Oxidative Intramolecular Cyclization of Diketoximes: Synthesis of 1,5-Dinitro-*cis*-bicyclo[3.3.0]octane[1]

Walter W. Zajac, Jr.,* Gary J. Speier, John H. Buzby, and Thomas R. Walters

Department of Chemistry, Villanova University, Villanova, PA 19085-1699

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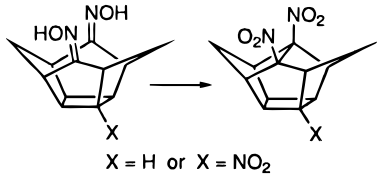
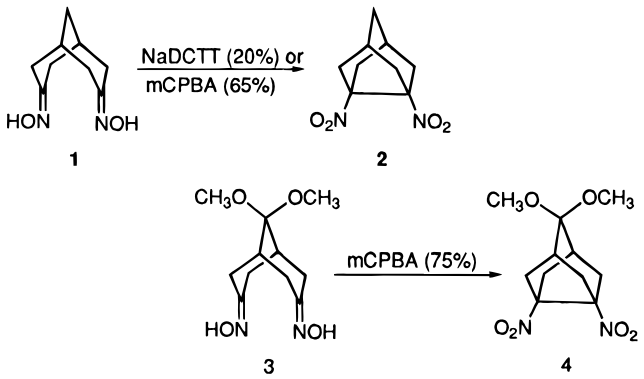
Introduction

Strained polycyclic molecules possessing multiple nitro groups are of particular interest because of there potential use as high-energy density materials. A review of the synthesis of this class of molecules indicates that one of the most successful strategies for the introduction of the nitro group is the oxidation of the corresponding amine precursor.[2] While this strategy has proven effective for isolated amino groups, attempts to extend it to vicinal diamines, in order to generate the corresponding vicinal dinitro compounds, have thus far proven unsuccessful.[3] The problem with the oxidation of vicinal diamines appears to result from the cleavage of the bond connecting the nitrogen-substituted carbons.[4] It is postulated that the cleavage occurs as the stepwise oxidation proceeds via either a Grob-type fragmentation[5] or a "push-pull" mechanism.[6]

This problem has limited the number of polycyclic vicinal dinitro compounds which have been synthesized to date.[7,8] Most of the successful syntheses generate the key vicinal dinitro function through either the oxidative cyclization of dioximes or the coupling of carbons already bearing nitro substituents. The dioxime strategy was deemed to be more generally applicable because many of the synthetic sequences used to assemble the polycyclic framework often result in the integration of carbonyls into the carbon skeleton and thus obviate the need for the independent synthesis of the requisite dinitro precursor. The syntheses of 2,3-dinitrohexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{4,8}$.$0^{9,12}$]dodecane and its 2,6,9-trinitro analog are representative examples which employ the oxidative cyclization of the appropriate dioxime precursor as the key step for generating the vicinal dinitro groups[8a,b] (*vide infra*).



The publication of two recent communications[9,10] regarding the transannular cyclization of dioximes has prompted us to report our related findings. Our interest in the use of diketoximes as precursors for polycyclic vicinal dinitro compounds was stimulated by an earlier observation that the reaction of 1-sodio-3,5-dichloro-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione (NaDCTT) with the dioxime of bicyclo[3.3.1]nonane-3,7-dione **(1)** resulted in the formation of not only the isomeric bis-geminal chloronitro compounds expected from the oxidative chlorination but also provided 3,7-dinitronoradamantane **(2)** in 20% yield.[11] It was subsequently determined that the oxidative cyclization of dioxime **1** to **2** could be accomplished more efficiently (65%) using 3-chloroperoxybenzoic acid (MCPBA) in refluxing acetonitrile containing urea and dibasic sodium phosphate.[8,9] The utility of the MCPBA-mediated cyclization was further demonstrated by the cyclization of the dioxime of 9,9-dimethoxybicyclo[3.3.1]nonane-3,7-dione **(3)** to 9,9-dimethoxy-3,7-dinitronoradamantane **(4)** in 75% yield.[12] These results suggested that oxidative cyclizations might be feasible in other related systems.



Results and Discussion

The reactions of cyclooctane-1,5-dione dioxime[13] **(5)** were investigated because of the structural homology between **1** and **5**, with **5** representing the less conformationally restricted desmethylene analog of the bicyclic **1**, and the fact that transannular reactions are well prece-

(1) Presented at the 27th Middle Atlantic Reginal Meeting of the American Chemical Society, Hofstra University, Hemstead, NY, June 2−4, 1993.

