Efficient Synthesis of 2,2,4,4,6,6-Hexanitroadamantane under Mild Conditions

Yifei Ling,[a] Pingping Zhang,[a] Lu Sun,[a] Weipeng Lai,[b] Jun Luo*[a]

[a] School of Chemical Engineering, Nanjing University of Science and Technology, Nanjing 210094, P. R. of China
Fax +86(25)84315030; E-mail: luojun@njust.edu.cn

[b] Xi'an Modern Chemistry Research Institute, Xi'an 710065, P. R. of China

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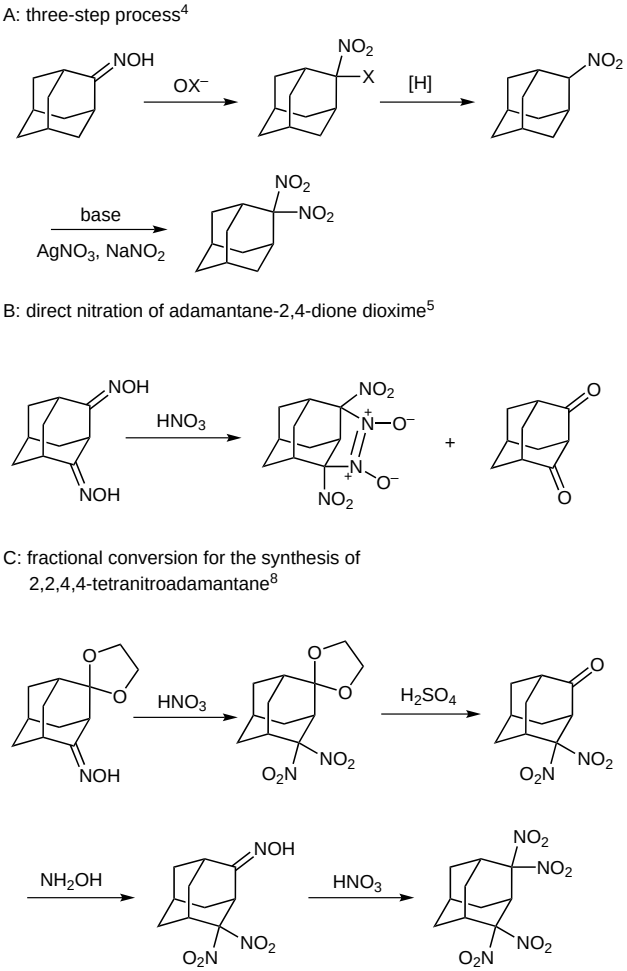
Abstract: Two strategies have been developed for the synthesis of 2,2,4,4,6,6-hexanitroadamantane (HNA). Both strategies used the readily available diethyl malonate and paraformaldehyde as the starting materials, and utilized acylation followed by intramolecular aldol condensation to construct the adamantane skeleton. The clean nitration to introduce the *gem*-dinitro groups onto the adamantane skeleton was conducted using dinitrogen pentoxide in refluxing dichloromethane in the presence of urea and 4 Å molecular sieves. The acetylation route was accomplished via 12 steps and afforded HNA in an overall yield of 4.7%, and the formylation route was achieved via 11 steps in 14% overall yield.

Key words: total synthesis, cage compounds, acylations, aldol reactions, cyclizations

The improvement of high energy density materials (HEDMs) is an ongoing challenge due to the inherent contradiction between explosive potential and stability. HEDMs are widely used in propellants, explosives and pyrotechnics. Polynitropolycyclic cage compounds such as octanitrocubane (ONC)[1] are particularly attractive due to their excellent explosive characteristics which are a result of high crystal densities and symmetrical structures, particularly in combination with high strain energies, and the accumulation of nitro groups tending to high energy.

Polynitroadamantanes, as a class of polynitropolycyclic cage compounds, have attracted widespread attention since Sollott and Gilbert first synthesized and demonstrated that the bridgehead-substituted 1,3,5,7-tetranitroadamantane exhibited moderate power output and low shock and impact sensitivity.[2] Polynitroadamantanes are considered to be prospective propellants and explosives due to their high energy and good stability.

In general, polynitroadamantanes bearing *gem*-dinitro groups on bridge carbons have been synthesized from oximinoadamantanes by direct nitration[3] or, alternatively, by a three-step process (Scheme 1, A) including reaction with aqueous hypobromite, reduction of the intermediate *gem*-bromonitroadamantanes and oxidative nitration.[4] Several members of these compounds have been reported, including 2,2-dinitroadamantane, 2,2,6,6-tetranitroadamantane[5] and 1,2,2-trinitroadamantane.[6] Attempts to prepare 2,2,4,4-tetranitroadamantane by direct nitration of adamantane-2,4-dione dioxime (Scheme 1, B) were unsuccessful, and an intramolecular ring-closure product, 2,4-dinitro-2,4-dinitrosoadamantane, was formed predominantly.[5] Oxidative nitration of 2,4-dinitroadamantane also did not produce 2,2,4,4-tetranitroadamantane. In order to synthesize polynitroadamantanes from the corresponding 2,4-dioximino derivatives, fractional conversion of the carbonyls into *gem*-dinitro groups proved to be a feasible strategy. Another reason for doing this is to overcome the problems associated with steric crowding.[7]



Scheme 1 Strategies for the synthesis of polynitroadamantanes containing *gem*-dinitro groups: (A) three-step process,[4] (B) direct nitration of adamantane-2,4-dione dioxime,[5] (C) fractional conversion for the synthesis of 2,2,4,4-tetranitroadamantane.[8]

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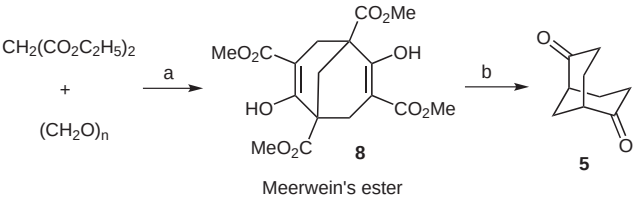
This strategy has been successfully employed in the synthesis of 2,2,4,4-tetranitroadamantane (Scheme 1, C)[8] and 2,2,4,4,6,6-hexanitroadamantane (HNA, **1**).[9]

Dave and co-workers synthesized HNA from dimethyl malonate and paraformaldehyde via a 10-step route in 0.24% overall yield.[9a] The construction of the adamantane framework was accomplished via a sulfuric acid catalyzed cyclization of bicyclo[3.3.1]nonane-2,6-dione with acetic anhydride, and the key intermediate 4-methyleneadamantane-2,6-dione was obtained in 31% yield (see Scheme 4).[10] *gem*-Dinitro groups were introduced step by step through direct nitration of the corresponding oximino derivatives with excess nitric acid in 37% yield (nitration of the 4-oximino derivative) and 21% yield (nitration of the 2,6-dioximino derivative), respectively. To develop more efficient synthetic protocols for polynitroadamantanes, herein we report two new and efficient approaches for the synthesis of HNA. The key steps of the two synthetic routes are C-acylation, proline-catalyzed intramolecular aldol condensation and clean nitration with dinitrogen pentoxide (N_2O_5).

