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Design and Synthesis of Nitro Containing Cage Heterocycles as High-Density Materials Derived from Pentacycloundecane (PCUD) Systems

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Abstract

A variety of pentacycloundecane (PCUD) based cage compounds containing nitro groups were synthesized via a simple synthetic method starting with cage diones. Eight PCUDs were used for nitro functionalization. These cage diones were prepared starting with easily accessible starting materials such as 2,3-dimethylhydroquinone, 1,4-dihydroxybenzene, and cyclopentadiene. Here, we have used Diels–Alder (DA) reaction, [2+2] photocycloaddition, and Henry reaction as key steps. Transannular cyclization plays an important role to generate a nitro substituted cage heterocycles via base promoted reaction using nitromethane as a reagent. Some of these oxa-cage structures have been further supported by single-crystal X-ray diffraction studies.

Keywords

Diels–Alder reaction, photocycloaddition, Henry reaction, transannular cyclization, heterocycles, nitro compounds, cage diones, PCUD, and oxa-cages

Introduction

The enhanced research activity in the synthesis of cage molecules was due to their applications in diverse scientific fields such as material science, medicinal and pharmaceutical chemistry.[1-3] Because of the strain involved in their architecture, synthesis of these compounds is considered as a challenging task. These molecules serve as key building blocks for the design of drug candidates, fuel additives, propellants, polymers, chiral ligands and also useful in molecular recognition.[4] Some of the unique features of cage compounds such as high symmetry, rigid and compact structure, and strain energy makes them remarkable substrates to study intricate rearrangements. These rearrangement studies produce valuable products suitable for the design of energetic compounds, medicinally and pharmaceutically important motifs.[5]

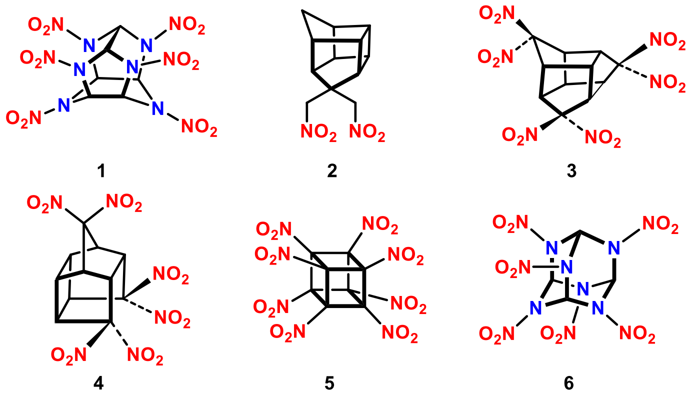
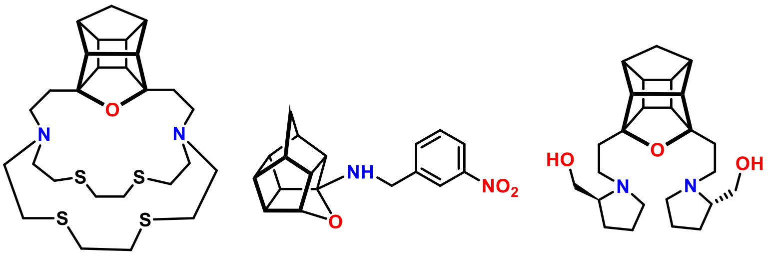


Figure 1 Different nitro-derived carbocyclic cage hydrocarbons

High-energy–density (HED) hydrocarbons display attractive features for combustion systems due to their high density (1.2–1.3 g/cm^3) and contain strain energy which contributes to the energy output during their combustion. Some selected examples of nitro-substituted cage systems reported in literature (**1**-**6**) are shown in Figure 1.[6] Pentacycloundecane systems such as **11** comprising of cyclobutane ring with high-nitrogen content function well as high-energy density materials (HEDMs).[7] In view of their anticipated energetic properties of high-nitrogen cage hydrocarbons such as detonation performance, large positive heats of formation, good oxygen balance, high density, good thermal stability, and high burning rate have shown promising effects in material science applications. The high nitrogen content leads to an increased density within the cage framework. High nitrogen-containing heterocycles represent a unique family of energetic materials.[8]

