Research Article

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A new method for functionalizing α,γ-dinitro compounds at the β-position: application to the cyclization of β-alkoxy-α,γ-dinitro compounds

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Treatment of 2,4-dinitropentane with bromine and sodium methoxide in methanol, affords formation of an ether product, 2,4-dibromo-3-methoxy-2,4-dinitropentane, in 59% yield as a mixture of three diastereomers. This observation has led to a general synthesis of 3-alkoxy-2,4-dibromo-2,4-dinitropentanes, obtained in 75-86% yield from 2,4-dibromo-2,4-dinitropentane as the preferred reactant. 4-Bromo-2,4-dinitro-2-pentene has been identified as an intermediate in these reactions. The nitroalkene has been isolated and undergoes conjugate addition with alkoxides to afford the same ether products after brominative work-up. The nitroalkene undergoes conjugate addition with sodium azide to give 3-azido-2,4-dibromo-2,4-dinitropentane in 38% yield as a mixture of two isomers in which the (*R,*R**) isomer predominates. Sequential treatment of 2,4-dibromo-2,4-dinitropentane with sodium methoxide followed by sodium iodide and acetic acid gives 3-methoxy-2,4-dinitropentane in 63% yield, the overall product of simple methoxylation of 2,4-dinitropentane. However, attempted complete debromination of 2,4-dibromo-3-methoxy-2,4-dinitropentane with excess sodium iodide and acetic acid results only in monodebromination to give 2-bromo-3-methoxy-2,4-dinitropentane in 86% yield. Likewise, 2-bromo-3-ethoxy-2,4-dinitropentane is formed in 93% yield from the ethoxy analog. A mechanistic rationale is offered for condition-specific removal of the second Br atom in these reactions. Treatment of 3-methoxy-2,4-dinitropentane with potassium acetate/iodine in dimethyl sulfoxide affords formation of 4,5-dihydro-3,4-dimethyl-3-methoxy-4-nitroisoxazole 2-oxide in 30% yield as a single diastereomer. Conversion of 2-bromo-3-methoxy-2,4-dinitropentane in 15% yield to 4,5-dihydro-3,4-dimethyl-3-methoxy-4-nitroisoxazole 2-oxide is also possible by using potassium acetate in dimethyl sulfoxide. The mechanistic pathways for formation of 4,5-dihydro-3,4-dimethyl-3-methoxy-4-nitroisoxazole 2-oxide apparently involve unstable 3-methoxy-1,2-dimethyl-1,2-dinitrocyclopropane as the common intermediate. Similarly, 2-bromo-3-ethoxy-2,4-dinitropentane affords 4,5-dihydro-3-ethoxy-3,4-dimethyl-4-nitroisoxazole 2-oxide in 13% yield.**

Supporting information may be found in the online version of this article.

Keywords: debromination; methoxylation; nitro; nitronate; push–pull cyclopropane

INTRODUCTION

The introduction of a new group at the β-site to an existing nitro group is an important synthetic transformation not readily accomplished. Nitroalkanes usually undergo reactions at the α-position (i.e., the carbon bearing the nitro group) rather than the β-position. There are, however, some known exceptions where reaction does occur at the β-position. For instance, heptanitrocubane undergoes substitution at the one remaining unsubstituted C atom, a site that is located β to three nitro groups.[1] Substitution of the H atom at this site by an eighth nitro group is a key synthetic transformation in the synthesis of octanitrocubane. Nevertheless, it is uncommon for H atom substitution at the β-site of nitro compounds to occur readily. Here, a new method for introducing alkoxy groups at the central C atom of 2,4-dinitropentane is reported. This new method amounts to substitution of an H atom located β to two nitro groups.

Several methods for the cyclization of 1,3-dinitro compounds to *trans*-1,2-dinitrocyclopropanes were previously reported.[2] Thus, 2,4-dinitropentane (**1**) can be converted to *trans*-1,2-dimethyl-1,2-dinitrocyclopropane. A similar cyclization approach to synthesis of *trans*-1,2-dinitrospiro[2.2]pentane was also reported.[3] These compounds have potential uses as energetic materials.[4] Here, we describe the corresponding cyclizations of 3-alkoxy-2,4-dinitropentane derivatives. These reactions, however, take a much different course than cyclization of simple 1,3-dinitro compounds.

RESULTS

During a routine bromination of 2,4-dinitropentane in the presence of sodium methoxide, we observed a surprising result. The main product formed was the ether **2a–c**, isolated in 59% yield as a mixture of three separable diastereomers. (Scheme 1). During the course of bromination, an H atom located β to both nitro groups has been replaced by a methoxy group.

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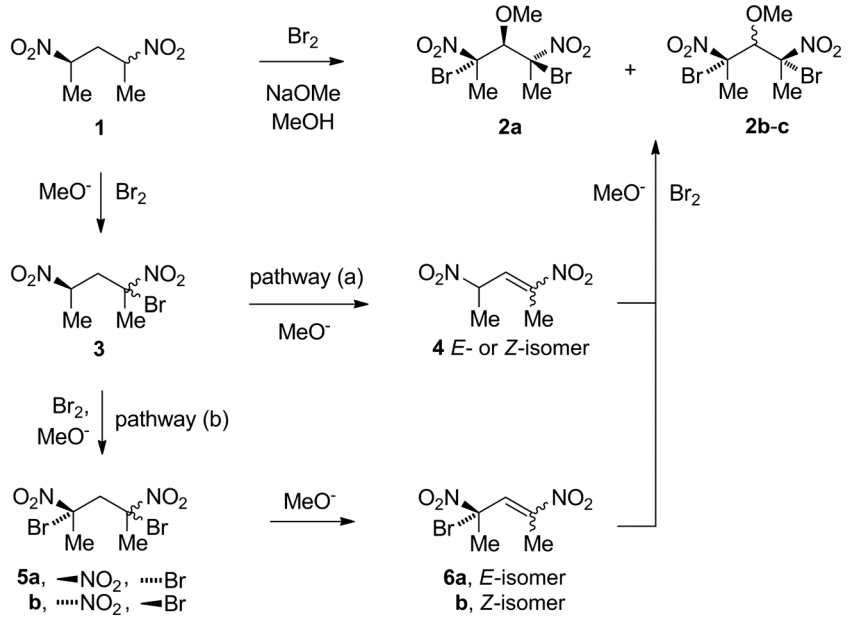


Scheme 1. Pathways for formation of 2,4-dibromo-3-methoxy-2,4-dinitropentane (**2a–b**)

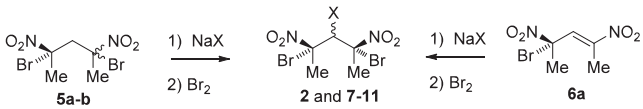
It seemed likely that formation of ether **2a–c** involved a nitroalkene intermediate formed by bromination and subsequent dehydrobromination. Conjugate addition reactions of nitroalkenes do indeed lead to β-functionalized nitro compounds.[5] However, it was not clear whether monobromination or dibromination occurred prior to nitroalkene formation. Thus, either nitroalkene **4** or nitroalkene **6** could be the precursor for incorporation of the methoxy group. Initially, pathway (a) involving conversion of 2-bromo-2,4-dinitropentane (**3**) to nitroalkene **4** was considered more likely. It was thought that conjugate addition to nitroalkene **4** was more plausible than conjugate addition to the more hindered nitroalkene **6**. Conjugate additions are usually quite sensitive to the steric environment at the site undergoing attack, and therefore, nitroalkene **6** seemed unlikely as the intermediate in ether formation. However, 2,4-dibromo-2,4-dinitropentane (**5a–b**) is readily preparable. It was therefore possible to probe pathway (b) as a potential route to the observed ether products.

Initially, dibromide **5a–b** was prepared by employing sodium *n*-butoxide as the base in the bromination reaction.[2] Here, the main product was **5a–b**, although a small amount of easily separated side product (likely the ether but this was not confirmed) was also present. Subsequently, conditions for bromination with sodium methoxide as base leading to dibromide **5a–b** were developed and were thereafter routinely employed.

When dibromide **5a–b** is treated with sodium methoxide followed by bromine, ether **2a–c** is obtained in 83% yield (Table 1). Thus, pathway (b) is confirmed as a route to the ether products. However, pathway (a) might be a minor competing reaction when 2,4-dinitropentane (**1a–b**) is the starting material: this has not been excluded as a possibility. Similarly, treatment of **5a–b** with other sodium alkoxides in the corresponding alcohol followed by bromine gives the ether products **7–9** in 75–90% yield. This method is preferential to direct reaction of **1a–b** that also gives ethers **7–8**, because it is generally cleaner and gives better yields of the ether products.

