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Rearrangement of Hexabenzylhexaazaisowurtzitane

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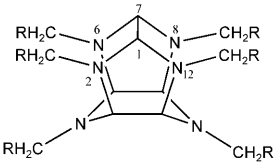
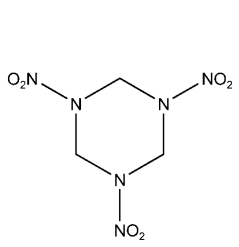
Dedicated to the memory of A. I. Meyers

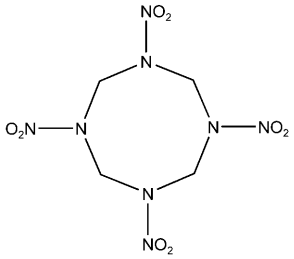
The condensation of amines[1] and amides[2] with glyoxal has yielded a variety of often unexpected and spectacular molecular systems. Of particular importance is the acid-catalyzed condensations of glyoxal with benzylamine or substituted benzylamines, which produce 2,4,6,8,10,12-hexabenzyl-2,4,6,8,10,12-hexaazatetracyclo[5.5.0.0^{5,9}.0^{3,11}]dodecanes, also known as hexabenzylhexaazaisowurtzitane (HBIW; **1**) in good yield.[3]



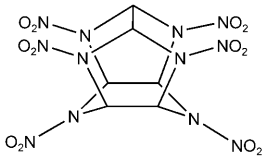
R=Ph (**1**), PHX, 1-Naphthyl, 3-Py, 2-Thienyl, 2-Furfuryl
R= CH=CH$_2$ (**2**)
R=C≡CH (**3**)



RDX **4**



HMX **5**



HNIW **6**

Only recently, this condensation was extended to benzylic heteroaromatic, allylic, and propargylic amines (**2**,**3**).[4] The new skeleton has opened a new era in energetic materials chemistry, from the standard monocyclic polynitramine energetics 1,3,5-trinitro-1,3,5-triazacyclohexane (RDX; **4**) and 1,3,5,7-tetranitro-1,3,5,7-tetraazacyclooctane (HMX; **5**) to the "three-dimensional" cage system hexanitrohexaazaisowurtzitane (HNIW; **6**).[5]

To this end, a variety of debenzylation methods were developed for gradual replacement of the pending benzyl groups in **1**. First, on the upper four nitrogen atoms and then on the lower nitrogen atoms on the six-membered ring, with moieties that can undergo nitrolysis,[6] such as acetyl,[7] nitroso,[8] formyl,[9] hydrogen,[10] or carbamoyl,[11] for the preparation of **6**. Other approaches to preparing suitable precursors for the nitrolysis reaction are based on oxidation of the benzyl moieties. Attempted oxidation of **1** usually affects the bridgehead C1–C7 bond, connecting the two five-membered rings. Depending on the oxidation agent, the tricyclic urea **7** (O_2/CuCl/Py/$(CH_3)_2CHNO_2$)[12] or the diimidazolium salt **8** (PDC; $K_2Cr_2O_7$; PCC; CrO_3/Py; CAN; nBuONO$_2$)[13,14] are formed. The hexabenzoylhexaazaisowurtzitane was obtained in a low yield by oxidation under forcing conditions with CrO_3/Ac_2O[13]. Oxidation of the benzylic position with $KMnO_4$ in acetic anhydride/acetyl bromide[15] yielded a mixture of all possible benzoylated and acetylated tetra oxidized products (on positions N2,N6,N8,N12).