The burning rate of the cage hydrocarbon is as fast as conventional hydrocarbons. High nitrogen content moieties such as polynitroderivatives, azides, triazoles, and tetrazoles are considered as excellent synthons for the design of high-density fuels. Based on these aspects, a new strategic approach to the design of HEDMs[9] is conceived. Oxidizers, energetic fuels, and propellants have been discovered for importance in civil, industrial, defence and also usages in aerospace industry.[2(b)] Because of their importance in energy aspects, current studies have been focussed on the enhancement of efficient synthetic protocols towards nitrogen-rich cage molecules.[10]



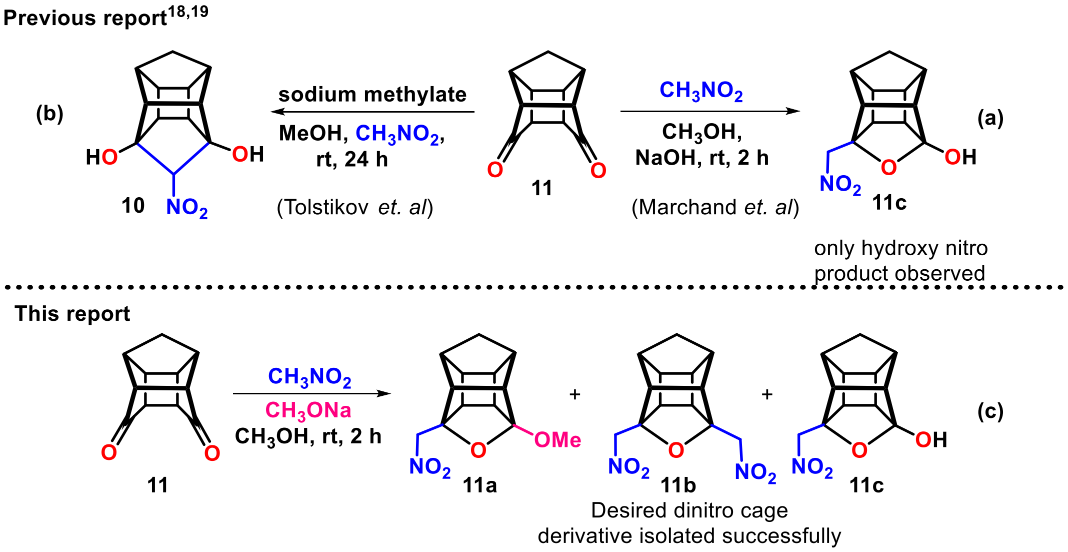
7 8 9

Figure 2 Examples of hetero-cage frameworks **7-9**

PCUD based oxa-cage compounds are identified as desirable scaffolds for supramolecular chemistry assembly, drug development, as well as in asymmetric catalysis.[11] The heterocyclic cage compounds are excellent precursors for molecular recognition (chelation with metal ions).[12] Cage heterocycles (**7-9**) which are useful in various fields are represented in Figure 2.[13] Several synthetic routes are accessible in the literature for the synthesis of hetero-cage systems.[14]