The nitroalkene **6a–b** can be isolated as a separable mixture of *E* and *Z* isomers. Under optimized conditions using sodium ethoxide as base and quenching with bromine after 7.5 min, the *E* isomer **6a** is obtained in 30% yield. The *E* isomer both predominates and is more stable to storage, although early in the reaction, a significant amount of *Z* isomer **6b** is present. Using a reaction time of only 15 s, the *Z* isomer **6b** is obtained in 3% yield accompanied by the *E* isomer in 5% yield. Structure assignments are based in part by analogy to the known compounds (*E*)-2-nitro-2-butene and (*Z*)-2-nitro-2-butene.[6] The vinyl proton signals for 2-nitro-2-butene are at δ 7.20 for the *E* isomer and δ 5.87 for the *Z* isomer, respectively. Nitroalkene isomers

Table 1. Products obtained from the reactions of 2,4-dibromo-2,4-dinitropentane (**5a-b**) and (*E*)-4-bromo-2,4-ditropentene (**6a**) with NaX/bromine



Product	X	Yield, % from **5a–b**	Yield, % from **6a**	Isomer ratios from **5a–b** (from **6a**)		
				R, R**	First meso	Second meso
2a–c	OMe	83[a]	72[b]	83 (72)	11 (13)	6 (15)
2a–c	OMe	59[c]		40	5	55
7a–c	OEt	86[b]	75[b]	85 (81)	9 (10)	6 (8)
8a–c	OPr	90[b]		75	13	12
9a–b	OCH_2Ph	75[d]		83	17	
10a–c	OPr-*i*	0	18[b]	(42)	(29)	(29)
11a–b	N_3	32[e]	38[b]	87 (60)	13 (40)	

[a]0.1 M NaOMe. [b]0.1-0.24 M NaX. [c]1.7 M NaOMe. [d]0.8 M $NaOCH_2Ph$. [e]0.15 M NaN_3 and 0.03 M NaOEt

6a–b exhibit somewhat more deshielded vinyl proton signals at δ 7.57 and δ 6.34, respectively.

Nitroalkene **6a** also undergoes reaction with alkoxides in the corresponding alcohols producing the same products after subsequent bromination during work-up as obtained from **5a–b**. In one case, reaction with sodium 2-propoxide, nitroalkene **6a** gives the ether product **10a–c** in 18% yield, whereas 2,4-dibromo-2,4-dinitropentane (**5a–b**) fails to give any **10a–c**. Failure to obtain **10a–c** from **5a–b** is attributed to failure of the elimination step. The somewhat hindered base is apparently unable to deprotonate the hindered central C atom of **5a–b**.

The major diastereomer (**2a** and **7a–11a**) produced in the previous reactions is typically the (*R**, *R**) diastereomer (an enantiomer pair). Isomer structure assignment is based on the four separate ^{13}C NMR signals attributable to C-2/C-4 (diastereotopic) and C-1/C-5 (diastereotopic) C atoms. There are also separate signals attributable to the C 1 and C 5 methyl protons in the ^{1}H NMR spectrum. The remaining meso isomers, (*R,r,S*) diastereomers and/or (*R,s,S*) diastereomers, give just one ^{13}C NMR signal for the C-2/C-4 enantiotopic atom pair and another signal for the C-1/C-5 enantiotopic atom pair. In each case, a single signal is present attributable to the C-1 and C-5 methyl protons in the ^{1}H NMR spectrum. However, the assignment of minor isomers as either the (*R,r,S*) diastereomer or the (*R,s,S*) diastereomer is not unambiguous and has not been made.

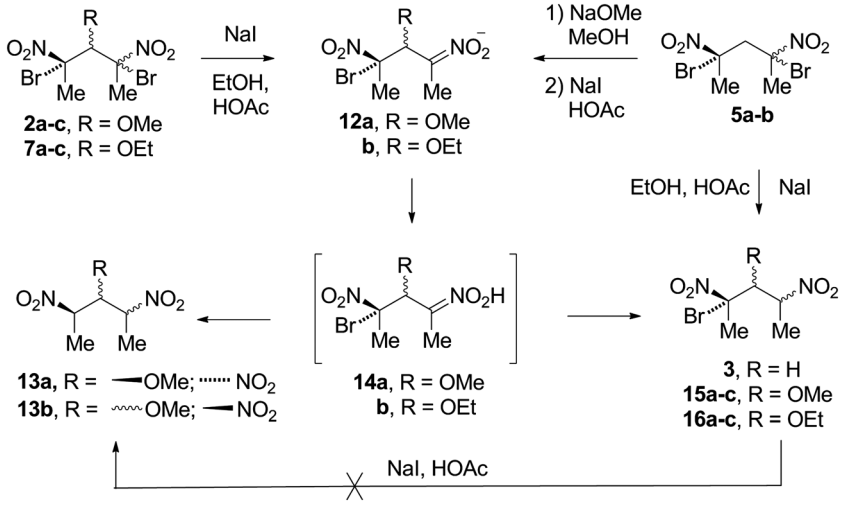
Although the (*R**, *R**) isomer is typically major from reactions of both **5a–b** and **6a**, the isomer ratios are somewhat different. The preference for the (*R**, *R**) isomer is somewhat greater (**2a/2b/2c** 83:11:06, respectively) when **5a–b** is used as the starting material than when nitroalkene **6a** is employed (**2a/2b/2c** 72:13:15, respectively). There is also a marked sodium methoxide concentration dependence for reaction of **5a–b**. Concentrated methoxide gives a significantly different isomer ratio (**2a/2b/2c** 40:05:55, respectively) compared with reaction with dilute methoxide (**2a/2b/2c** 83:11:06, respectively). Thus **2c** (one of the meso isomers) becomes the predominant product from reaction of **5a–b** with concentrated sodium methoxide. The reason for this concentration dependence is unclear. Perhaps the ratio favoring meso isomer **2c** at high base concentration is the kinetic product ratio, whereas the ratio with more dilute base is the ratio after equilibration of the nitronate products present before quenching with bromine.[7]

A broader range of nucleophiles has been examined for the functionalization of dibromide **5a–b** and nitroalkene **6a**. This has met with only limited success. When **5a–b** is treated with a solution of sodium ethoxide and sodium azide followed by bromine, a mixture of the azide **11a–b** (two diastereomers) and ethyl ether **7a–c** is obtained. Azide **11a–b** is the minor product, obtained as a 45:55 mixture with the ether. The azide minor diastereomer **11b** is obtained pure in 5% yield, but the major diastereomer **11a** cannot be chromatographically separated from the ether. Using sodium methoxide as the base, azide competition with ether formation is less successful. Here the product ratio is 28:72 azide **11a–b**/ether **2a–c**. It is thought that the ether/azide ratios in these reactions reflect the difference in nucleophilicity of the salts involved.

The kinetic equation $\log k = s_N(E + N)$ has been used to correlate nucleophile reactivity in conjugate addition reactions of benzylidenemalonitriles.[8] The equation should be applicable to conjugate addition reactions of **6a**, at least for semi-quantitative nucleophile comparison. In the equation, s_N = a nucleophile-dependent sensitivity factor, N = a nucleophilicity parameter, and E = an electrophilicity parameter. Of paramount importance are the pertinent values of N. The nucleophilicity parameters of methoxide ion,[9] $N = 14.51$, and azide ion,[10] $N = 14.54$, are very nearly equal (both values determined in 91:9 methanol–acetonitrile). Sodium ethoxide has a slightly lower nucleophilicity parameter, $N = 16.08$,[9] than does azide ion, $N = 16.30$,[10] (both values in 91:9 ethanol–acetonitrile). It is therefore not surprising that both alkoxide ions compete favorably with azide ion. Considering the steric environment at C-3, the terminal C atom of the conjugated system present in **6a**, the linear azide ion might be expected to perform somewhat better than less approachable nonlinear alkoxide ions. Nevertheless, alkoxide ions proved to be the better nucleophiles.

Reaction of nitroalkene **6a** with sodium azide in aqueous ethanol eliminates the competition for ether formation, allowing **11a-b** to be isolated free from ether products. Even so, reaction is slow and the best yield of **11a–b** attainable is 38%.