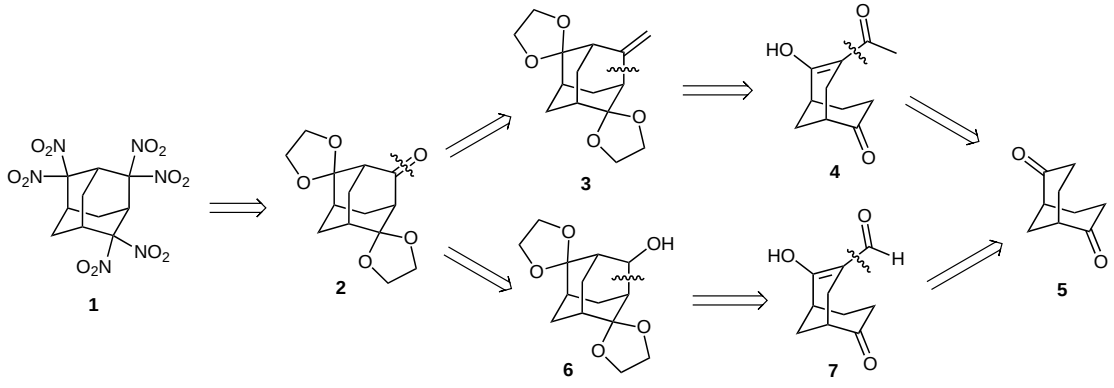
The retrosynthetic analysis for HNA (**1**) is summarized in Scheme 2. The target product **1** could be prepared from the keto derivative **2** via oximation and nitration. We envisaged two routes for the preparation of compound **2**. One route can be realized by ozonization of olefin **3**. According to the method described by McCabe et al.,[10] **3** was prepared via a path from bicyclo[3.3.1]nonane-2,6-dione (**5**) and acetic anhydride in the presence of concentrated sulfuric acid. In view of the low yield, high reaction temperature and use of concentrated sulfuric acid, we modified the original method and envisioned that **3** could be prepared via intramolecular aldol condensation and dehydration[11] from compound **4**, which could be synthesized from **5** by C-acetylation.[12] Alternatively, we presumed that key precursor **2** could also be prepared from the corresponding adamantanol **6** through oxidation of the hydroxy group. Compound **6** could be prepared from **7** using a similar strategy to the acetylation route, and compound **7** could be derived from dione **5** by formylation at the α-position to the carbonyl group.[13] Clearly, the formylation route would be more efficient and atom-economic.

Initially, bicyclo[3.3.1]nonane-2,6-dione (**5**) was prepared from diethyl malonate through two steps (Scheme 3). The continuous Knoevenagel condensation and Michael addition between diethyl malonate and paraformaldehyde led to Meerwein's ester (**8**),[14] which was decarboxylated to give **5**. Meerwein's ester was synthesized by referring to the standard conditions reported by Wallentin and co-workers,[15] with some modifications: diethyl malonate was used as starting material in place of dimethyl malonate, and *N*-methylpiperazine was utilized as the catalyst. The product **8** was obtained in good yield (70%). Decarboxylation[16] of **8** in acetic acid with hydrochloric acid (6 M) afforded **5** in 78% yield.



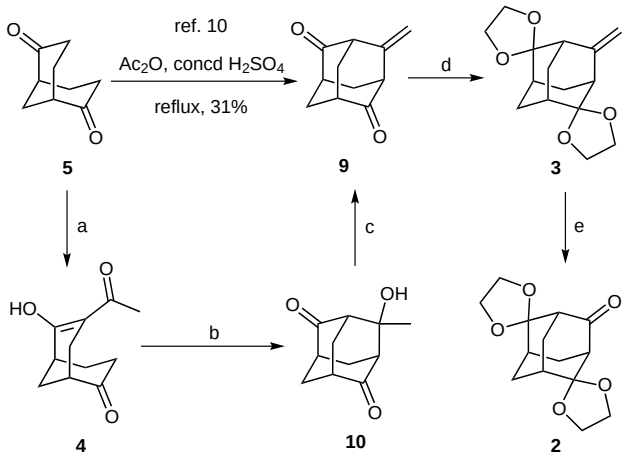
Scheme 3 *Reagents and conditions*: a) i) *N*-methylpiperazine, toluene, 100 °C, 8 h; then 120 °C, 10 h; ii) MeONa, MeOH, reflux, overnight; iii) 6 M HCl, 70% for 3 steps; b) AcOH, 6 M HCl, reflux, 24 h, 78%.

The key transformation involves the formation of the adamantane skeleton. In previous research, the adamantane skeleton was constructed by 'one-pot' sulfuric acid catalyzed tandem reactions from bicyclo[3.3.1]nonane-2,6-dione (**5**) in refluxing acetic anhydride, and provided compound **9** in 31% yield.[10] To improve this result, a three-step process was investigated, as shown in Scheme 4. Enamines are considered to be ideal intermediates in acylation reactions due to their high reactivity.[17] Thus, the enamine of **5** was prepared by condensation with morpholine using *p*-toluenesulfonic acid as the catalyst. Acetylation of the enamine was conducted with acetyl chloride in dichloromethane. Treatment of the acetylated product with dilute hydrochloric acid afforded **4** in high yield (80%). Aldol condensation is an important reaction and can be catalyzed by a variety of acids and bases.[18–23] In our case, *p*-toluenesulfonic acid was first used as a catalyst in the intramolecular aldol condensation of **4**, and afforded