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(4) Zajac, W. W., Jr.; Gagnon, J. L. *Tetrahedron Lett.* **1995**, *36*, 1803.

(5) (a) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535. (b) Grob, C. A.; Schiess, P. W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1.

(6) If the bond scission is the result of a Grob fragmentation, then it is likely to occur when one, or both, of the nitrogen atoms is oxidized to the hydroxylamino oxidation state wherein the hydroxyl function may serve as an effective leaving group. The "push-pull" mechanism is postulated to become operational when electron pair donation from a less oxidized nitrogen (e.g., amino or hydroxylamino) provides "the push" toward a more highly oxidized nitrogen, "the pull" (e.g., nitroso or nitro) which facilitates the bond scission process. Theoretical aspects of the latter mechanism are considered in the following: (a) Murray, J. S.; Concha, M.; Seminario, J. M.; Politzer, P. *J. Phys. Chem.* **1991**, *95*, 1601. (b) Murray, J. S.; Seminario, J. M.; Politzer, P. *Struct. Chem.* **1991**, *2*, 153.

(7) (a) Methyl 3,9-dinitro-*exo*-10-methoxypentacyclo[5.3.0.$0^{2,5}$.$0^{3,9}$.$0^{4,8}$]-decane-8-carboxylate: Marchand, A. P.; Jin, P.-W.; Flippen-Anderson, J. L.; Gilardi, R.; George, C. *J. Chem. Soc., Chem. Commun.* **1987**, 1108. (b) 1,2,2-Trinitroadamantane: Dave, P. R.; Axenrod, T.; Qi, L.; Bracuti, A. *J. Org. Chem.* **1995**, *60*, 1895.

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(9) Camps, P.; Munoz-Torrero, D. *Tetrahedron Lett.* **1994**, *35*, 3187. This reference reports a 59% yield for the **1** to **2** conversion.

(10) Dave, P. R.; Forohar, F.; Axenrod, T.; Qi, L.; Watnick, C.; Yazdekhasti, H. *Tetrahedron Lett.* **1994**, *35*, 8965.

(11) Walters, T. R.; Zajac, W. W., Jr.; Woods, J. M. *J. Org. Chem.* **1991**, *56*, 316.

(12) U.S. Patent 5,105,301, Zajac, W. W., Jr., 1992.

(13) Micheli, R.; Hojas, Z.; Cohen, N.; Paritosh, D.; Portland, L.; Sciamanna, W.; Scott, M.; Wehrli, P. *J. Org. Chem.* **1975**, *40*, 675.

(14) For example: 1,5-diamino-3,3,7,7-tetracarbethoxy-*cis*-bicyclo-[3.3.0]octane is formed by reductive cyclization of the dioxime of 3,3,7,7-tetracarbethoxycyclooctane-1,5-dione: Cope, A. C.; Kagan, F. *J. Am. Chem. Soc.* **1958**, *80*, 5499. Bicyclo[3.3.0]octane-1-carboxaldehyde is formed by the acid-catalyzed cyclization of the enol form of 5-methylenecyclooctanecarboxaldehyde: Graham, S. H.; Jonas, D. A. *J. Chem. Soc., Chem. Commun.* **1968**, 1091.

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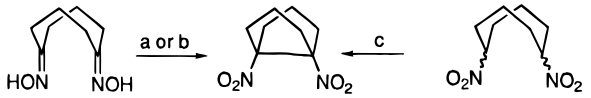
dented in the cyclooctane system.[12] It was found that when **5** was reacted with either MCPBA[6] or with NaDCTT,[9] the same product was isolated in 57% and 51% yields, respectively. Although the ^{13}C NMR spectrum of the product was in accordance with that expected for 1,5-dintro-*cis*-bicyclo[3.3.0]octane **(6)**, the structure was conclusively proven by X-ray crystallography.[26]



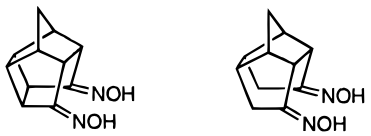
5 **6** **7**

a: m-CPBA, urea, NaH_2PO_4, CH_3CN, reflux; b: NaDCTT/EtOAc, $NaHCO_3$; c: aq. NaOH, $K_3Fe(CN)_6$, pentane.

