2.24 (br s, 1 H), 2.54-2.82 (m, 5 H), 3.22 (br s, 1 H), 4.35 (q, *J* = 9.0 Hz, 2 H), 7.30 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.5 (q), 21.4 (t), 29.6 (t), 34.6 (d), 36.2 (d), 38.5 (d), 41.9 (d), 42.0 (d), 42.3 (d), 43.9 (d), 46.9 (d), 47.2 (d), 62.9 (t), 90.8 (d), 156.5 (s), 160.6 (s), 161.1 (s), 171.5 (s), 190.3 (s). Anal. Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70. Found: C, 64.57; H, 5.53.

X-Ray Crystal Structure of 6. All data were collected on an Enraf-Nonius CAD-4 diffractometer by using the ω-2θ scan technique, Mo Kα radiation (λ = 0.71073 Å) and a graphite monochromator. Standard procedures used in our laboratory for this purpose have been described previously.[12] Pertinent X-Ray data are given in Table 1, and a structure drawing for **6** appears in Figure 3. Data were corrected for Lorentz and polarization effects but not for absorption. The structure was solved by direct methods (SHELXS-86)[13] and the model was refined by using full-matrix least-squares techniques. The oxygen and nitrogen atoms were refined by using anisotropic thermal parameters. Hydrogen atoms were located on difference maps and then were included in the model in idealized positions {U(H) = 1.3 B_{eq}(C)] where possible. All computations other than those specified were performed by using MolEN.[14] Scattering factors were taken from the usual sources.[15]

Table 1. X-Ray structure data for **6**

Formula	$C_{20}H_{21}NO_6$	D_c (g-cm^{-3})	1.386
Size (mm)	0.14 x 0.18 x 0.21	μ (cm^{-1})	0.96
Space Group	$P2_1/a$	2θmax	44
a (Å)	8.0568 (7)	Total refl.	2441
b (Å)	18.989 (2)	Unique refl.	2265
c (Å)	12.0344 (9)	Rint	0.023
α (°)	90	I ≥ 3σ(I)	820
β (°)	104.843 (6)	Parameters	114
γ (°)	90	R, wR	0.0473; 0.0480
V ($Å^3$)	1779.7 (3)	$(\Delta/\sigma)_{max}$	<0.01
Z	4	ρ_{min}; ρ_{max}	0.20, -0.23

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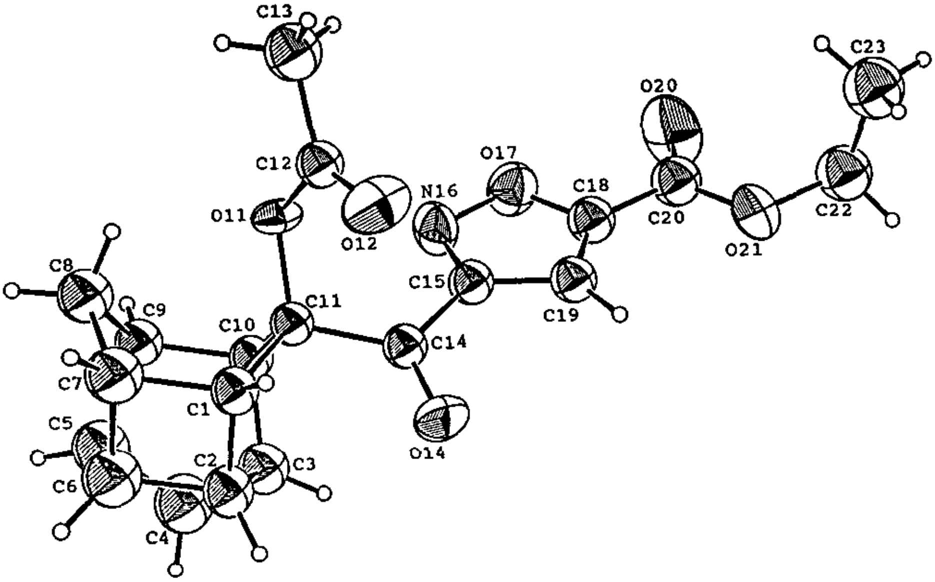

Figure 3. X-Ray structure drawing of **6.**

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