Reaction of nitroalkene **6a** with either sodium benzenethiolate or sodium ethanethiolate gives none of the expected thioether product. Thiolates are generally much better nucleophiles than alkoxides, so these results are unexpected. Sodium cyanide also fails to give a nitrile product on reaction with **6a**. Two possible explanations have been considered, both centered on preferential reactivity at the geminal bromonitro site rather than the C,C double bond site. Possibly the bromonitro site is debrominated giving nitronate formation. Geminal bromonitro compounds transfer the Br atom to thiolate anions[11] and carbanions.[12,2] Iodide ion also displaces bromine from geminal bromonitro compounds, a reaction that will be described later. Displacement of bromine from **6a** would give a nitronate that is presumably unstable based on the absence of identifiable products. It is also possible that single-electron transfer at the bromonitro site could occur. Geminal bromonitro compounds readily accept a single electron from either thiolates[11] or cyanide,[13] although synthetically useful reactions are normally carried out in polar aprotic solvents.



Scheme 2. Debromination of 3-alkoxy-2,4-dibromo-2,4-dinitropentanes **2a–c** and **7a–c**

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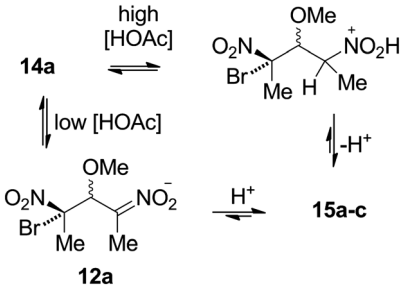
Treatment of ether **2a–c** with sodium iodide in methanolic acetic acid leads to mono debromination and formation of 2-bromo-3-methoxy-2,4-dinitropentane (**15a–c**) in 81% yield as an inseparable mixture of diastereomers. Four diastereomers are possible, but only three were detected by nuclear magnetic resonance (NMR). Of these three, one is major (81:13:6 ratio, Scheme 2). Ether **7a–c** behaves similarly to give 2-bromo-2,4-dinitro-3-ethoxypentane (**16a–c**) in 93% yield again as an inseparable mixture of three discernible diastereomers where one predominates (77:15:08 ratio). Surprisingly, neither of the monobromo ethers undergoes a second debromination with sodium iodide. Treatment of 2,4-dibromo-2,4-dinitropentane (**5a–b**) proceeds similarly to give 2-bromo-2,4-dinitropentane (**3**) as a 5:1 mixture of two diastereomers and without removal of the second bromine atom. However, successive treatment of **5a–b** with sodium methoxide and excess methanolic sodium iodide/acetic acid at an appropriate concentration affords 3-methoxy-2,4-dinitropentane **13a–b** as the major product (**13a**/**13b**/**15** 52:36:11 ratio) from which **13a–b** can be isolated as a 66:34 mixture. Only two of the three theoretically possible diastereomers have been observed, the racemic diastereomer **13a** and one of the two meso diastereomers **13b** for which the configuration at C-3 was not readily assignable by NMR. In conjunction with the initial dibromination of 2,4-dinitropentane, this sequence provides an overall method for methoxylating 2,4-dinitropentane at the 3-position.

The pathway followed for complete debromination is unusual. Monobromo ether **15a–c** cannot lie on the pathway to **13a–b** because it is not converted to **13a–b** by treatment with excess sodium iodide/acetic acid. We offer the following series of events as a probable explanation. Dehydrobromination of **5a–b** followed by conjugate addition should give the nitronate **12a** as an intermediate. Reaction of **12a** with methanolic sodium iodide/acetic acid should give initially the kinetic protonation product, nitronic acid **14a**. Before **14a** is able to tautomerize to the nitro compound **15a–c**, it is intercepted by an iodide ion ultimately affording the nonbromo ether **13a–b**. However, if **14a** tautomerizes first, the second debromination fails to occur. Consistent with this explanation, it is possible to favor formation of monobromo ether **15a–c** or nonbromo ether **13a-b** simply by manipulating the amount of acetic acid present (Table 2). The initial results where 14 equivalents of acetic acid were employed are optimum for formation of **13a–b**. If either less acid (9 equivalents) or more acid (24 equivalents or above) is employed, **15a–c** becomes the major product. These results indicate a window where the conversion of nitronic acid is sufficiently slow for iodide ion to intercept the nitronic acid and displace the second Br atom. Low acid concentration would appear to favor a significant concentration of nitronate **12a** in equilibrium with **14a**, a base-catalyzed tautomerization process for rapid formation of **15a–c** (Scheme 3). At high acetic acid concentrations, protonation of **14a** would lead to rapid formation of **15a–c**. If, indeed, the rate of nitronic acid tautomerization can be controlled by the amount of acetic acid present, general application to the synthesis of nitronic acids might be possible. However, that matter has not yet been investigated.

Table 2. Debromination dependence on quantity of acetic acid

HOAc mol equiv[a]	13a	13b	15a–c
9	<5	<2	>93
14	52	36	11
20	34	21	45
24	19	16	65
57	<5	<2	>93
108	<2	<2	>96

[a]Reaction of **5a–b** and NaOMe in MeOH/Et_2O followed by NaI/HOAc.



Scheme 3. Tautomerization of **14a**

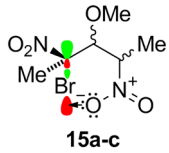
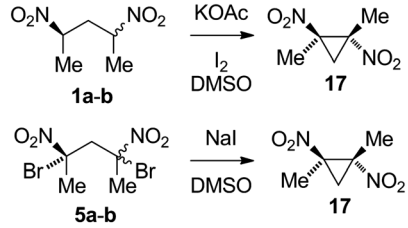


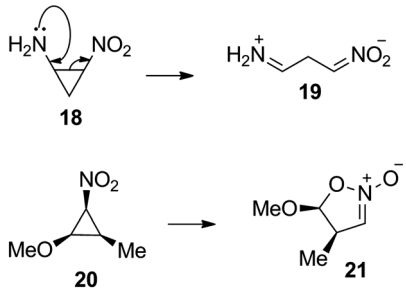
Figure 1. Electron donation to the C–Br σ* orbital

Simple α-bromonitro compounds are readily debrominated by sodium iodide/acetic acid. The nonreactivity of monobromo dinitro compounds is exceptional and seems inconsistent with a mechanistic pathway involving simple nucleophilic displacement of bromine by iodide. A stereoelectronic effect whereby the second nitro group donates electron density to the Br-lobe of the C–Br σ* orbital has been considered (Fig. 1). Such donation would presumably protect bromine from displacement by iodide ion. However, the infrared stretching frequencies for **3** and **15–16** assigned to the nitro groups are not atypical. Significant electron donation from the nitro group might be expected to alter these frequencies. Further study is underway to elucidate the actual pathway.

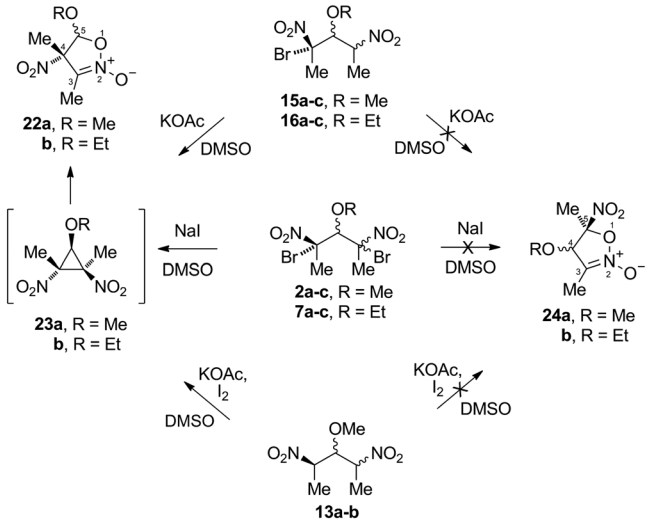
One goal of the current project was to obtain starting materials for the synthesis of functionalized dinitrocyclopropanes. Pursuant to that goal, we have now developed improved methods for preparation of *trans*-1,2-dimethyl-1,2-dinitrocyclopropane (**17**) (Scheme 4). Treatment of 2,4-dinitropentane (**1a–b**) with a DMSO solution of potassium acetate/iodine affords **17** in 56% yield. Conversion of 2,4-dinitropentane (**1a-b**) to **17** in 36% yield using dimsylsodium/iodine was previously reported.[2] Treatment of dibromide **5a-b** with sodium iodide/dimethyl sulfoxide (DMSO) gives cyclopropane **17** in 25% yield. We previously reported[2]



Scheme 4. New methods of preparing 1,2-dimethyl-1,2-dinitrocyclopropane



Scheme 5. Ring-opening reactions of push–pull nitrocyclopropane derivatives



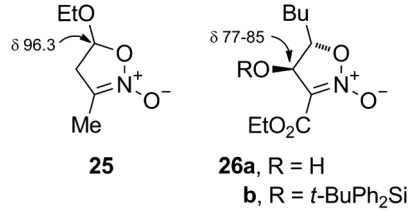
Scheme 6. Reactions generating 4,5-dihydroisoxazole-2-oxides

the conversion of **5a–b** in 25% yield to **17** by using lithium 2-nitropropanate/DMSO. That procedure, however, requires separation of 2,3-dimethyl-2,3-dinitrobutane formed as the side product. Is it then possible that the ethers **2a–c**, **7a–c**, and **13a–b** can be converted similarly to β,β′-dinitrocyclopropyl ethers by any of these methods?