It should be noted that this result is consistent with a recent communication which reports related ring closures for the dioximes of 1,5-diazacyclooctane-3,7-diones which lead to 1,5-dinitro-3,7-diaza-*cis*-bicyclo[3.3.0]octanes under similar conditions.[10]

The scope of the oxidative cyclization was further investigated using a number of readily available dioximes. It was determined that the dioximes of *cis*-bicyclo[3.3.0]octane-3,7-dione,[9] 2,6-heptanedione, 1,4-cyclohexanedione,[15] and 2,5-hexanedione were oxidized but failed to cyclize and yielded instead the corresponding dinitro compounds 3,7-dinitro-*cis*-bicyclo[3.3.0]octane,[9] *dl*/*meso* 2,6-dinitroheptane,[16b] 1,4-dinitrocyclohexane,[15] and *dl*/*meso*-2,5-dinitrohexane[16b] in 51%, 50%, 50%, and 10% yields, respectively. The yields of the oxime oxidations were modest due to the formation of significant amounts of ketone and/or lactone byproducts. The generation of the ketones[17] may result from simple hydrolysis of the oxime or oxidative cleavage of the oximino group via an *aci*-nitro intermediate. Subsequent peracid-mediated Baeyer−Villiger reactions of the ketones yields the corresponding lactones.

Finally, the dioximes of two polycyclic cage diketones, pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione[18] **(8)** and tetracyclo[6.3.0.0^{4,11}.0^{5,9}]undecane-2,8-dione[19] **(9)**, were subjected to the oxidative cyclization reaction conditions.

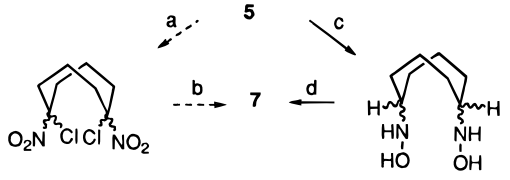


8 **9**

A very complex reaction mixture was obtained in each case, and the ^1H and ^{13}C NMR spectra of the crude product contained no peaks consistent with the presence of the cyclized vicinal dinitro compound. The prominent peaks in the spectra were again consistent with the presence of both ketone and lactone byproducts (*vide supra*).[8c,20]

The availability of the uncyclized dinitro derivatives from a number of the oxime oxidations (*vide supra*) afforded the serendipitous opportunity to investigate an alternative cyclization strategy. This method is based upon a recent report detailing the ferricyanide-mediated intramolecular coupling of acyclic 1,5-dinitronates to yield vicinal dinitrocyclopentanes.[16] The *dl*/*meso*-2,6-dinitroheptane was successfully cyclized to a mixture of isomeric 1,2-dimethyl-1,2-dinitrocyclopentanes, in accordance with the published report.[16b] However, this method did not result in cyclization for any of the other substrates obtained from the above dioxime oxidations.

The attempt to extend the dinitronate cyclization to the cyclooctane system required the synthesis of the requisite precursor, 1,5-dinitrocyclooctane **(7)**. Several strategies for the synthesis of **7** were evaluated. The reductive dehalogenation[22] of 1,5-dichloro-1,5-dinitrocyclooctane **(10)**, prepared by oxidative chlorination of dioxime **5**, was not viable due to the competitive cyclization which occurs during the oxidative chlorination of the dioxime and precludes the formation of **10**. The ozonolysis of phosphine imines, available from the reaction of the appropriate azide with a phosphine, was also investigated.[23] Although 1,5-diazidocyclooctane was available from the ditosylate and a vigorous exothermic reaction of the diazide with tri-*n*-butylphosphine was observed, no phosphine imine could be isolated. Furthermore, the attempted ozonolysis of the crude product without isolation of the putative bis-phosphine imine also failed to yield **7**.



10 **11**

a: NaDCTT, EtOAc, $NaHCO_3$; Pd/C, H_2; c: $NaBH_3CN$, HOAc; d: O_3, EtOAc, -78°.

A successful strategy for the synthesis of dinitro derivative **7** involved the initial reduction of dioxime **5** to what is presumably the dihydroxylamine **11** and subsequent ozone-mediated oxidation to the requisite **7**. The crucial step proved to be the **5** to **11** transformation which required a modification[24] of the standard conditions for affecting the sodium cyanoborohydride-mediated reduction of oximes.[25] The oxidation of the crude reduction mixture with ozone permitted the isolation of **7** as a mixture of stereoisomers in 40% yield from **5**. It was determined that the major loss of yield was associated with the reduction step. The ^1H and ^{13}C NMR spectra of the crude reduction products indicated mixtures containing two major components whose relative ratios were observed to vary with the reaction conditions. Ozonolysis of the crude reduction mixtures resulted in the formation of **7** and 5-nitrocyclooctanone in ratios consistant with those observed for the two major reduc-

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(17) Olah, G. A.; Ramaiah, P.; Lee, C.-S.; Prakash, G. K. S. *Synlett* **1992**, 337.
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(26) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

tion products. One was assigned the structure of dihydroxylamine **11,** based on spectroscopic data and ozonolysis behavior, while the other remains unidentified but was observed to yield 5-nitrocyclooctanone upon subsequent oxidation by ozone.