Apart from these reactions, little is known on the chemistry of the parent hexaazaisowurtzitane skeleton. Recently, the reaction of 2-azidobenzylamine and glyoxal yielded the

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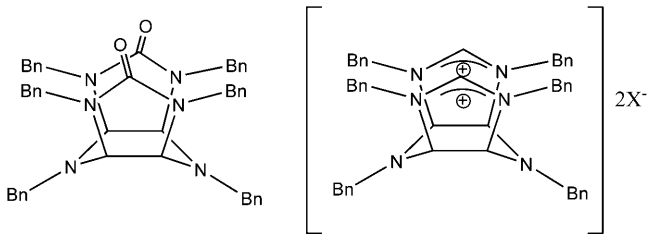
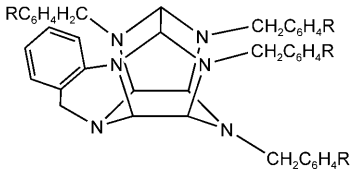


7 8

Bn = benzyl

expected isowurtzitane product (**1**; R = *ortho*-N_3-Ph) together with an interesting novel pentacyclic material **9**.[16]



9 R=*ortho*-N_3

Herein, a novel rearrangement of **1** that provides a simple entry to a new type of hexaaza-cage system otherwise not readily available is described. In the course of exploring different procedures for reductive acylation of the pending benzyl substituents in **1**, a catalytic hydrogenolysis in ethyl formate as solvent and formylating agent was attempted. Although no debenzylation/formylation product was obtained, the recovered starting material (**1**) was accompanied by a low yield of a slightly more polar material **10**, identified as an isomer of **1** (Table 1). It was assumed that the use of ethyl formate in the reaction resulted in the formation of the new product. To corroborate this, compound **1** was suspended in ethyl formate, at ambient temperature, but only little dissolution occurred. However, when the mixture was heated to reflux, a slow gradual change in color, from colorless to deep yellow–orange was observed. Compound **1** dissolved and almost entirely disappeared from the reaction mixture (TLC) and transformed to **10** in 58.6% yield after evaporation and column chromatography.

The principle spectroscopic features for **10** are summarized in Table 1. Chemical ionization mass spectrometry (isobutane) or LC–MS (electrospray; 1% acetic acid in acetonitrile) showed that this is an isomer with the same molecular weight (709 g mol^{-1}) as **1**. NMR spectroscopy analysis exhibited a highly complicated proton and carbon NMR spectra in comparison with the parent **1**,[3a] reflecting a complete loss of structural symmetry and indicating a major change of the cage skeleton. The new material has six benzylic methylene (CH_2) fragments as in the parent compound, but only five methine (CH) units, and a new sp^2-type carbon at $\delta =$ 159.3 ppm. IR spectroscopy showed two distinct vibrations present at 1639 (C=N) and 3296 cm^{-1} (NH).

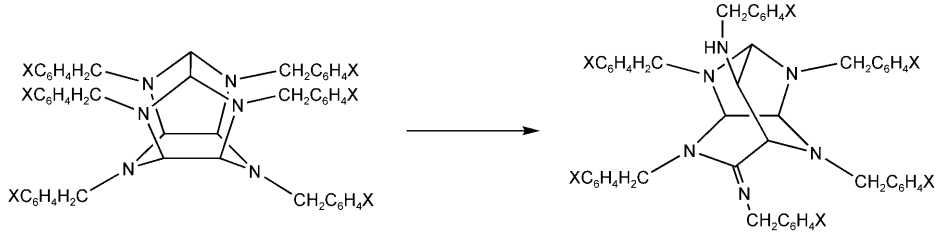
The data indicated that **1** had undergone a substantial structural change, probably through a rearrangement, resulting in a material with carbon–nitrogen double bond and secondary amine functionalities.

Attempts at proposing a structure of the material by using CH correlations failed. It became clear that the task required information on nitrogen chemical shifts. Due to the low natural abundance of ^{15}N, we obtained these indirectly through an N–H correlation spectra.[17] Although we were able to suggest a structure for **10**, the complexity mandated an X-ray crystallographic determination. Unfortunately, all attempts to crystallize the rearranged product failed and attention was directed to modified benzylamines with a heavy atom or polar substituents to be used in the condensation reaction with glyoxal.

Thus, condensation of 4-bromobenzylamine with glyoxal gave the 4-bromo-substituted-HBIW **11** (Scheme 1) in 19.7% yield which was rearranged in ethyl formate to the 4-bromo-substituted product **12** (Scheme 1).