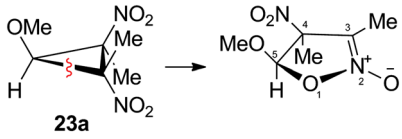
There is reason to doubt that β,β′-dinitrocyclopropyl ethers would be stable compounds because of the push–pull vicinal substituents. In a prior study, Pollitzer *et al*. reported computational results that indicate high instability for β-nitrocyclopropyl amine **18**.[14] They concluded that facile ring cleavage will occur affording conversion of **18** to open-chain zwitterion **19** (Scheme 5). One can imagine a similar cleavage process for β,β′-dinitrocyclopropyl ethers, although this cleavage may be slowed by the reduced stability of an oxonium zwitterion relative to the corresponding ammonium zwitterion.

While our work was in progress, a computational study was published by Schneider and Werz indicating that β-nitrocyclopropyl ether **20** is unstable and should spontaneously convert to the cyclic nitronate **21**.[15] Such rearrangements are known to occur both thermally and by acid catalysis.[16] Finally, an unsuccessful attempt to prepare β-nitrocyclopropyl ethers via rhodium catalyzed cycloaddition of α-nitrodiazo compounds to vinyl ethers has been reported.[16]

Attempts to prepare and isolate the β,β′-dinitrocyclopropyl ether **23a** did prove unsuccessful. However, the cyclic nitronate **22a** is obtained from three different methyl ether starting materials and the corresponding nitronate **22b** is obtained from



Scheme 7. Selected ^{13}C chemical shifts



Scheme 8. Proposed ring opening of **23a**

two different ethyl ether starting materials (Scheme 6). Treatment of **13a–b** with potassium acetate/iodine in DMSO, treatment of **15a–c** with potassium acetate/DMSO, and treatment of **2a–c** with sodium iodide/DMSO all gave **22a** as the major component of the crude product. No other new product has been identified in these reactions. Treatment of **16a–c** with potassium acetate/DMSO and treatment of **7a–c** with sodium iodide/DMSO give **22b** as the major material present in the crude product. Here, too, no other new product has been identified. These cyclic nitronates are relatively unstable and consequently difficult to characterize. During chromatographic purification on silica gel, they decompose, although rapid flash chromatography does afford a low yield of substantially purified samples (85% and 90% pure by ^1H NMR, respectively) of **22a–b**.

Two different routes were considered that could result in the formation of cyclic nitronate products. Formation of **22a–b** likely requires the intermediacy of β,β′-dinitrocyclopropyl ethers **23a–b**. Direct internal O-alkylation of the nitronate intermediates would produce the isomeric cyclic nitronates **24a–b**. The structure assignment for nitronates **22a–b** rests on a combination of typical spectral data. Thus, compounds **22a–b** each have a strong IR absorption at 1652 cm^{-1} assigned as the nitronate C,N double bond stretching frequency based on published values for related five-member cyclic nitronates.[17] Additional IR bands characteristic of a nitro compound are present for compounds **22a–b**. The ^1H NMR and ^{13}C NMR data are consistent with the structure assignments for **22a–b**. In particular, the observed ^{13}C NMR chemical shifts for CH signals attributed to C-5 (δ 100.7 and δ 99.7, respectively) are consistent with structures **22a–b** but are inconsistent with the isomeric structures **24a–b** in which the CH signals would be attributed to C-4. Chemical shift values for compounds **25**[17] and **26a–b**[18] are illustrative (Scheme 7). For **24a–b**, the CH chemical shifts should be δ 77–85 by comparison to C-4 signals of **26a–b**. The actual values of the CH signals are similar to the value for C-5 in compound **25** (δ 96.3). Finally, a nuclear Overhauser effect (NOE) experiment supports structure **22a**. Irradiation centered at δ 5.7 to saturate the H-5 atom of **22a** results in enhancement of the methoxy protons (δ 3.6, 7.9% enhancement) and C-4 methyl protons (δ 1.8, 3.1% enhancement: presumably cis to H-5) but not the C-3 methyl signal at δ 2.1. For structure **24a**, irradiation at δ 5.7 would saturate the H-4 atom. Enhancement of the C-3 methyl protons (δ 2.1) as well as the methoxy protons (δ 3.6) would be anticipated, but only the latter enhancement was observed.

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CONCLUSIONS

The formation of 3-alkoxy-2,4-dibromo-2,4-dinitropentane derivatives in the presence of bromine and base involves conjugate addition to 4-bromo-2,4-dinitro-2-pentene and subsequent bromination of the nitronate intermediate. This is a synthetically useful reaction and can be extended to the preparation of 3-azido-2,4-dibromo-2,4-dintropentane. Partial and complete debromination of the ether products is possible and can be controlled by proper choice of conditions. A variety of 3-alkoxy-2,4-dintropentane dervivatives can be converted to cyclic nitronates, a process that appears to involve β,β′-dinitrocyclopropyl ethers as intermediates. This provides experimental verification of the prediction[15] made that compounds such as 1-methoxy-2-methyl-3-nitrocyclopropane (**20**) should rearrange to cyclic nitronates. On the basis solely of the NOE enhancement of the C-4 methyl group in **22a**, it would seem that cyclopropane ring-opening occurs between the methoxy donor group and the *trans*-nitro acceptor group (Scheme 8).

EXPERIMENTAL SECTION

General

Alkoxide solutions were prepared under nitrogen from the reaction of the appropriate anhydrous alcohol with pre-cleaned sodium cut into small pieces. After the initially exothermic reaction, the mixture was refluxed briefly until all sodium was consumed, and the resulting homogenous solution was then cooled. 2,4-Dinitropentane (**1**) (1:1 mixture of meso and racemic diastereomers) was prepared by a published procedure[2] and was normally used as the mixture (chromatographic separation of the two diastereomers was previously described).

Synthesis

*2,4-dibromo-2,4-dinitropentane (**5a–b**)*

2,4-Dinitropentane (50:50 diastereomer mixture, 0.352 g, 2.2 mmol) was added dropwise over 1 min to a cold (0–5 °C) solution of sodium methoxide (0.329 g, 6.1 mmol) in methanol (5 mL), and the resulting solution was stirred for an additional 19 min. This cold solution was then added dropwise over 5 min to a second cold (0–5 °C) solution of bromine (1.04 g, 6.5 mmol) in dichloromethane (5 mL). Sufficient 10% sodium bisulfite solution was added to decolorize excess bromine. Water (25 mL) was added, and the mixture was extracted with dichloromethane (three 10-mL portions). The combined organic extracts were washed with water (25 mL), dried over anhydrous $MgSO_4$, and concentrated at a reduced pressure affording 0.485 g (70% yield) of an oil consisting of **5** as a 45:55 **a**/**b** mixture by ^{1}H NMR. Flash chromatography on silica gel (hexanes, EtOAc, 95:5 elution) provided racemic isomer **5b** as the more mobile fraction and meso isomer **5a** as the less mobile fraction. Both isomers were obtained as oils that crystallized after protracted storage at −20 °C. Recrystallization from ethanol gave the analytical samples.

*(R, S)-2,4-dibromo-2,4-dinitropentane (**5a**).* White solid, mp 64–65.5 °C, R_f 0.43 (80:20 hexanes/EtOAc). ^{1}H NMR[2] ($CDCl_3$): δ 4.06 (d, 1H, J = 16.6 Hz), 3.92 (d, 1H, J = 16.6 Hz), 2.28 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 89.4, 52.3, 29.8.

(R, R*)-2,4-dibromo-2,4-dinitropentane (**5b**).* White solid, mp 62–62.5 °C, R_f 0.50 (80:20 hexanes/EtOAc). ^{1}H NMR[2] ($CDCl_3$): δ 4.07 (s, 2H), 2.17 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 87.1, 52.8, 27.4.