The same facility with which the cyclization of the acyclic 1,5-dinitronate took place to generate the cyclopentane derivatives[16] was manifested in the ferricyanide-mediated intramolecular coupling reaction of **7** which lead to the expected product **6** in 80% yield. Although the yield from the cyclization of the dinitronate is superior to that obtained from the direct oxidative cyclization of dioxime **5**, the modest yield obtained for the synthesis of requisite precursor **7** makes the overall transformation less efficient (32% versus >50% overall from **5**).

In summary, the reactivities of the substrates were observed to fall into three distinct reactivity categories in which both, neither, or only one of cyclization methods was successful. Both methods were successful in generating 1,5-dinitro-*cis*-bicyclo[3.3.0]octane from the appropriate cyclooctane precursor. The *dl*/*meso*-2,6-dinitroheptanes[16b] could be successfully cyclized to a mixture of stereoisomeric 1,2-dimethyl-1,2-dinitrocyclopentanes while the corresponding dioxime strategy failed. Neither method was successful for the majority of the substrates examined. Studies to elucidate the reasons for these differences in reactivity are continuing.

Experimental Section

General Methods. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were determined in $CDCl_3$ solutions at 200 and 53.3 MHz, respectively. Infrared spectra were obtained on an Analect FX-6160 FT-IR spectrophotometer. Preparative layer chromatography (PLC) was carried out on 0.1 × 20 × 20 cm silica gel 60 F_{254} plates (Merck). Microanalyses were performed by Galbraith Laboratories, Knoxville, TN.

1,5-Dinitro-*cis*-bicyclo[3.3.0]octane (6). Method A. A mixture of the bisoxime of 1,5-cyclooctanedione **(5)** (150 mg, 0.96 mmol), anhydrous dibasic sodium phosphate (2.0 g, 14 mmol), crushed urea (530 mg, 9 mmol), and dry acetonitrile (30 mL) was refluxed for 0.5 h under nitrogen. Portions (six) of MCPBA (1.1 g, 3.0 mmol) were then added at 15 min intervals. Reflux was maintained for 2 h following the addition and the reaction mixture allowed to cool to room temperature. The yellow-green solution was decanted from the white precipitate and the residue was washed with cold acetonitrile (100 mL). The combined organic fractions were concentrated to a solid residue which was dissolved in CH_2Cl_2 (50 mL). The CH_2Cl_2 solution was washed with saturated aqueous $NaHCO_3$ (50 mL) containing $NaHSO_3$ (5 g), saturated aqueous $NaHCO_3$ (3 × 50 mL), water (50 mL) and dried (Na_2SO_4). Following the removal of the solvent *in vacuo*, the resultant yellow solid was purified by PLC. Isolation of the band at $R_f = 0.78$ ($CHCl_3$) yielded 1,5-dinitro-*cis*-bicyclo-[3.3.0]octane **(6)** (100 mg, 57%) as a white amorphous solid, mp 170−181 °C dec: ^{1}H NMR ($CDCl_3$) δ 2.6−3.0 (m, 4H), 2.0−2.4 (m, 4H), 1.6−2.0 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 102.6, 38.8, 22.5. Anal. Calcd for $C_8H_{12}N_2O_4$: C, 48.00; H, 6.04; N, 13.99. Found: C, 47.98; H, 5.98; N, 13.88.

Method B. A mixture of the bisoxime of 1,5-cyclooctanedione **(5)** (800 mg, 4.7 mmol), $NaHCO_3$ (10 g), H_2O (100 mL) and EtOAc (100 mL), was stirred at room temperature for 5 min, and 1-sodio-3,5-dichloro-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione (10.75 g 47 mmol) was added portionwise (six at 5 min intervals). The reaction mixture was stirred vigorously for 24 h. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed sequentially with NaOH (0.2 N, 100mL), H_2O (3 × 50 mL), and brine (100 mL) and dried (Na_2SO_4). The removal of the solvent *in vacuo* and PLC afforded **6** (480 mg, 51%).