Results and Discussion

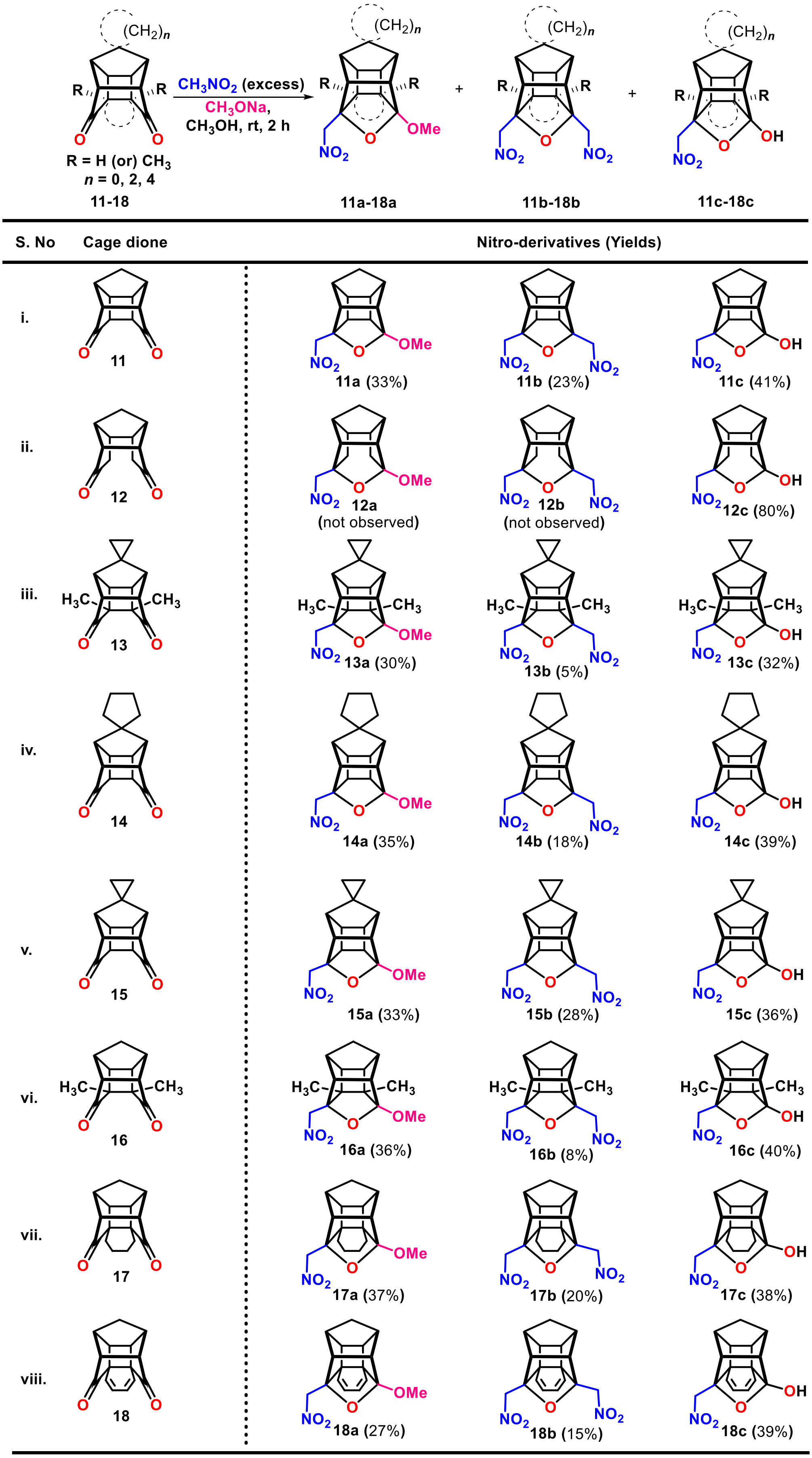
To expand metathesis strategy[15] and other synthetic methods to polycycles and heterocycles, we reported various interesting cage heterocycles and oxa-cage systems via olefin metathesis and transannular cyclization.[16, 17] Marchand *et.al* reported a nitro-substituted cage heterocyclic scaffold **11c** and utilized in ring-rearrangement studies via Tiffeneau-Demjanov method. In this regard, they used nitromethane and aq. NaOH for the preparation of required cage heterocycle **11c** bearing nitro group, useful as a key precursor for the ring-homologation (Scheme 1 [a]).[18] Similarly, Tolstikov *et.al* also reported nitro substituted hexacyclic system (bird-cage type) and hexacyclotridecane from PCUD dione **10** with the aid of base and nitromethane (Scheme 1 [b]).[19] In this report IR, CHN analysis and melting point were only given. There are no details about ^{1}H-NMR and ^{13}C-NMR or mass spectrometric data. Inspired by their reports, here, we communicate a new approach to dinitro hetero-cages involving base-promoted reaction of cage diones with nitromethane (Scheme 1 [c]). These nitro group containing oxa-cages were assembled from various functionalized cage diones. The diones are synthesized from different functionalized hydroquinones and freshly cracked cyclopentadiene via a sequence involving thermal (4+2) and photochemical (2+2) cycloadditions.