The *para*-bromo-substituted **12** crystallized without difficulty and the structure was determined by X-ray crystallographic analysis (Figure 1).

Although this reaction was discovered with ethylformate, other acid derivatives could be used (EtOAc reflux/7 d in 51.4%; Ac_2O (20 mol%)/EtOAc reflux/6 d, in 58.1%; tri-



1: X=H
11: X=*para*-Br

10: X=H
12: X=*para*-Br

Scheme 1. Rearrangement reaction.

Table 1. Spectral data for compounds **1** and **10**.

Analysis		Structural feature	**1**	**10**
MS	CI (isobutane) or ESI-H^+ [m/z]	$[M+1]^+$	710	710
IR	1600–4000 [cm^{-1}]	functional groups	none	1639, 3296
NMR	^{13}C [ppm]	CH (skeletal)	77, 81	52, 58, 75, 76, 77
		CH_2 (benzyl)	56, 57	48, 49, 51, 52, 57, 60
		C (sp^2)	126–141 (aryl type)	127–141 (aryl type); 159.3
	^{15}N [ppm]	N	−297, −317	−136, −273, −302, −311, −335

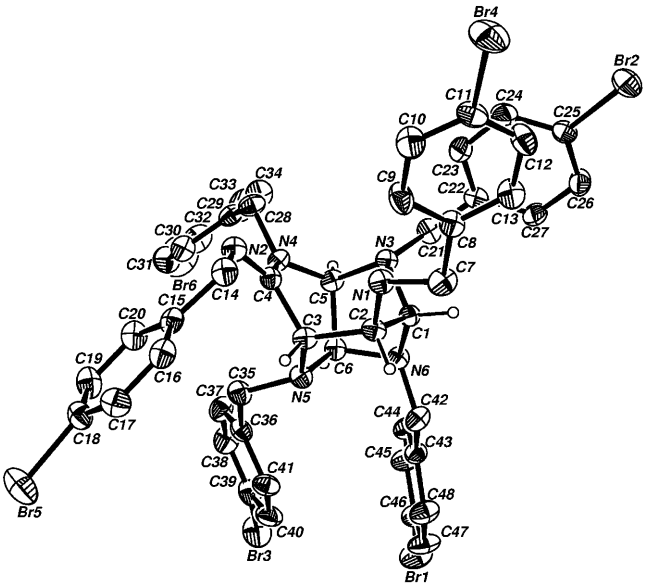


Figure 1. X-ray structure of *para*-bromo-substituted analogue **12**.

fluoroacetic anhydride (20 mol%)/EtOAc reflux/5 h in 70% yield).

A plausible mechanism for this internal rearrangement reaction is shown in Scheme 2. The key structural feature, is probably responsible for this avalanche of fragmentations and reconnections, is the N-C-N motif, which is well suited for a push–pull-type cleavage of a carbon–nitrogen bond upon iminium ion formation. The first step, presumably an acylation of one of the upper nitrogen atoms, is governed by the type of acylation reagent. The next step is cleavage of the carbon–nitrogen bonds in the N-C-N$^+$-COX feature. The following steps are more speculative and a series of iminium ion shifts and enamine imine cyclizations are suggested, much like the mechanism proposed for the formation of **1** by Nielsen et al.[3a] However, without regard to the actual mechanism the reaction represents an efficient and simple entry to the new cage system.

Experimental Section

Rearrangement of 1: Preparation of 10

Ethyl formate: A suspension of HBIW **1** (700 mg 0.987 mmol) in ethyl formate (25 mL) was heated at reflux for 16 h. Conversion was monitored by TLC (hexane/ethyl acetate/triethylamine 92:7:1). When the reaction was completed, excess ethyl formate was evaporated and the crude compound was purified by column chromatography with the same solvent mixture as used for the TLC development to give a slightly yellow viscous gum of the rearranged product **10** (410 mg, 58.6%).