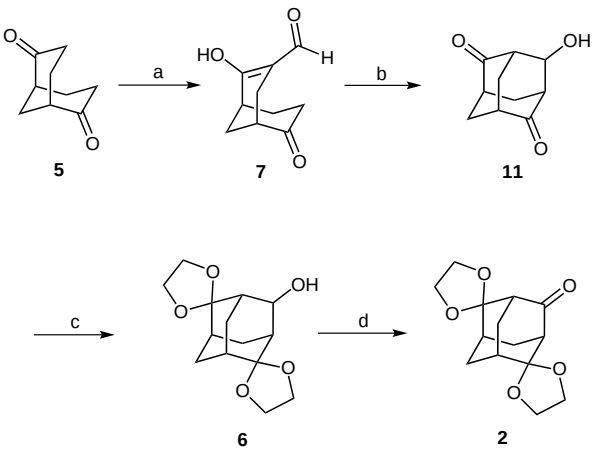
Scheme 2 Retrosynthetic analysis for HNA (**1**)

compound **10** in 80% yield. On the other hand, when some inorganic bases (K_2CO_3, KOH, NaOH) were utilized, only unreacted **4** was detected. The organic base pyrrolidine gave similar results. To our delight, however, when L-proline was used, the desired product alcohol **10** was obtained in quantitative yield. Dehydration of alcohol **10** was achieved using thionyl chloride and pyridine to generate the olefin **9** in 80% yield. Consequently, compound **9** was synthesized from compound **5** via three steps in an overall yield of 61%. The two carbonyl groups of olefin **9** were protected as the ethylene ketal derivative **3** in 94% yield, following the classical procedure. After ozonization of **3**, reduction was carried out using sodium thiosulfate as the reductant in the presence of 4 Å molecular sieves (MS), and afforded compound **2** in 51% yield.



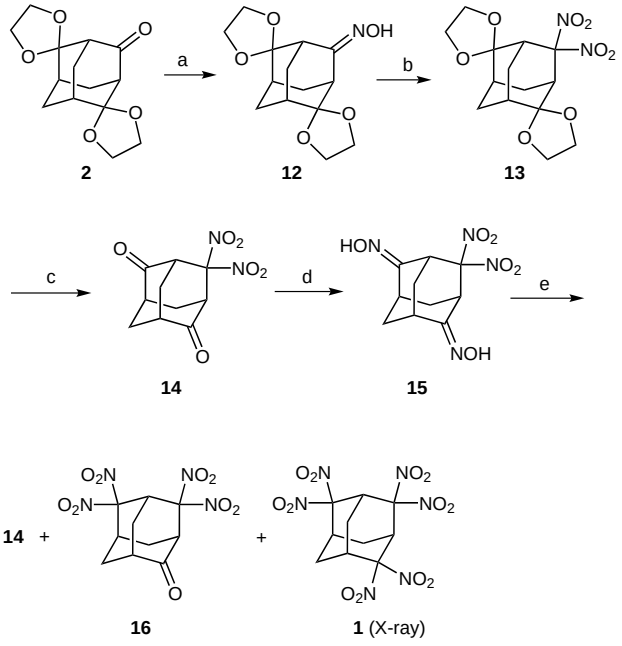
Scheme 4 *Reagents and conditions*: a) i) morpholine, PTSA, toluene, reflux, 8 h; ii) AcCl, Et_3N, CH_2Cl_2, 0 °C to r.t., 3 h; iii) H_3O^+, 80% for 3 steps; b) L-proline, MeCN, 60 °C, 12 h, 95%; c) $SOCl_2$, pyridine, CH_2Cl_2, 45 min, 80%; d) ethylene glycol, PTSA, toluene, reflux, 6 h, 94%; e) i) O_3, EtOAc, –40 °C, 4 Å MS, 1.5 h; ii) $Na_2S_2O_3$, 1 h, 51%.

Encouraged by the success of the above acetylation route, we set out to test whether this intramolecular aldol condensation method would be compatible with the formylated derivative **7** (Scheme 5). C-Formylation of ketones has been widely investigated.[24] In our case, ethyl formate was applied in the reaction with dione **5** to prepare compound **7**. Preliminarily, several reaction conditions were screened. As a result, we established that the formylation carried out in a methanolic sodium methoxide (1.2 equiv) system at 40 °C gave a better conversion (95%) than reactions conducted with sodium methoxide in toluene (80%) or sodium hydride in tetrahydrofuran (no reaction). Gratifyingly, **7** served as an excellent substrate in the L-proline-catalyzed intramolecular aldol condensation to provide the desired adamantanol **11** in quantitative yield. The carbonyl groups of **11** were protected as ethylene ketals, and the product **6** was then oxidized with sodium 2-iodoxybenzenesulfonate and Oxone® under nonaqueous conditions[25] to afford compound **2** in almost quantitative yield. Following this strategy, the intermediate **2** was isolated in 87% yield from dione **5**.



Scheme 5 *Reagents and conditions*: a) HCO_2Et, MeONa, MeOH, 40 °C, 12 h, 95%; b) L-proline, MeCN, 70 °C, 7 h, 96%; c) ethylene glycol, PTSA, toluene, reflux, 3 h; d) Oxone®, sodium 2-iodoxybenzenesulfonate, Na_2SO_4, EtOAc, 70 °C, 6 h, 95% for 2 steps.

Having the key intermediate **2** in hand, the last major task for completion of the synthesis of HNA (**1**) was the conversion of the carbonyls into *gem*-dinitro groups. Ketoximes are capable of undergoing nitration to provide the corresponding *gem*-dinitro compounds. Thus, the free carbonyl group of compound **2** was converted firstly into the corresponding oxime **12** (Scheme 6). Fortunately, this reaction proceeded smoothly at room temperature, following the classical procedure. Direct nitration of **12** with nitric acid in refluxing dichloromethane, as suggested by Dave and co-workers,[9a] afforded *gem*-dinitro compound **13** in only 37% yield.



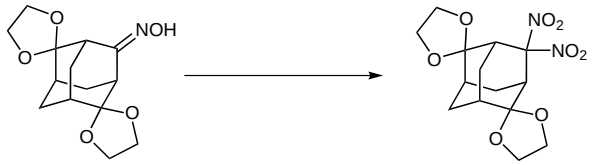
Scheme 6 *Reagents and conditions*: a) $NH_2OH{\cdot}HCl$, EtOH, r.t., 12 h, 95%; b) N_2O_5, urea, 4 Å MS, CH_2Cl_2, 50 °C, 30 min, 65%; c) concd H_2SO_4, CH_2Cl_2, r.t., 3 h, 95%; d) $NH_2OH{\cdot}HCl$, MeOH, reflux, 24 h, 92%; e) N_2O_5, urea, 4 Å MS, CH_2Cl_2, 50 °C, 30 min, 35%.