Scheme 1 Synthesis of various nitro derived cage oxacycles

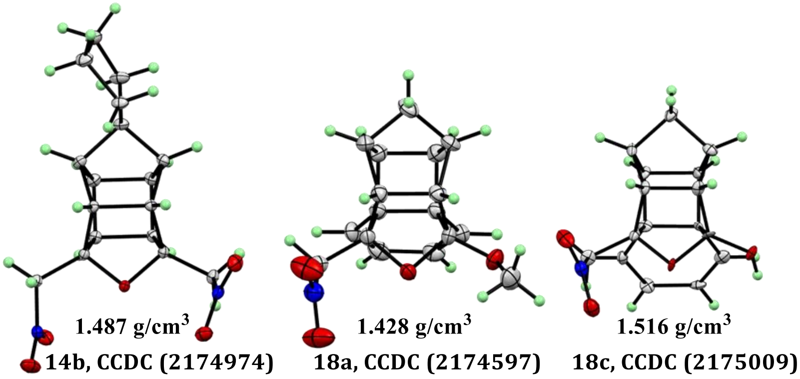
The required cage diones **11-18** were synthesized from easily accessible and inexpensive starting materials such as cyclopentadiene and hydroquinone and its derivatives through the oxidation, Diels-Alder (DA) reaction, and [2+2] photocycloaddition involving the known literature procedures.[20] Having access to various cage diones, next we attempted the base-promoted reaction with nitromethane (Henry reaction). In this regard, pentacyclic dione (Cookson's dione) **11** and tetracyclic dione **12** were treated with an excess amount of nitromethane (CH_3NO_2) and base such as sodium methoxide (CH_3ONa) in methanol solvent at room temperature (rt) for 2 h to produce the nitro substituted oxa-cage derivatives like methoxy, symmetrical dinitro and hydroxyl derivatives **11a**-**11c**. Structures of these three products were assigned on the basis of spectral data. The least polar compound **11a** was identified by the characteristic singlet methyl peak at δ 3.48 ppm of -OMe group in ^{1}H NMR spectra. The compound **11b** with dinitro groups has half number of peaks in ^{13}C NMR spectra (e. g δ 93.24, 76.60, 57.81, 47.53, 44.36, 43.71, 41.59 ppm.) which indicate the presence of symmetry. The most polar compound **11c** was the expected product and easier to characterize. Surprisingly, in the case of tetracyclic system, we observed only hydroxy derivative **12c**, and this might be due to the absence of cyclobutane ring which opens up the cage structure (Scheme 2).

Similarly, the other cage diones **13-15** bearing spiro systems ($R_1 = R_2$ = Me, H; n = 2, 4) were reacted with CH_3NO_2 and CH_3ONa in methanol at rt for 2 h to deliver the three different nitro substituted oxa-cage derivatives such as methoxy (**13a-15a**), symmetrical dinitro (**13b-15b**), and hydroxy (**13c-15c**) derivatives respectively in moderate to good combined yields. Also, dimethyl cage dione **16** produced similar derivatives such as **16a**-**16c** under same reaction conditions. In the case of cyclohexane fused cage diones such as **17** and **18,** we got parallel products; methoxy (**17a** and **18a**), symmetrical dinitro (**17b** and **18b**) and hydroxy (**17c** and **18c**) derived oxa-cages respectively in good yields (Scheme 2).



Scheme 2 Synthesis of nitro substituted oxa-cages by base-promoted reaction

The addition of strong base and excess amount of nitromethane might be playing a key role to generate transannular cyclization products containing two nitro groups. These oxa-nitro-cages were fully characterized with appropriate spectral data (^{1}H-NMR and ^{13}C-NMR) as well as HRMS data. The structures of compounds **18a, 14b** and **18c** were unambiguously established by single crystal X-ray diffraction studies (Figure 3).



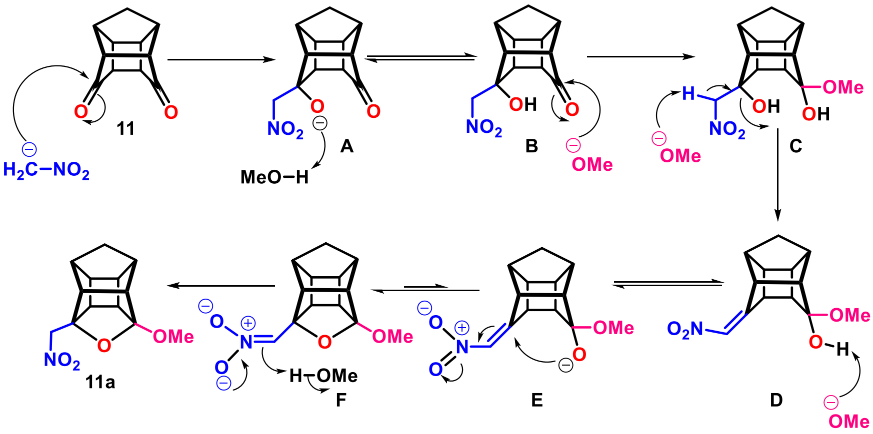
1.487 g/cm^3 14b, CCDC (2174974)