*(E)-4-bromo-2,4-dinitro-2-pentene (**6a**)*

A cold (0–5 °C) solution of sodium ethoxide (0.051 g, 0.75 mmol) in ethanol (6 mL) was added to a cold (0–5 °C) solution of **5a–b** (45:55 ratio; 0.080 g, 0.25 mmol) in anhydrous diethyl ether (1 mL), and the resulting solution was stirred for 7.5 min. A solution of bromine (0.15 g, 0.94 mmol) in dichlormethane (1 mL) was then added over 30 s followed by 25% aqueous acetic acid (1 mL). Solvents were removed at high vacuum over 10 min, and the residue was taken up in dichloromethane (three 10-mL portions). The combined organic layer was filtered, washed with water (5 mL), dried over anhydrous $MgSO_4$, and concentrated at reduced pressure. The crude product amounted to 0.068 g of an oil. ^{1}H NMR indicated that this was a 35:60:5 mixture of **6a**, ether isomers (**7a**/**7b**/**7c**, 85:6:9 ratio) and starting material **5a–b**, respectively. Under these conditions, **6b** was not detected. Flash chromatography on silica gel (hexanes/EtOAc, 95:05 elution) gave a mixture of ether **7a–c** and starting material **5a–b** as the most mobile fraction followed by pure **6a** as an oil. R_f 0.30 (95:5 hexanes/EtOAc). IR (film) 1568 (NO_2, ν_{as}), 1539 cm^{-1} (conj NO_2, ν_{as}). ^{1}H NMR ($CDCl_3$): δ 7.57 (s, 1H), 2.50 (s, 3H), 2.29 (s, 3H). ^{13}C NMR ($CDCl_3$): δ153.1, 131.6, 86.7, 32.5, 14.0. HRMS CI (NH_3) *m/z* calcd for $C_5H_{11}^{79}BrN_3O_4$ $(M+NH_4)^+$ 255.9933, found 255.9939.

*(Z)-4-bromo-2,4-dinitro-2-pentene (**6b**)*

The preceding experiment for preparation of **6a** was repeated except that the bromine solution was added to the reaction solution after only 15 s. After work-up, ^{1}H NMR showed that the crude product consisted of a 10:8:71:11 mixture of **6a**, **6b**, ethyl ethers **7a**/**7b**/**7c** (73:4:23 ratio), and starting material **5a–b**, respectively. Chromatography on silica gel (95:5, hexanes/EtOAc elution) afforded a mixture of **7a–c** and **5a–b** as the most mobile fraction followed by **6a** and finally **6b**. The fraction containing **6b** was subjected to preparative TLC (80:20 hexanes/EtOAc elution) to obtain a pure sample as an oil. R_f 0.17 (95:5 hexanes/EtOAc). IR (film) 1567 (NO_2, ν_{as}), 1533 cm^{-1} (conj NO_2, ν_{as}). ^{1}H NMR ($CDCl_3$): δ 6.34 (s, 1H), 2.48 (s, 3H), 2.33 (s, 3H). ^{13}C NMR ($CDCl_3$): δ148.2, 127.1, 85.5, 30.7, 19.8. HRMS CI (NH_3) *m/z* calcd for $C_5H_{11}^{79}BrN_3O_4$ $(M+NH_4)^+$ 255.9933, found 255.9940.

*General procedure A for synthesis of 3-alkoxy-2,4-dibromo-2,4-dinitropentane derivatives. Preparation of 2,4-dibromo-3-methoxy-2,4-dinitropentane (**2a–c**) from **5a–b***

A cold (0–5 °C) 0.1-M solution of sodium methoxide in methanol (10 mL, 1 mmol NaOMe) was added to compound **5a–b** (0.130 g, 0.4 mmol; 45:55 **a**/**b**). The resulting solution was stirred for 15 min and then a cold (0–5 °C) solution of bromine (0.096 g, 0.6 mmol) in dichloromethane (10 mL) was added. The resulting solution was stirred for 10 min and was poured into a solution of sodium bisulfite (0.1 g, 1 mmol) in water (35 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (three 10-mL portions). The combined organic layers were washed with water (25 mL), dried over anhydrous $MgSO_4$, and concentrated at reduced pressure. The crude light yellow product (0.109 g, 83% yield, 83:11:06 **2a**/**2b**/**2c** ratio) was purified by flash chromatography on silica gel thin-layer chromatography (TLC) (elution with hexanes/EtOAc, 95:5) to give the three separate isomers.

(R, R*)-2,4-dibromo-3-methoxy-2,4-dinitropentane (**2a**).* Viscous oil, R_f 0.51 (95:5 hexanes/EtOAc). IR (film) 1565 cm^{-1} (NO_2, ν_{as}). ^{1}H NMR ($CDCl_3$): δ 5.38 (s, 1H), 3.51 (s, 3H), 2.48 (s, 3H), 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$): δ98.6, 90.3, 86.8, 63.7, 29.4, 25.5. HRMS CI (NH_3) *m/z* calcd for $C_6H_{14}^{79}Br^{81}BrN_3O_5$ $(M+NH_4)^+$ 367.9280, found 367.9279.

*(R,r,S or R,s,S)-2,4-dibromo-3-methoxy-2,4-dinitropentane (**2b**).* Viscous oil, R_f 0.38 (95:5 hexanes/EtOAc). IR (film) 1571 cm^{-1} (NO_2, ν_{as}). ^{1}H NMR ($CDCl_3$): δ 5.42 (s, 1H), 3.48 (s, 3H), 2.42 (s, 6H). ^{13}C NMR ($CDCl_3$): δ92.1, 87.4, 63.7, 27.2. HRMS CI (NH_3) *m/z* calcd for $C_6H_{14}^{79}Br^{81}BrN_3O_5$ $(M+NH_4)^+$ 367.9280, found 367.9281.

*(R,r,S or R,s,S)-2,4-dibromo-3-methoxy-2,4-dinitropentane (**2c**).* Viscous oil, R_f 0.55 (95:5 hexanes/EtOAc). IR (film) 1560 cm^{-1} (NO_2, ν_{as}). ^{1}H NMR ($CDCl_3$): δ 5.14 (s, 1H), 3.74 (s, 3H), 2.27 (s, 6H). ^{13}C NMR ($CDCl_3$):

δ96.8, 86.9, 64.7, 27.4. HRMS CI (NH_3) *m/z* calcd for $C_6H_{14}^{79}Br^{81}BrN_3O_5$ $(M+NH_4)^+$ 367.9280, found 367.9279.

*Preparation of 2,4-dibromo-3-methoxy-2,4-dinitropentane (**2a-c**) using concentrated base*

A cold (0–5 °C) 1.7-M solution of sodium methoxide in methanol (1.5 mL, 2.5 mmol NaOMe) was added to **5a–b** (0.13 g, 0.4 mmol; 45:55 **a/b**). Further reaction and work-up as described in general procedure A gave 0.08 g (59% yield) of **2** (**2a/2b/2c** 5:40:55 ratio, respectively, by ^{1}H NMR).

*2,4-Dibromo-3-ethoxy-2,4-dinitropentane (**7a–c**)*

Prepared in 86% yield as a mixture of **7a**/**7b**/**7c** (85:6:9, respectively) following general procedure A, but the alkoxide concentration was 0.24 M (less solvent). Repetitive preparative TLC (elution with hexanes/EtOAc, 95:5) on the product mixture gave enriched (>90% purity) samples of **7a** and **7b**. The sample of **7c** was obtained as a 50:50 **7c/7a** mixture.

(R, R*)-2,4-dibromo-3-ethoxy-2,4-dinitropentane (**7a**).* Viscous oil, R_f 0.57 (95:5 hexanes/EtOAc). IR (film) 1566 cm^{-1} (NO_2, ν_{as}). ^{1}H NMR ($CDCl_3$): δ 5.44 (s, 1H), 3.78 (ABX_3, 1H, J = 7.1, 8.8 Hz), 3.56 (ABX_3, 1H, J = 7.1, 8.8 Hz), 2.48 (s, 3H), 2.38 (s, 3H), 1.10 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$) δ98.7, 90.6, 85.7, 72.5, 29.2, 25.4, 15.2. HRMS CI (NH_3) *m/z* calcd for $C_7H_{16}^{79}Br^{81}BrN_3O_5$ $(M+NH_4)^+$ 381.9436, found 381.9423.