Although considerable research on the conversion of ketoximes into *gem*-dinitro compounds has been reported, little attention has been paid to aliphatic ketones in general. Dinitrogen pentoxide (N_2O_5) has proved to have unique properties in some nitration reactions.[26] It is an environmentally friendly, efficient nitrating reagent with many advantages over conventional reagents such as mixed acid (H_2SO_4 and HNO_3). The advantages include: (1) faster reactions, (2) easier temperature control, (3) easier product isolation, (4) higher purity products and (5) the absence of large amounts of acid waste for disposal. N_2O_5 has the ability to facilitate the nitration of reactive, acid-sensitive or easily oxidized substrates. Thus, it was applied in the oxidative nitration of the oximino group of **12** to give the corresponding *gem*-dinitro compound **13**, as shown in Scheme 6. In control experiments, reaction of oxime **12** with NO_2 resulted in deoximation to give ketone **2** only. Thus, any NO_2 generated from the decomposition of N_2O_5 may decrease the yield of dinitro derivative **13**. It is well known that urea is generally used to deplete excess HNO_2 in diazotization reactions. In a similar way, we anticipated that urea could be used to deplete NO_2 in the N_2O_5-based nitration reactions of oximes. In our experiments, we found that evolution of NO_2 was reduced and the reaction mixture, which was yellowish without the addition of urea, finally turned colorless when urea was used. We also found that *gem*-dinitro compounds are converted into ketones in the presence of aqueous mineral acids. In fact, HNO_3 would also be generated in the nitration of oximes with N_2O_5. Therefore, molecular sieves were used as an absorbent of water. The results from optimization of the oxidative nitration reaction conditions are listed in Table 1.

Eventually, the nitration of **12** was conducted using N_2O_5 (3 equiv) in refluxing dichloromethane in the presence of urea and molecular sieves to afford *gem*-dinitro derivative **13** (65%) and some ketone **2** (18%). This may be due to the high nitrating and oxidizing ability of N_2O_5 compared to HNO_3. The recovered ketone **2** was subjected to another oximation and nitration; the combined yield of **13** was 76%. The optimized reaction conditions were extended to adamantane-2,6-dione. Particularly noteworthy is the fact that direct nitration of the adamantanedione dioxime under the optimized conditions resulted in the expected *gem*-dinitro compound 2,2,6,6-tetranitroadamantane in 50% yield combined with some 2,2-dinitroadamantan-6-one (20%) and recovered adamantane-2,6-dione (15%); in contrast, only adamantane-2,6-dione was recovered when direct nitration of the dioxime was carried out under other reaction conditions and only 11% yield of the tetranitro derivative was obtained via a three-step process.[5] In separate experiments, we found that the optimized reaction conditions are applicable to aromatic and aliphatic ketones. Attempts to deprotect ketal **13** in aqueous mineral acid solutions failed; ketone **2** was found to be the main product, which indicated that hydrolysis of the *gem*-dinitro groups to carbonyl is favored in aqueous media. Deketalization of **13** finally succeeded upon use of concentrated sulfuric acid in dichloromethane, and afforded the desired product **14** in excellent yield (95%, Scheme 6). Subsequently, treatment of **14** with hydroxylamine hydrochloride in refluxing methanol gave the corresponding dioximino derivative **15** in excellent yield (92%). ^{1}H and ^{13}C NMR spectra indicated that compound **15** was a mixture of three diastereomers. Oxidative nitration of **15** under the above-optimized conditions afforded the final hexanitro product **1** in 35% yield. A byproduct, 4,4,6,6-tetranitroadamantan-2-one (**16**), was obtained in 40% yield and some dione **14** (15%) was recovered. The obtained **16** was subjected to another oximation and nitration; the combined yield of **1** was 47%.

The structure of HNA (**1**) was confirmed by ^{1}H NMR, ^{13}C NMR, IR and elemental analysis. Conclusive evidence for the structure of HNA was obtained by X-ray diffraction techniques (Figure 1). Single crystals of HNA suitable for X-ray diffraction analysis were obtained by slow recrys-

Table 1 Oxidative Nitration of **12** in the Preparation of **13**



12 **13**

Entry	N_2O_5 (equiv)	Temp (°C)	Time (min)	Additive	Solvent[a]	Yield[b] (%)
1	1.25	0	30	–	CH_2Cl_2	trace
2	1.25	40	30	–	CH_2Cl_2	17
3	2	40	30	–	CH_2Cl_2	32
4	2.5	40	30	–	CH_2Cl_2	36
5	3	40	30	–	CH_2Cl_2	40
6	3.5	40	30	–	CH_2Cl_2	39
7	4	40	30	–	CH_2Cl_2	33
8	3	40	30	4 Å MS	CH_2Cl_2	55
9	3	40	30	urea	CH_2Cl_2	52
10	3	40	30	4 Å MS, urea	CH_2Cl_2	59
11	3	45	30	4 Å MS, urea	CH_2Cl_2	62
12	3	50	30	4 Å MS, urea	CH_2Cl_2	65
13	3	50	25	4 Å MS, urea	CH_2Cl_2	52
14	3	50	35	4 Å MS, urea	CH_2Cl_2	59
15	3	50	30	4 Å MS, urea	$CHCl_3$	57
16	3	50	30	4 Å MS, urea	$MeNO_2$	51
17	3	50	30	4 Å MS, urea	DCE	55

[a] Solvent (0.05 M).
[b] Isolated yield.

tallization from chloroform. In HNA, the various bond lengths and angles of the adamantane skeleton are almost unchanged, which indicates that no distortion occurs in the adamantane structure, while the parameters associated with the dinitromethylene moiety change significantly. Similar to 2,2-dinitroadamantane[27] and 2,2,4,4-tetranitroadamantane,[8] the C–N bond lengths of HNA are stretched to 1.550 and 1.578 Å, longer than the typical C(sp^3)–NO_2 distance (1.46–1.50 Å), and the N–C–N angle is diminished to 96°. These distortions observed in the nitroadamantanes may be attributed to the *gem*-dinitro groups that, due to the strong electron demand placed on C, require an enrichment of the amount of p-character in the exocyclic orbitals at C. The crystal density was found to be 1.78 g·cm^{-3}, which is less than the calculated value (1.94 g·cm^{-3}, Table 2). This observation tends to substantiate the postulate that the existence of the *gem*-dinitro groups and the cage structure results in less tightly packed units of HNA in the crystal lattice, which would decrease the crystal density of HNA. The physicochemical properties of HNA including thermal and detonation properties were calculated using the Gaussian 09 (A.02) program (Table 2).[28] HNA has a calculated detonation pressure of 33.03 GPa and a detonation velocity of 8443 m·s^{-1}, which makes it possible to be used as a high-energy material.