1.428 g/cm^3 18a, CCDC (2174597)

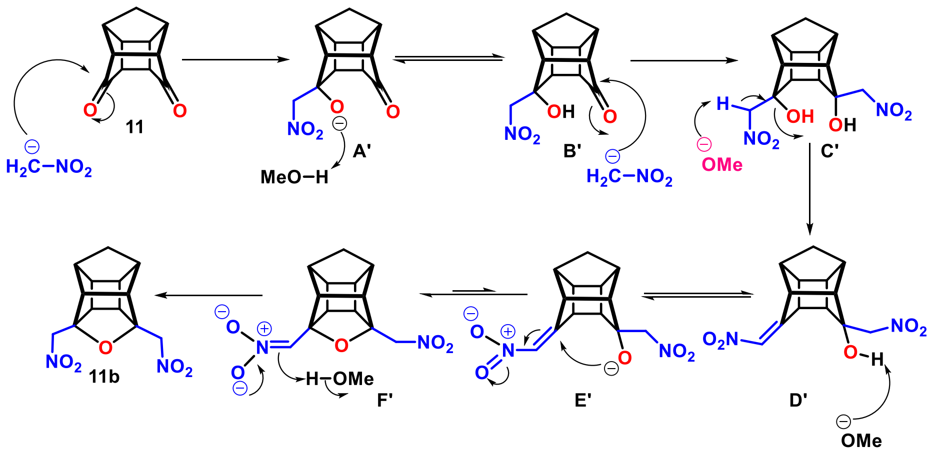
1.516 g/cm^3 18c, CCDC (2175009)

Figure 3 Single-crystal X-ray structures of compound **14b, 18a 18c.**

To optimize the yields of dinitro compounds (**11b-18b**), we also attempted the Henry reaction of compound **11** under DBU/CH_3CN and KF/CH_3CN conditions and found only hydroxy derivative **11c** and obtained 85% yield.



Scheme 3 Plausible Mechanism for the Formation of **11a**



Scheme 4 Plausible Mechanism for Formation of **11b**

On the basis of earlier studies,[21] and our experimental results, we have proposed a possible mechanism for the formation of transannular methoxy compound **11a** (Scheme 3). The reaction is initiated by a strong base such as CH_3ONa. CH_3ONa abstracts the acidic proton of nitromethane and forms the carbanion which acts as a nucleophile, and attacks the ketone of cage dione **11** to form intermediate **B** through intermediate **A.** Afterwards, CH_3ONa as a nucleophile attack on the electrophilic ketone to form the intermediate **C**. Hence CH_3ONa exhibits dual role here acting as a base as well as a nucleophile. Further, CH_3ONa abstracts the alpha proton of the nitro group and forms a conjugate carbanion which eliminates the hydroxide group via the conjugate base elimination mechanism (E1cB) and produces alkene **D**. Further, oxyanion **E** derived from hydroxy group of compound **D** attacks the α, β-unsaturated nitro group to give the nitro substituted methoxy derivative **11a** through intermediate **F.** Along similar lines, the mechanism for the formation of symmetrical dinitro oxa-cage compound **11b** from cage dione **11** is illustrated in Scheme 4.

Conclusion

In summary, we successfully synthesized several nitro substituted PCUD cage ethers by a simple synthetic method starting with diverse cage diones. Here, we have utilized DA reaction, [2+2] photocycloaddition, and Henry reaction as key steps. Transannular cyclization in PCUD diones has been observed with base, nitromethane and CH_3ONa. Nitro groups generated here can be further manipulated synthetically by hydrogenation, by radical reaction or oxidation by Nef reaction. Three structures **14b, 18a** and **18c** have been fully confirmed by single-crystal X-ray diffraction studies. These derivatives are likely to be useful as high energy materials. We have determined the densities of three compounds (**14b, 18a,** and **18c**) from single crystal X-ray data and the values range from 1.42-1.51 g/cm^3 (Refer Supporting Information, page S11-S13).

Supporting Information

Supporting information text

Supporting Information File 1:

File Name: Text

File Format: Text

Title: Text

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