*(R,r,S or R,s,S)-2,4-dibromo-3-ethoxy-2,4-dinitropentane (**7b**).* Viscous oil, R_f 0.50 (95:5 hexanes/EtOAc). IR (film) 1567 cm^{-1} (NO_2, ν_{as}). ^{1}H NMR ($CDCl_3$): δ 5.49 (s, 1H), 3.62 (q, 2H, J = 6.8 Hz), 2.42 (s, 6H), 1.07 (t, 3H, J = 6.8 Hz) (signals assigned to **7b**). ^{13}C NMR ($CDCl_3$): δ 92.3, 86.4, 27.1, 15.4 (signals assigned to **7b**; a signal at 72.6 was coincident with a signal of **7a**). HRMS CI (NH_3) *m/z* calcd for $C_7H_{16}^{79}Br^{81}BrN_3O_5$ $(M+NH_4)^+$ 381.9436, found 381.9434.

*(R,r,S or R,s,S)-2,4-dibromo-3-ethoxy-2,4-dinitropentane (**7c**).* Viscous oil, R_f 0.62 (95:5 hexanes/EtOAc). IR (film) 1563 (NO_2, ν_{as}) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.21 (s, 1H), 3.93 (q, 2H, J = 6.8 Hz), 2.29 (s, 6H), 1.25 (t, 3H, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$): δ97.2, 85.8, 73.4, 27.5, 15.3. HRMS CI (NH_3) *m/z* calcd for $C_7H_{16}^{79}Br^{81}BrN_3O_5$ $(M+NH_4)^+$ 381.9436, found 381.9429.

*2,4-Dibromo-2,4-dinitro-3-propoxypentane (**8a–c**)*

Prepared in 90% yield as a mixture (**8a**/**8b**/**8c**, 75:12:13, respectively, by ^{1}H NMR) following general procedure A, but the alkoxide concentration was 0.14 M, and the isomers were not separated. Viscous oil, IR (film) 1567 cm^{-1} (NO_2, ν_{as}). ^{1}H NMR ($CDCl_3$): δ 5.50 (s, 1H of **8c**), 5.45 (s, 1H of **8a**), 5.22 (s, 1H of **8b**), 3.82 (t, 2H of **8b**, J = 6.3 Hz), 3.67 (ABX_2, 1H of **8a**, J = 6.6, 8.8 Hz), 3.51 (t, 2H of **8c**, J = 6.3 Hz), 3.45 (ABX_2, 1H of **8a**, J = 6.6, 8.8 Hz), 2.49 (s, 3H of **8a**), 2.42 (s, 6H of **8c**), 2.38 (s, 3H of **8a**), 2.28 (s, 6H of **8b**), 1.62 (app sextet, 2H of **8c**, J = 6.8 Hz), 1.48 (app sextet, 2H of **8a**, J = 6.8 Hz) overlapping 1.44 (m, 2H of **8b**), 0.93 (t, 3H of **8c**, J = 7.3 Hz), 0.84 (t, 3H of **8a**, J = 7.3 Hz) overlapping 0.81 (t, 3H of **8b**). ^{13}C NMR δ 99.3, 97.2, 92.2, 90.6 ($C_{2,4}$ all isomers), 85.8, 85.3 (C_3 all isomers), 78.9, 78.2, 78.1 (C_6 all isomers), 29.8, 27.5, 27.1, 25.6 ($C_{1,5}$ all isomers), 23.1 (C_7 all isomers), 10.4, 10.2, 10.1 (C_8 all isomers). HRMS CI (NH_3) *m/z* calcd for $C_8H_{18}^{79}Br^{81}BrN_3O_5$ $(M+NH_4)^+$ 395.9593, found 395.9586.

*1-(1-Bromo-1-nitroethyl)-2-bromo-2-nitropropoxybenzene (**9a–b**)*

Prepared in 90% yield as a mixture (**9a–b**, 83:17, respectively, by ^{1}H NMR) following general procedure A, but the alkoxide concentration was 0.8 M, and the isomers were not separated. Viscous oil, IR (film) 1564 cm^{-1} (NO_2, ν_{as}). ^{1}H NMR ($CDCl_3$): δ 7.14–7.36 (m, 5H, both isomers), 5.75 (s, 1H of **9b**), 5.70 (s, 1 H of **9a**), 4.78 (d, 1H of **9a**, J = 10.3 Hz), 4.66 (s, 2H of **9b**), 4.51(d, 1H of **9a**, J = 10.3 Hz), 2.51 (s, 3 H of **9a**), 2.42 (s, 6H of **9b**), 2.38 (s, 3H, of **9a**). ^{13}C NMR ($CDCl_3$): δ 135.5, 128.6, 128.5, 128.3, 98.7, 90.4, 85.5 (weak), 84.9, 78.1, 69.6 (weak), 29.5, 27.2 (weak), 25.7 (weak signals are assignable to isomer **9b**). HRMS CI (NH_3) *m/z* calcd for $C_{12}H_{18}Br_2N_3O_5$ $(M+NH_4)^+$ 443.9593, found 443.9611.

*General procedure B for synthesis of 3-alkoxy-2,4-dibromo-2,4-dinitropentane derivatives. Preparation of 2,4-dibromo-3-ethoxy-2,4-dinitropentane (**7a–c**) from **6a***

A cold (0–5 °C) 0.6-M solution of sodium ethoxide in ethanol (3.5 mL, 2.1 mmol of NaOEt) was added to a cold solution of *E*-nitroalkene **6a** (0.17 g, 0.7 mmol) in ethanol (4 mL). The resulting solution was stirred for 10 min and then poured into a cold (0–5 °C) solution of bromine (0.27 g, 1.7 mmol) in dichloromethane (17 mL). This solution was added to a solution of sodium bisulfite (0.2 g, 2 mmol) in water (100 mL), and the resulting mixture was extracted with dichloromethane (three 20-mL portions). The combined extracts were washed with water (3 mL), dried, concentrated, and flash chromatographed on silica gel to give 0.19 g (75% yield) of an oil that by ^{1}H NMR consisted of **7a**/**7b**/**7c** (81:10:08, respectively).

*2,4-Dibromo-3-(1-methylethoxy)-2,4-dinitropentane (**10a–c**)*

Prepared following general procedure B by using a 0.16-M alkoxide solution for a reaction time of 40 min. The crude product consisted of a 30:30:20:20 mixture of **6a/10a/10b/10c**, respectively, by ^{1}H NMR. Flash chromatography (hexanes/EtOAc, 95:05) afforded a mixture of **10a–c** in 18% yield. Repetitive preparative TLC (elution with hexanes/EtOAc, 95:5) on the product mixture gave pure samples of **10a** and **10c**. A sample of **10b** (88:12, **10b/10a** by ^{1}H NMR) was also obtained.

(R, R*)-2,4-dibromo-3-(1-methylethoxy)-2,4-dinitropentane (**10a**).* Viscous oil, R_f 0.54 (95:5 hexanes/EtOAc). IR (film) 1560 cm^{-1} (NO_2, ν_{as}). ^{1}H NMR ($CDCl_3$): δ 5.58 (s, 1H), 3.81 (septet, 1H, J = 5.9 Hz), 2.49 (s, 3H), 2.35 (s, 3H), 1.14 (d, 3H, J = 5.9 Hz), 1.03 (d, 3H, J = 5.9 Hz). ^{13}C NMR ($CDCl_3$): δ 83.1, 77.1, 30.1, 26.1, 22.6, 21.7 (C atoms indirectly from HMQC spectra) and δ 100.4, 91.7 (quat C atoms indirectly from HMBC). HRMS CI (NH_3) *m/z* calcd for $C_8H_{18}^{79}Br^{81}BrN_3O_5$ $(M+NH_4)^+$ 395.9593, found 395.9593.

*(R,r,S or R,s,S)-2,4-dibromo-3-(1-methylethoxy)-2,4-dinitropentane (**10b**).* Viscous oil: an 88:12 mixture of **10b/10a**, R_f 0.49 (95:5 hexanes/EtOAc). IR (film) 1566 cm^{-1} (NO_2, ν_{as}). ^{1}H NMR ($CDCl_3$): δ 5.72 (s, 1H), 3.73 (septet, 1H, J = 6.3 Hz), 2.40 (s, 6H), 1.09 (d, 6H, J = 6.3 Hz). ^{13}C NMR ($CDCl_3$): δ 93.8, 83.4, 77.0, 28.0, 22.2. HRMS CI (NH_3) *m/z* calcd for $C_8H_{18}^{79}Br^{81}BrN_3O_5$ $(M+NH_4)^+$ 395.9593, found 395.9603.