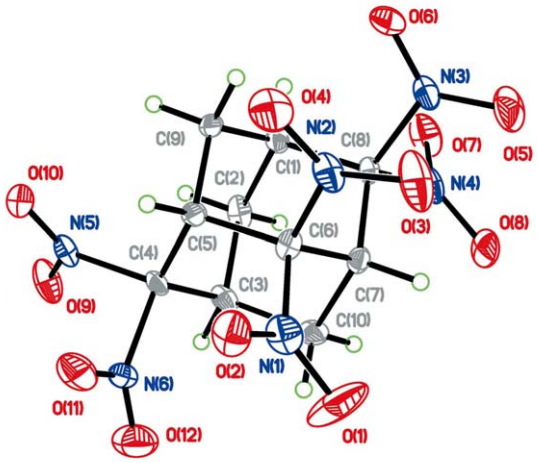


Figure 1 X-ray crystal structure of HNA (**1**)

Table 2 Physicochemical Properties of HNA (**1**)

Compound	ρ (g·cm^{-3})	ΔH_f (kJ·mol^{-1})	D (m·s^{-1})	P (GPa)	H (kJ·kg^{-1})
HNA	1.78 (calcd 1.94)	–226.08	8443	33.03	5814

In summary, two strategies have been developed for the synthesis of HNA (**1**). Both strategies used the readily available diethyl malonate and paraformaldehyde as the starting materials, and construction of the adamantane skeleton was via intramolecular aldol condensation in both cases. In the first strategy, we took advantage of the acetylation of **5** followed by an intramolecular aldol condensation to afford adamantane skeleton compound **10**. The second strategy utilized the formylation of **5** and accessed the adamantane skeleton compound **11** by the same method. The oxidative nitrations were conducted using N_2O_5 in refluxing dichloromethane in the presence of urea and 4 Å molecular sieves to give the corresponding *gem*-dinitro derivatives. The acetylation route was accomplished via 12 steps and afforded HNA in 4.7% overall yield, while the formylation route was achieved via 11 steps and gave HNA in 14% overall yield. These strategies provide mild and prospective ways for the synthesis of other polynitroadamantanes.

Unless otherwise specified, chemicals (AR grade) were obtained from commercial sources and were used without further purification. Petroleum ether (PE) refers to the fraction boiling in the 60–90 °C range. The progress of the reactions was monitored by TLC (silica gel, Polygram SILG/UV 254 plates). Column chromatography was performed on SiliCycle silica gel (200–300 mesh). Melting points were obtained using a Yamato melting point apparatus (model MP-21) and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained at 500 and 125 MHz, respectively, using a Bruker DRX spectrometer and $CDCl_3$ or DMSO-d_6 as the solvent. Chemical shifts (δ) are quoted in ppm and are referenced to TMS as internal standard. All Fourier transform infrared (FTIR) spectra were obtained using a Thermo Scientific Nicolet iS50 FTIR spectrometer. Elemental analyses were recorded using a Vario EL III CHN elemental analyzer. GC/MS spectra of new compounds were obtained using a Thermo Trace 1300 GC-ISQ mass spectrometer (GC temperature program: starting temperature 40 °C, gradient of 15 °C/min to 260 °C, hold for 5 min; MS operating conditions: EI ion source, 76 eV, injector temperature 250 °C, scan range 0–1000). The crystal data of 2,2,4,4,6,6-hexanitroadamantane (**1**)[29] were collected on an Enraf-Nonius CAD-4 four-circle diffractometer by using Mo Kα radiation (0.71073 Å). Known compounds were identified by comparison of their physical and spectroscopic data with literature data.

Meerwein's Ester (8)[15]

A mixture of diethyl malonate (228 mL, 1.5 mol), paraformaldehyde (37.5 g, 1.25 mol) and toluene (200 mL) was stirred in a round-bottomed flask equipped with a Dean–Stark apparatus until a homogeneous solution was formed, and then *N*-methylpiperazine (4.2 mL, 0.038 mol) was added. The solution was stirred and heated at 100 °C for 8 h, then at 120 °C for approximately 10 h until H_2O accumulation in the water trap ceased. The cooled solution was concentrated under reduced pressure to give a slightly yellowish oil (about 150 mL). The clear yellowish oil was added rapidly to a 1-L round-bottomed flask charged with a solution of MeONa (57.4 g, 1.06 mol) in MeOH (400 mL) under vigorous stirring. Large quantities of a white solid formed within 5–10 min. The reaction mixture was stirred and refluxed for 20 h, during which time the solid dissolved and a yellowish precipitated formed. The suspension was cooled in an ice–water bath for 2 h and then Et_2O (200 mL) was added to facilitate the precipitation. The mixture was filtered through a Büchner funnel and the solid was washed with a mixture of MeOH (100 mL) and Et_2O (100 mL); the white solid obtained was dissolved in H_2O (400 mL) and 6 M HCl (ca. 120 mL) was slowly introduced until no more solid precipitated. After filtration and washing with H_2O (200 mL), the product **8** was obtained as a white solid; yield: 101 g (70%).

Mp 153.5–153.9 °C.

FTIR: 2952, 1737, 1652, 1442, 1365, 1232 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.18 (s, 2 H), 3.79 (s, 6 H), 3.78 (s, 6 H), 2.88 (s, 4 H), 2.34 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.5, 171.9, 168.2, 96.9, 52.8, 51.9, 47.7, 35.3, 29.7.

Anal. Calcd for $C_{17}H_{20}O_{10}$: C, 53.13; H, 5.25. Found: C, 53.01; H, 5.32.

Bicyclo[3.3.1]nonane-2,6-dione (5)[16]
A mixture of Meerwein's ester (**8**; 101 g, 0.26 mol) and AcOH (240 mL) was stirred and heated to gentle reflux in a three-necked round-bottomed flask until a homogeneous solution was formed. 6 M HCl (165 mL, 0.99 mol) was added dropwise over 12 h. The reaction mixture was stirred for an additional 12 h under reflux. Concentration of the solution under reduced pressure gave a pale yellow, crude product. The solid was dissolved in a mixture of H_2O (200 mL) and CH_2Cl_2 (300 mL). The organic phase was washed with sat. $NaHCO_3$ solution (100 mL), followed by brine (50 mL), then dried over Na_2SO_4, filtered and concentrated. The residual solid was washed with Et_2O (2 × 50 mL) to afford **5** as a white solid; yield: 31.2 g (78%).