Method C. A single portion of $Na(CN)BH_3$ (500 mg, 8.3 mmol) was added to a vigorously stirred solution of bisoxime **5** (1 g, 5.8 mmol) in glacial HOAc (10 mL) which had been cooled to 0 °C, under N_2. After 3 h, the HOAc was removed *in vacuo*. The residue was suspended in H_2O (3 mL), and the pH was adjusted to 11 with 6 N KOH followed by saturation with NaCl. The mixture was extracted with EtOAc (2 × 75 mL) and CH_2Cl_2 (2 × 75 mL). The combined organic phases were dried (Na_2SO_4), the solvent was removed *in vacuo* to afford a white solid which was dissolved in EtOAc (70 mL) and cooled to −78 °C, and an O_3/O_2 steam was passed through the soluton for 30 min until a blue color persisted. The solution was allowed to warm to rt over an hour while a flow of oxygen was maintained. The solvent was removed in vacuo, and the residue was subjected to PLC. Two compounds were isolated: 5-nitrocyclooctanone as a yellow oil (397 mg, 40%), $R_f = 0.50$ (CH_2Cl_2) [^{1}H NMR ($CDCl_3$) δ 4.2−4.4 (pentet, 1H), 2.5−2.8 (m, 4H), 1.9−2.4 (m, 4H) 1.79 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 215.0, 85.6, 41.5, 32.3, 22.8; IR (thin film) 1550 (s), 1700 (s)], and a mixture of *cis*- and *trans*-1,5-dinitrocyclooctane **(7)** as a colorless oil (469 mg, 40%), $R_f = 0.70$ (CH_2Cl_2) [^{1}H NMR ($CDCl_3$) δ 4.4−4.6 (m, 2H). 1.8−2.4 (m, 8H), 1.5−1.8 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 86.5, 85.7, 30.9, 30.5, 21.2, 20.0; IR (thin film) 1548 (s), 1383 (m)]. A solution of **7** (320 mg, 1.6 mmol) in H_2O/MeOH (8 mL, 1:1) was added dropwise, under N_2, to a vigorously stirred biphasic pentane/H_2O mixture (35 mL/20 mL) containing $K_3Fe(CN)_6$ (5.4 g, 16 mmol) and NaOH (200 mg, 7.2 mmol). The reaction mixture was stirred for an additional 3 h after which time the layers were separated. The aqueous layer was saturated with NaCl and extracted with pentane (4 × 25 mL). The combined pentane layers were dried (Na_2SO_4), the solvent was removed *in vacuo*, and the solid residue was subjected to PLC to provide **6** (260 mg, 80%).

3,7-Dinitronoradamantane (2).[11] The bisoxime of bicyclo-[3.3.1]nonane-3,7-dione was subjected to the reaction conditions of method A (*vide supra*). A 65% yield of **2** was obtained following PLC ($R_f = 0.66$; silica gel, $CHCl_3$).

9,9-Dimethoxy-3,7-dinitronoradamantane (4).[12] The bisoxime of 9,9-dimethoxybicyclo[3.3.1]nonane-3,7-dione was subjected to the reaction conditions of method A (*vide supra*). A 75% yield of **4** was obtained following PLC ($R_f = 0.76$; silica gel, $CHCl_3$): ^{1}H NMR ($CDCl_3$) δ 2.3−2.8 (m, 8H), 3.2 (s, 6H), 3.4−3.6 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 99.94, 55.8, 42.89, 40.2, 15.2; IR (thin film) 1549 (s).

3,7-Dinitro-*cis*-bicyclo[3.3.0]octane.[9] The bisoxime of *cis*-bicyclo[3.3.0]octane-3,7-dione was subjected to the reaction conditions of method A (*vide supra*). A 51% yield of 3,7-dinitro-*cis*-bicyclo[3.3.0]octane, as a mixture of *exo-exo*, *exo-endo*, and *endo-endo* stereoisomers, was obtained following PLC ($R_f = 0.90$; silica gel, $CHCl_3$).

1,4-Dinitrocyclohexane.[15] The bisoxime of 1,4-cyclohexanedione was subjected to the reaction conditions of method A (*vide supra*). A 65% yield of 1,4-dinitrocyclohexane, as a mixture of *cis* and *trans* stereoisomers, was obtained following PLC ($R_f = 0.78$; silica gel, $CHCl_3$)

2,5-Dinitrohexane.[16b] The bisoxime of 2,5-hexanedione was subjected to the reaction conditions of method A (*vide supra*). A 10% yield of 2,5-dinitrohexane, as a mixture of *dl* and *meso* stereoisomers was obtained following PLC ($R_f = 0.88$; silica gel, $CHCl_3$).

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Supporting Information Available: NMR data (^{13}C) for compounds **7** and 5-nitrocyclooctanone (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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