Ethyl acetate: By using the same procedure, HBIW **1** (740 mg 1.044 mmol) was heated to reflux for 7 d. Evaporation and chromatography gave **10** (380.6 mg, 51.4%).

Acetic anhydride in ethyl acetate: HBIW **1** (1.48 g; 2.087 mmol) was heated to reflux in a solution of acetic anhydride (40 μL;0.423 mmol) and ethyl acetate (50 mL) for 7 d. The cooled solution was washed twice with saturated brine solution, twice with saturated sodium bicarbonate solution, and again twice with saturated brine, dried over magnesium sulfate, and evaporated. Column chromatography (hexane/EtOAc/triethylamine 88:10:2) gave starting material **1** (150 mg), , and **10** (860 mg, 58.1%).

Trifluoroacetic anhydride (TFAA) in ethyl acetate: HBIW (2.10 g; 2.962 mmol) was heated to reflux in a solution of TFAA (84 μL, 0.595 mmol) in ethyl acetate (75 mL) for 5 h. The reaction was worked up as described for Ac_2O/EtOAc and the rearranged product was isolated by using column chromatography (hexane/EtOAc/triethylamine 92:7:1) to yield **10** (1.47 g, 70%).

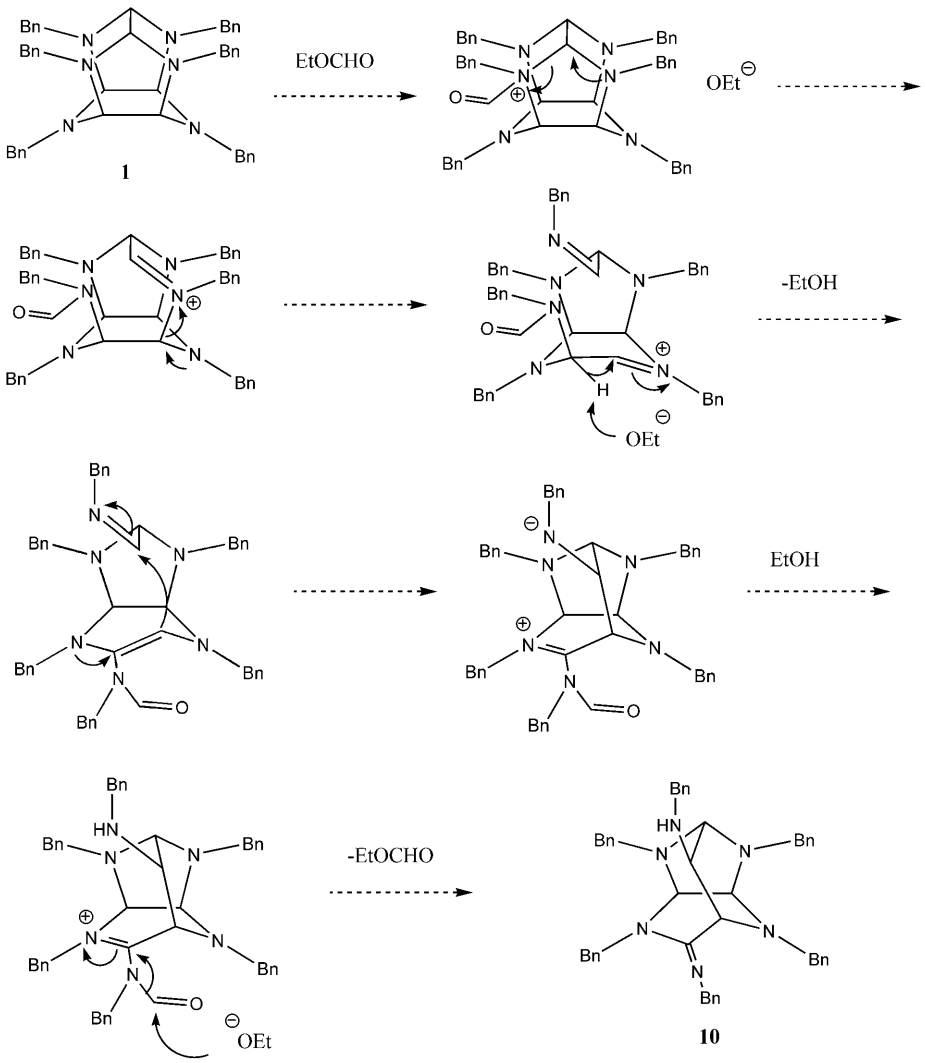
^{1}H NMR ($CDCl_3$): δ = 3.11 (dd, J = 6, 2.5 Hz, 1H), 3.21 (s, 2H), 3.59–3.79 (m, 6H), 3.90 (d, J = 13 Hz, 1H), 3.94 (dd, J = 5, 1.5 Hz, 1H), 4.12 (d, J = 13 Hz, 1H), 4.18 (d, J = 6 Hz, 1H), 4.24 (dd, J = 5.5, 1.5 Hz, 1H), 4.52 (d, J = 17 Hz, 1H), 4.78 (d, J = 17 Hz, 1H), 5.49 (d, J = 15 Hz, 1H), 7.02 (m, 2H), 7.17–7.37 ppm (m, 30H); ^{13}C NMR ($CDCl_3$): δ = 48.5, 49.1, 50.7, 51.1, 52.2, 56.9, 57.6, 60.1, 74.7, 76.4, 77.4, 78.6, 125.9, 126.6, 126.8 126.9, 127.2, 127.2, 127.5, 127.8, 128.0, 128.1, 128.3, 128.4, 128.4, 128.5, 128.6, 129.1, 129.4, 138.7, 139.4 (×2), 139.8, 140.6, 142.8, 159.3 ppm; FTIR (neat): $\tilde{\nu}$ = 3296, 3084, 3061, 3027, 2896, 2847, 1950, 1890, 1810, 1639, 1603, 1584, 1494, 1453 cm^{-1}; MS: m/z:709 [M^+], 602 [M^++1−C_7H_9N]; elemental analysis calcd (%) for $C_{48}H_{48}N_6$: C 81.32, H 6.84, N 11.85; found: C 78.33, H 6.60, N 11.14.