Mp 139.4–140.5 °C.

FTIR: 2935, 1694, 1439 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.71 (d, *J* = 1.7 Hz, 2 H), 2.61–2.52 (m, 2 H), 2.43–2.32 (m, 2 H), 2.18 (s, 2 H), 2.12–1.98 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 212.7, 43.6, 37.1, 31.4, 26.7.

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.15; H, 7.86.

3-Acetylbicyclo[3.3.1]nonane-2,6-dione (4)
A mixture of **5** (10.0 g, 65.7 mmol), morpholine (23.0 mL, 262.8 mmol) and PTSA·H_2O (2.5 g, 13.1 mmol) in toluene (250 mL) was heated under reflux in a round-bottomed flask equipped with a Dean–Stark apparatus for 8 h. The mixture was concentrated under reduced pressure. AcCl (5.11 mL, 72.3 mmol) was added dropwise to a mixture of the residual solid (21.6 g) and Et_3N (11.9 mL, 85.4 mmol) in CH_2Cl_2 (200 mL) at 0 °C. After that, the mixture was stirred for an additional 3 h at r.t.; then, 10% HCl (100 mL) was added and the mixture was stirred for 1 h. The organic phase was washed with sat. $NaHCO_3$ solution (200 mL), followed by brine (50 mL), then dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel column chromatography (EtOAc–PE, 1:12) to give **4** as a white solid; yield: 10.2 g (80%).

Mp 107.3–108.5 °C.

FTIR: 2940, 2860, 1700, 1590, 1420, 1230, 942 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 15.81 (s, 1 H), 2.86 (s, 1 H), 2.73–2.67 (dd, *J* = 16, 6.9 Hz, 2 H), 2.44–2.25 (m, 4 H), 2.15 (s, 3 H), 2.09–1.99 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 212.7, 199.8, 181.7, 105.1, 44.1, 36.6, 34.9, 29.8, 29.6, 27.7, 25.4.

MS (EI): *m*/*z* (%) = 194 (48) $[M]^+$, 151 (60), 108 (66), 95 (74), 55 (75), 43 (100).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.15; H, 7.31.

4-Hydroxy-4-methyladamantane-2,6-dione (10)
A mixture of **4** (7.78 g, 40 mmol), L-proline (0.92 g, 8 mmol) and MeCN (50 mL) was stirred at 60 °C for 12 h. The solvent was removed under reduced pressure, and the residual yellow solid was partitioned between CH_2Cl_2 (300 mL) and H_2O (100 mL). The organic layer was washed with brine (50 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the residue was recrystallized (CH_2Cl_2–*n*-hexane) to afford **10** as a pale pink solid; yield: 7.39 g (95%).

Mp 198.1–199.6 °C.

FTIR: 3380, 2950, 1700, 1480, 1370, 1300, 1110, 920 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.49 (s, 1 H), 2.74–2.70 (m, 1 H), 2.60–2.55 (m, 4 H), 2.26–2.14 (m, 2 H), 2.13–1.96 (m, 3 H), 1.33 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 213.9, 212.5, 78.1, 57.2, 44.0, 43.9, 40.2, 34.4, 33.6, 26.5.

MS (EI): *m*/*z* (%) = 194 (48) $[M]^+$, 151 (58), 96 (63), 79 (32), 55 (67), 43 (100).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.13; H, 7.34.

4-Methyleneadamantane-2,6-dione (9)[10]
To a solution of $SOCl_2$ (2.55 mL, 35.2 mmol) in CH_2Cl_2 (250 mL) and anhydrous pyridine (102 mL) was added a solution of **10** (6.22 g, 32 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The resulting solution was stirred at 0 °C for 45 min. Then, the reaction mixture was poured into an ice–water mixture (200 mL). The organic layer was washed with sat. $NaHCO_3$ solution (100 mL), followed by brine (50 mL), then dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the residue was recrystallized (CH_2Cl_2–*n*-hexane) to afford **9** as a white solid; yield: 4.5 g (80%).

Mp 159.6–161.3 °C.

FTIR: 3060, 2945, 1707, 1650, 1457, 903 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.83 (s, 2 H), 3.32 (m, 2 H), 2.76 (m, 2 H), 2.37–2.28 (m, 4 H), 2.25–2.21 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.0, 147.4, 109.3, 56.4, 44.8, 39.9, 39.3.

Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.09; H, 6.94.

2,2,6,6-Bis(ethylenedioxy)-4-methyleneadamantane (3)[9a]
4-Methyleneadamantane-2,6-dione (**9**; 4.4 g, 25 mmol), ethylene glycol (4.2 mL, 75 mmol), PTSA·H_2O (0.475 g, 2.5 mmol) and toluene (200 mL) were added to a round-bottomed flask equipped with a Dean–Stark apparatus. The mixture was heated at 120 °C for 6 h until H_2O accumulation in the water trap ceased. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between CH_2Cl_2 (150 mL) and H_2O (100 mL). The organic layer was washed with brine (50 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the residue was recrystallized (CH_2Cl_2–*n*-hexane) to afford **3** as white crystals; yield: 6.3 g (94%).

Mp 119.6–120.3 °C.

FTIR: 3081, 2936, 1659, 1450, 1232, 904 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.78 (s, 2 H), 4.07–3.92 (m, 8 H), 2.41 (s, 2 H), 2.07–1.98 (m, 4 H), 1.93–1.87 (m, 2 H), 1.83–1.81 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.5, 110.3, 107.0, 64.4, 46.4, 35.0, 32.2, 31.3.

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.32; H, 7.52.

2,2,6,6-Bis(ethylenedioxy)adamantan-4-one (2)[9a]

Procedure A
Ozone was bubbled through a solution of **3** (4.35 g, 16.5 mmol) in EtOAc (300 mL) containing 4 Å molecular sieves (10 g) at –40 °C until the solution had taken on a characteristic blue color. The clear solution was allowed to warm to r.t. and stirred for an additional 1 h after saturated $Na_2S_2O_3$ (8 mL) was added. The organic layer was washed with brine (50 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel column chromatography (EtOAc–PE, 1:4) to give **2** as a white solid; yield: 2.21 g (51%).

Mp 164.6–165.8 °C.