*(R,r,S or R,s,S)-2,4-dibromo-3-(1-methylethoxy)-2,4-dinitropentane (**10c**).* Viscous oil, R_f 0.61 (95:5 hexanes/EtOAc). IR (film) 1567 cm^{-1} (NO_2, ν_{as}). ^{1}H NMR ($CDCl_3$): δ 5.32 (s, 1H), 4.06 (septet, 1H, J = 5.9 Hz), 2.28 (s, 6H), 1.22 (d, 6H, J = 5.9 Hz). ^{13}C NMR ($CDCl_3$): δ 82.7, 77.0, 27.8, 22.3 (C atoms indirectly from HMQC spectra) and δ 98.4 (quat C atom indirectly from HMBC). HRMS CI (NH_3) *m/z* calcd for $C_8H_{18}^{79}Br^{81}BrN_3O_5$ $(M+NH_4)^+$ 395.9593, found 395.9593.

*Preparation of azide **11a–b** from nitroalkene **6a***

A cold (0–5 °C) solution of sodium azide (41 mg; 0.63 mmol) in water (1 mL) was added dropwise over 3 min to a cold (0–5 °C) solution containing **6a** (27 mg; 0.11 mmol), methanol (4 mL), and water (1 mL). The resulting solution was stirred for 1 h and a solution of bromine (56 mg, 0.35 mmol) in dichloromethane (3.5 mL) was added followed by 10% sodium bisulfite (5 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (three 10-mL portions). The combined organic layers were washed with water (10 mL), dried, and concentrated to give an oil consisting of **11a/11b/6a** (52:35:13, respectively, by ^{1}H NMR). Preparative TLC (95:5 hexanes/EtOAc elution) gave in order

of elution 6 mg (13% yield) of **11b**, 9 mg (23% yield) of **11a**, and 5 mg of recovered **6a**. No third azide isomer was detected.

(R, R*)-3-azido-2,4-dibromo-2,4-dinitropentane (**11a**).* Viscous oil, R_f 0.44 (95:5 hexanes/EtOAc). IR (film) 2123 (N_3, ν_{as}), 1568 cm^{-1} (NO_2, ν_{as}), 1388 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.80 (s, 1H), 2.46 (s, 3H), 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 89.0, 71.1, 28.4, 25.9. HRMS CI (NH_3) *m/z* calcd for $C_5H_{11}^{79}Br^{81}BrN_6O_4$ $(M+NH_4)^+$ 378.9188, found 378.9203.

*(R,r,S or R,s,S)-3-azido-2,4-dibromo-2,4-dinitropentane (**11b**).* Viscous oil, R_f 0.55 (95:5 hexanes/EtOAc). IR (film) 2122 (N_3, ν_{as}), 1568 cm^{-1} (NO_2, ν_{as}). ^1H NMR ($CDCl_3$): δ 5.62 (s, 1H), 2.25 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 71.4, 26.8. HRMS CI (NH_3) *m/z* calcd for $C_5H_{11}^{79}Br^{81}BrN_6O_4$ $(M+NH_4)^+$ 378.9188, found 378.9198.

*Preparation of azide **11a–b** from **5a–b***

A 0.06-M solution of sodium ethoxide in ethanol (10 mL, 0.6 mmol NaOEt) was added dropwise over 2 min to a cold (0–5 °C) solution of **5a–b** (0.124 g, 0.39 mmol; 45:55 **a/b** ratio), sodium azide (0.235 g, 3.6 mmol), ethanol (10 mL), and water (4 mL). The resulting solution was stirred for 20 min, and a solution of bromine (0.12 g, 0.76 mmol) in dichloromethane (10 mL) was added followed by 10% sodium bisulfite (10 mL). Water (10 mL) was added, the layers were separated, and the aqueous layer was extracted with dichloromethane (three 10-mL portions). The combined organic layers were washed with water (10 mL), dried, and concentrated to give 0.11 g of an oil consisting of **11a/11b/7a–c/5a–b** (35:5:50:10, respectively, by ^1H NMR). The amount of azide **11a–b** present was therefore 44 mg (32% yield). Preparative TLC (95:5 hexanes/EtOAc elution) gave 7 mg of pure isomer **11b** as the most nonpolar fraction but isomer **11a** obtained as a more polar fraction was contaminated with ether **7a–c**.

*Monodebromination of 2,4-dibromo-3-ethoxy-2,4-dinitropentane (**7a–c**)*

A cold (0–5 °C) solution of sodium iodide (1.68 g, 11 mmol) in ethanol (30 mL) was added to a second cold solution (0–5 °C) consisting of **7a–c** (1.64 g, 4.5 mmol, 85:9:6 **7a**/**7b**/**7c** ratio) dissolved in acetic acid (25 mL; 0.44 mol) and ethanol (25 mL). The resulting solution was stirred for 30 min at 0–5 °C. Water (500 mL) was added, and the organic products extracted with dichloromethane (three 20-mL portions). The combined organic layers were washed with water (three 25-mL portions), dried over anhydrous $MgSO_4$, and concentrated at reduced pressure. The crude product was purified by flash chromatography (80:20, hexanes/EtOAc elution) to give 1.2 g (93% yield) of **16** as a 77:15:08 mixture of three diastereomers **a–c** by (^1H NMR). Viscous oil, R_f 0.50 (80:20 hexanes/EtOAc). IR (film) 1564 cm^{-1} (NO_2, ν_{as}). ^1H NMR ($CDCl_3$):δ 5.11 (d, 1H, J = 2.4 Hz), 4.99 (qd, 1 H, J = 2.4, 6.8 Hz), 3.77 (dq, 1H, J = 6.8, 9.3 Hz), 3.56 (dq, 1H, J = 6.8, 9.3 Hz), 2.16 (s, 3H), 1.66 (d, 3H, J = 6.8 Hz), 1.12 (t, 3H, J = 6.8 Hz) (prominent signals attributed to main isomer **a**) and δ 4.87–4.97 (m), 4.64 (d of **b** J = 6.3 Hz overlapping m of **c**), 3.84 (dq, J = 7.3, 9.3 Hz), 3.61–3.72 (m), 2.29 (s, 3H of **b**), 2.27 (s, 3H of **c**), 1.77 (d, 3 H of **b**, J = 7.3 Hz), 1.67 (d of isomer **c** overlapping signal of **a**), 1.20 (t, 3H of **c**, J = 6.8 Hz), 1.05 (t, 3H of **b**, J = 6.8 Hz) (weak signals attributed to two minor isomers, **b** and **c**). ^{13}C NMR ($CDCl_3$): δ91.7 (quat), 83.1, 83.0, 70.3, 23.5, 15.1, 14.9. (prominent signals only). HRMS CI (NH_3) *m/z* calcd for $C_7H_{17}^{79}BrN_3O_5$ $(M+NH_4)^+$ 302.0352, found 302.0343.

*Monodebromination of **2a–c***

Carried out on **2a–c** (83:11:06 **2a**/**2b**/**2c** ratio) similarly to debromination of **7a–c** to give 0.91 g (81% yield) of **15** as an 81:13:06 mixture of three isomers **a–c** (by ^1H NMR). Viscous oil, R_f 0.50 (80:20 hexanes/EtOAc). IR (film) 1560 cm^{-1} (NO_2, ν_{as}). ^1H NMR ($CDCl_3$): δ 5.03 (d, 1H, J = 2.4 Hz), 4.99 (qd, 1 H, J = 2.4, 7.3 Hz), 3.50 (s, 3H), 2.15 (s, 3H), 1.67 (d, 3H, J = 7.3 Hz) (prominent signals attributed to main isomer **a**) and δ 4.87–4.97 (m), 4.58 (d of **b** J = 6.3 Hz) overlapping m of **c**), 3.60 (s, 3H of **c**, 3.46 (s, 3H of **b**), 2.28 (s, 3H of **b**), 2.26 (s, 3H of **c**), 1.67 (d, 3H of **b**, J = 6.8 Hz) 1.69 (d, 3H of **c**, J = 7.3 Hz) (weak signals attributed to two minor isomers (greater **b** and lesser **c**)). ^{13}C NMR ($CDCl_3$): δ 91.3 (quat), 84.3, 83.0, 61.8, 23.4, 14.8 (prominent signals only). HRMS CI (NH_3) *m/z* calcd for $C_6H_{15}^{79}BrN_3O_5$ $(M+NH_4)^+$ 288.0195, found 288.0194.