FTIR: 2941, 1723, 1452, 1232 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.05–3.91 (m, 8 H), 2.67 (m, 2 H), 2.15–2.05 (m, 4 H), 2.05–1.95 (m, 2 H), 1.91–1.88 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.3, 111.1, 64.8, 64.6, 54.6, 35.1, 30.9, 29.4.

Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 62.95; H, 7.08.

Procedure B

A mixture of **6** (6.1 g, 22.7 mmol), powdered Oxone® (11.45 g, 18.6 mmol), sodium 2-iodoxybenzenesulfonate (0.14 g, 0.45 mmol) and anhydrous Na_2SO_4 (23 g) in EtOAc (120 mL) was rigorously stirred at 70 °C for 6 h. After the reaction was complete, the mixture was cooled to r.t. and filtered. The filtrate was washed with H_2O (2 × 50 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure to afford **2** as a white solid; yield: 6.05 g (100%).

2,6-Dioxobicyclo[3.3.1]nonane-3-carbaldehyde (7)

A freshly prepared solution of MeONa (4.26 g, 78.8 mmol) in MeOH (5 mL) was added dropwise to a mixture of **5** (10 g, 65.7 mmol) and ethyl formate (15.8 mL, 197.1 mmol) in MeOH (75 mL) at 0 °C. The reaction mixture was stirred at 40 °C for an additional 12 h. The solvent was removed under reduced pressure, and the residual solid was dissolved in CH_2Cl_2 (150 mL) before washing with 10% aq HCl solution (30 mL). The organic phase was washed with sat. $NaHCO_3$ solution (100 mL), followed by brine (50 mL), then dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure, and the residual solid was purified by silica gel column chromatography (EtOAc–PE, 1:4) to afford **7** as a white solid; yield: 11.3 g (95%).

Mp 96.4–97.8 °C.

FTIR: 2940, 2850, 1710, 1650, 1590, 1310, 1240, 862 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 14.31 (d, *J* = 1.8 Hz, 1 H), 8.82 (d, *J* = 1.4 Hz, 1 H), 2.84 (m, 1 H), 2.76–2.70 (m, 2 H), 2.45–2.40 (m, 2 H), 2.33–2.22 (m, 2 H), 2.07–2.06 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 212.2, 189.6, 183.3, 106.7, 43.6, 36.6, 34.9, 29.7, 29.3, 26.2.

MS (EI): *m*/*z* (%) = 180 (88) $[M]^+$, 152 (48), 123 (32), 105 (38), 95 (66), 77 (52), 55 (100).

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.81; H, 6.76.

4-Hydroxyadamantane-2,6-dione (11)

A mixture of **7** (9.0 g, 50 mmol), L-proline (2.3 g, 20 mmol) and MeCN (75 mL) was stirred at 70 °C for 7 h. The solvent was removed under reduced pressure, and the residual yellow solid was partitioned between CH_2Cl_2 (300 mL) and H_2O (100 mL). The organic layer was washed with brine (50 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the residue was recrystallized (CH_2Cl_2–*n*-hexane) to afford **11** as a white solid; yield: 8.6 g (96%).

Mp 298.4–299.8 °C.

FTIR: 3380, 2940, 1700, 1460, 1290, 1080, 924 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.36 (m, 1 H), 3.73 (s, 1 H), 2.81–2.79 (m, 2 H), 2.76–2.73 and 2.32–2.27 (m, 2 H), 2.59 (s, 2 H), 2.22–2.12 (m, 2 H), 2.09–2.04 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 213.4, 211.7, 76.0, 52.5, 52.4, 45.1, 43.7, 39.6, 33.9, 33.2.

MS (EI): *m*/*z* (%) = 180 (56) $[M]^+$, 152 (45), 107 (59), 95 (88), 67 (48), 55 (100).

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.83; H, 6.74.

2,2,6,6-Bis(ethylenedioxy)adamantan-4-ol (6)

Dione **11** (5.4 g, 30 mmol), ethylene glycol (5.2 mL, 90 mmol), PTSA·H_2O (0.57 g, 3 mmol) and toluene (200 mL) were charged into a round-bottomed flask equipped with a Dean–Stark apparatus and the mixture was heated at 120 °C for 3 h until H_2O accumulation in the water trap ceased. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between CH_2Cl_2 (150 mL) and H_2O (100 mL). The organic layer was washed with brine (50 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure to afford **6** as a white solid; yield: 7.6 g (95%). The product was used directly for the next step without purification.

Mp 263.5–264.3 °C.

FTIR: 3490, 2940, 1460, 1370, 1060, 928 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.24–4.21 (d, *J* = 10.4 Hz, 1 H), 4.10–4.09 (d, *J* = 1.9 Hz, 1 H), 4.08–3.89 (m, 8 H), 2.16–2.12 (dd, *J* = 13.5, 2.8 Hz, 1 H), 1.98–1.82 (m, 7 H), 1.81–1.70 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 110.8, 110.4, 72.9, 64.5, 64.4, 64.2, 63.8, 42.7, 39.9, 35.0, 34.2, 31.5, 28.8, 25.8.

MS (EI): *m*/*z* (%) = 268 (22) $[M]^+$, 223 (36), 178 (18), 151 (17), 113 (22), 99 (100).

Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.82; H, 7.55.

2,2,6,6-Bis(ethylenedioxy)-4-(hydroxyimino)adamantane (12)[9a]

A mixture of **2** (4.3 g, 16.15 mmol), NH_2OH·HCl (3.37 g, 48.44 mmol), NaOAc (3.97 g, 48.44 mmol) and EtOH (160 mL) was stirred at r.t. for 12 h. The reaction mixture was concentrated and the residue was partitioned between CH_2Cl_2 (150 mL) and H_2O (100 mL). The organic layer was washed with brine (50 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the residue was recrystallized (CH_2Cl_2–*n*-hexane) to provide the corresponding oxime **12** as a white solid; yield: 4.33 g (95%).

Mp 221.2–223.0 °C.

FTIR: 3249, 2937, 1645, 1451, 1236, 912 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 10.1 (s, 1 H), 4.0–3.8 (m, 8 H), 3.40 (m, 1 H), 2.33 (m, 1 H), 2.0–1.6 (m, 8 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.2, 110.2, 110.1, 64.7, 64.6, 64.6, 43.7, 36.6, 35.6, 35.4, 31.1, 31.0, 29.9.

Anal. Calcd for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N, 4.98. Found: C, 59.62; H, 7.06; N, 4.82.

2,2,6,6-Bis(ethylenedioxy)-4,4-dinitroadamantane (13)[9a]

(**CAUTION**: N_2O_5 is a strong oxidizing agent that forms explosive mixtures with organic compounds. The decomposition of N_2O_5 produces highly toxic NO_2 gas. N_2O_5 must be handled in closed systems under a well-ventilated hood.) A mixture of **12** (4 g, 14.3 mmol), urea (2.57 g, 42.9 mmol), 4 Å molecular sieves (15 g) and CH_2Cl_2 (300 mL) was stirred and heated to 50 °C. A solution of N_2O_5 (4.6 g, 42.9 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 5 min, during which time a green color occurred initially and then faded as more N_2O_5 was added. The reaction mixture was stirred for an additional 30 min, then poured into an iced sat. solution of $NaHCO_3$ (200 mL). The organic layer was washed with brine (50 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel column chromatography (EtOAc–PE, 1:32) to afford **13** as a white solid; yield: 3.1 g (65%). Compound **2** was recovered as a white solid (0.67 g, 18%); oximation and nitration of the recovered ketone **2** according to the above-described procedure afforded **13** as a white solid (0.5 g). Finally, **13** was obtained as a white solid; combined yield: 3.6 g (76%).

Mp 235.4–236.5 °C.

FTIR: 2945, 1568, 1460, 1371, 1238, 946, 843 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.08–4.02 (m, 2 H), 3.96–3.89 (m, 4 H), 3.85–3.79 (m, 2 H), 3.29 (s, 2 H), 2.38 (d, *J* = 10 Hz, 2 H), 2.23–2.18 (m, 2 H), 1.99 (s, 2 H), 1.74 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 121.6, 108.9, 64.8, 64.4, 40.3, 34.7, 30.9, 27.9.

Anal. Calcd for $C_{14}H_{18}N_2O_8$: C, 49.12; H, 5.30; N, 8.18. Found: C, 49.23; H, 5.18; N, 8.34.

4,4-Dinitroadamantane-2,6-dione (14)[9a]

A mixture of **13** (2.5 g, 7.3 mmol), concd H_2SO_4 (45 mL) and CH_2Cl_2 (200 mL) was stirred at r.t. for 3 h. Then, the reaction mixture was poured into an ice–water mixture (300 mL). The organic layer was washed with sat. $NaHCO_3$ solution (50 mL) and brine (50 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure to give **14** as a white solid; yield: 1.76 g (95%).

Mp 246.5–247.8 °C.

FTIR: 2932, 1738, 1558, 1463, 1371, 952, 848 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.84 (s, 2 H), 2.71 (s, 2 H), 2.51–2.35 (m, 4 H), 2.03–1.99 (m, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 203.7, 123.9, 51.0, 43.3, 41.8, 32.9.

Anal. Calcd for $C_{10}H_{10}N_2O_6$: C, 47.25; H, 3.97; N, 11.02. Found: C, 47.36; H, 4.12; N, 10.83.

2,6-Bis(hydroxyimino)-4,4-dinitroadamantane (15)[9a]

A mixture of **14** (1.52 g, 6 mmol), $NH_2OH{\cdot}HCl$ (1.25 g, 18 mmol), NaOAc (1.48 g, 18 mmol) and MeOH (150 mL) was stirred under reflux for 24 h. The reaction mixture was concentrated and the residue was partitioned between CH_2Cl_2 (150 mL) and H_2O (100 mL). The organic layer was washed with brine (50 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the residue was recrystallized (CH_2Cl_2–*n*-hexane) to provide the corresponding oxime **15** as a white solid; yield: 1.56 g (92%).

Mp 209.8–210.5 °C.

FTIR: 3285, 2945, 1671, 1581, 1458, 1361, 957, 839 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.19–11.15 (m, 2 H), 4.81–4.73, 3.89–3.85 (m, 2 H), 3.54, 2.68 (m, 2 H), 2.19–2.15, 2.08–1.97 (m, 2 H), 1.93–1.68 (m, 4 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 155.2, 153.8, 122.2, 122.1, 42.6, 42.4, 41.1, 38.8, 36.4, 35.4, 35.1, 34.8, 34.5, 33.8, 33.7, 33.2, 32.9, 26.8, 26.7.

Anal. Calcd for $C_{10}H_{12}N_4O_6$: C, 42.26; H, 4.26; N, 19.71. Found: C, 42.37; H, 4.32; N, 19.59.

2,2,4,4,6,6-Hexanitroadamantane (1)[9a]

(Caution: N_2O_5 is a strong oxidizing agent that forms explosive mixtures with organic compounds. The decomposition of N_2O_5 produces highly toxic NO_2 gas. N_2O_5 must be handled in closed systems under a well-ventilated hood.) A mixture of **15** (1.2 g, 4.2 mmol), urea (0.76 g, 12.6 mmol), 4 Å molecular sieves (10 g) and CH_2Cl_2 (100 mL) was stirred and heated to 50 °C. A solution of N_2O_5 (1.36 g, 12.6 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 5 min, during which time a green color occurred initially and then faded as more N_2O_5 was added. The reaction mixture was stirred for an additional 30 min, then poured into an iced sat. solution of $NaHCO_3$ (100 mL). The organic layer was washed with brine (50 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel column chromatography (EtOAc–PE, 1:12) to afford the desired product **1** as a white solid (0.6 g, 35%), 4,4,6,6-tetranitroadamantan-2-one (**16**) as a white solid (0.56 g, 40%) and dione **14** as a white solid (0.16 g, 15%). Oximation and nitration of **16** according to the above-described procedure for **14** gave the target product **1** as a white solid (0.21 g). Finally, **1** was obtained as a white solid; combined yield: 0.81 g (47%).

Mp 198.9–200.4 °C.

FTIR: 3010, 1580, 1474, 1358, 935, 839 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.82–4.77 (m, 2 H), 3.40–3.10 (m, 4 H), 2.76–2.68 (m, 2 H), 2.07–2.03 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 119.7, 119.4, 37.5, 32.7, 30.3, 29.8.

Anal. Calcd for $C_{10}H_{10}N_6O_{12}$: C, 29.57; H, 2.48; N, 20.69. Found: C, 29.43; H, 2.56; N, 20.48.

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Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000084.

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(29) The crystal data for compound **1** have been deposited with the Cambridge Crystallographic Data Centre (no. CCDC 953576). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk] or via www.ccdc.cam.ac.uk/data_request/cif.