*Monodebromination of **5a–b***

Carried out on **5a–b** (45:55 **a**/**b** mixture) similarly to debromination of **7a–c** to give 0.89 g (77% yield) of **3** as a 91:9 mixture of two isomers **a–b** (by ^1H NMR). Viscous oil. IR (film) 1550 cm^{-1} (NO_2, ν_{as}). ^1H NMR ($CDCl_3$): δ 4.91 (ABMX$_3$ pattern, 1H), 3.30 (dd, 1H, J = 7.8, 16.3 Hz), 2.85 (dd, 1H, J = 2.4, 16.3 Hz), 2.22 (s, 3H), 1.67 (d, 3H, J = 6.8 Hz) (prominent signals attributed to main isomer **a**) and δ 4.66 (ABMX$_3$ pattern, 1H), 3.45 (dd, 1H, J = 8, 16.3 Hz), 2.91 (dd, J = 2.2, 16.3 Hz), 2.23 (s, 3H), 1.66 (d, 3H, J = 6.8 Hz) (weak signals attributed to minor isomer **b**). ^{13}C NMR ($CDCl_3$): δ 91.9 (quat), 80.9, 46.2, 30.4, 21.3 (prominent signals attributed to **3a**) and δ 80.4, 47.0, 29.1, 21.6 (weak signals attributed to **3b**). HRMS EI *m/z* calcd for $C_6H_9^{79}BrNO_2$ $(M-NO_2)^+$ 193.9817, found 193.9826.

*Preparation of 3-methoxy-2,4-dinitropentane (**13a–b**)*

A cold (0–5 °C) solution of sodium methoxide (0.97 g, 18 mmol) in methanol (50 mL) was rapidly added to a cold (0–5 °C) solution of **5a–b** (1.94 g, **a/b** 45:55 ratio, 6 mmol) in diethyl ether (50 mL), and the resulting solution was stirred for 20 min. A cold solution of sodium iodide (3.38 g, 23 mmol) and acetic acid (5 mL, 87 mmol) in methanol (20 mL) was rapidly added, and the resulting solution stirred at 0–5 °C for 30 min and then concentrated at reduced pressure. Dichloromethane (50 mL) was added, and the resulting mixture was filtered. The filtrate was sequentially washed with saturated aqueous sodium bisulfite (50 mL) and water (two 50-mL portions), dried over anhydrous $MgSO_4$, and concentrated at reduced pressure. A 1.03-g portion of a mixture containing **13** and **15** was obtained (**13a**/**13b**/**15** 52:36:11 ratio). Partial separation was obtained by flash chromatography (70:30 hexanes – EtOAc). An early fraction containing 0.27 g (23% yield) of **13b** contaminated with **15a–c** (85:15 **13b**/**15a–c** ratio) and a later fraction containing 0.56 g (48% yield) of **13a**/**13b** 66:34 ratio were obtained. Analytical data are for the latter fraction. Viscous oil, R_f 0.77 (70:30 hexanes/EtOAc). IR (film) 1560 cm^{-1} (NO_2, ν_{as}). ^1H NMR (C_6D_6): δ 4.18 (dd, 1H, J = 2.9, 9.2 Hz), 3.88 (dq, 1H, J = 6.8, 9.2 Hz), 3.50 (dq, 1H, J = 2.9, 6.8 Hz), 2.93 (s, 3H), 0.82 (d, 3H, J = 6.8 Hz), 0.57 (d, 3H, J = 6.8 Hz) (signals attributed to **13a** with confirmation from the early fraction) and δ 4.06 (t, 1H, J = 5.4 Hz), 3.78 (dq, 2H, J = 5.4, 6.8 Hz), 2.79 (s, 3H), 0.95 (d, 6H, J = 6.8 Hz) (signals attributed to **13b**). ^{13}C NMR ($CDCl_3$): δ 84.5, 83.0, 81.6, 61.7 (two maxima), 16.2, 12.0 (signals attributed to **13a** with confirmation from the early fraction and HMQC spectra) and δ 82.6, 82.2, 61.7 (two maxima), 13.8 (signals attributed to **13b**). HRMS CI (NH_3) *m/z* calcd for $C_8H_{16}N_3O_5$ $(M+NH_4)^+$ 210.1090, found 210.1092.

*Preparation of 4,5-dihydro-5-methoxy-3,4-dimethyl-4-nitroisoxazole N-oxide (**22a**)*

A cool (16–18 °C) solution of potassium acetate (0.23 g, 2.3 mmol) in DMSO (8 mL) was added to a cool (16–18 °C) solution containing **13a–b** (66:34 **a/b** ratio, 0.15 g, 0.77 mmol) in DMSO (8 mL). The resulting solution was stirred at 16–18 °C for 5 min and iodine (0.4 g, 1.6 mmol) was added. This mixture was stirred for 4 min and the resulting solution poured into a solution of sodium bisulfite (0.52 g, 5 mmol) in water (100 mL). The aqueous solution was extracted with dichloromethane (three 10-mL portions). The combined extracts were washed with water (10 mL), dried over anhydrous $MgSO_4$, and concentrated at reduced pressure to give 0.074 g of oil. By ^1H NMR this contained about 60% **22a** (30% yield) and several unidentified materials. Rapid flash chromatography gave an analytical sample that was partially purified (85% pure, low recovery). Analytical data are for this sample. Small samples could also be purified by rapid preparative TLC. Samples of crude **22a** were completely consumed when chromatography was insufficiently rapid.

Treatment of **15a–c** with a cool DMSO solution of potassium acetate afforded **22a** in 50% purity and 15% yield. Addition of a cool DMSO solution of **2a–c** to a cool DMSO solution of sodium iodide gave **22a** in 60% purity and 7% yield.

*4,5-Dihydro-5-methoxy-3,4-dimethyl-4-nitroisoxazole N-oxide (**22a**).* Viscous oil, R_f 0.31 (88:12 hexanes/EtOAc). IR (film) 1652 (C = N), 1558 cm^{-1} (NO_2, ν_{as}). ^1H NMR ($CDCl_3$): δ 5.68 (s, 1 H), 3.61 (s, 3 H), 2.10 (s, 3 H), 1.80 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 110.6, 100.7, 100.0, 57.2, 16.9, 9.5 (signals confirmed indirectly from HMQC and HMBC spectra). HRMS CI (CH_4) *m/z* calcd for $C_6H_{11}N_2O_5$ $(M+H)^+$ 191.0668, found 191.0665.

*Preparation of 4,5-dihydro-5-ethoxy-3,4-dimethyl-4-nitroisoxazole N-oxide (**22b**)*

A cool (16–18 °C) solution of potassium acetate (0.56 g, 5.7 mmol) in DMSO (40 mL) was added to a cool (16–18 °C) solution containing **16a–c** (77:15:08 **a/b/c** ratio, 0.52 g, 1.81 mmol) in DMSO (60 mL). The resulting solution was stirred at 16–18 °C for 8 min and was poured into ice water (500 mL). The aqueous solution was extracted with dichloromethane (three 30-mL portions). The combined extracts were washed with water (30 mL), dried over anhydrous $MgSO_4$, and concentrated at reduced pressure to give 0.094 g of a oil. By ^1H NMR, this contained about 50% **22b** (13% yield) and several unidentified materials. Rapid flash chromatography gave an analytical sample that was substantially purified (90% pure, low recovery). Analytical data are for this sample. Addition of a cool DMSO solution of **7a–c** to a cool DMSO solution of sodium iodide also gave **22b** in 50% purity and 5% yield.

*4,5-Dihydro-5-ethoxy-3,4-dimethyl-4-nitroisoxazole N-oxide (**22b**).* Viscous oil, R_f 0.4 (88:12 hexanes/EtOAc). IR (film) 1652(C = N), 1559 cm^{-1} (NO_2, ν_{as}). ^1H NMR ($CDCl_3$): δ 5.76 (s, 1H), 3.98 (dq, 3H, *J* = 7.1, 9.8 Hz), 3.73 (dq, 3H, *J* = 7.1, 9.8 Hz), 2.10 (s, 3H), 1.80 (s, 3H), 1.28 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): δ 99.7, 66.2, 17.1, 14.8, 9.7 (C atoms indirectly from HMQC spectra) and δ 110.9 (one quat C atom indirectly from HMBC; a second quat C atom was not detected). HRMS CI (CH_4) *m/z* calcd for $C_7H_{13}N_2O_5$ $(M+H)^+$ 205.0824, found 205.0826.

SUPPORTING INFORMATION

^1H NMR spectra of **2a–c**, **3**, **6a–b**, **7a–c**, **8–9**, **10a-c**, **11a–b**, **13**, **15–16**, **22a–b** and ^{13}C NMR spectra of **2a–c**, **3**, **6a–b**, **7a–c**, **8–9**, **10b**, **11a–b**, **13**, **15–16**, **22a**.

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