Hexa(4-Bromobenzyl)hexaazaisowurtzitane (11): A solution of 40% glyoxal at pH 6 (pH adjusted with aqueous sodium bicarbonate) was added dropwise to a solution of *p*-bromobenzylamine (4.3 g, 23.1 mmol) in acetonitirle (30 mL) containing a few drops of 70% perchloric acid while keeping the temperature below 10°C. The reaction was left to warm gradually overnight with stirring. An oil was separated from the reaction mixture and liquids decanted from the oily product. The oil was washed several times with methanol by shaking and decanting the solvent. The oily residue was than recrystallized from a dichloromethane/hexane mixture to yield colorless crystals of **11** (900 mg, 19.7%). M.p. 205–207°C; ^{1}H NMR ($CDCl_3$): δ = 3.55 (s, 2H), 3.87 (s, 4H), 3.97 (d, J = 4.2 Hz, 8H), 4.06 (s, 4H), 6.93 (d, J = 8.5 Hz, 4H), 7.05 (d, J = 8 Hz, 8H), 7.36 (d, J = 8.5 Hz, 4H) 7.41 ppm (d, J = 8.5 Hz, 8H); ^{13}C NMR ($CDCl_3$): δ = 55.6 (2C; benzylic), 56.2 (4C; benzylic), 76.5 (4C; cage), 80.9 (2C; cage), 129.7, 130.8, 131.3, 131.4, 132.2, 132.6, 139.0, 139.1 ppm; FTIR (neat): $\tilde{\nu}$ = 3078, 3040, 2917, 1899, 1668, 1589, 1486 cm^{-1}; MS: m/z: 1181 [M−1].

Rearrangement of 11: Preparation of 12: A suspension **11** (1 g, 0.846 mmol) in ethyl formate (40 mL) was heated at reflux for 5 d. After 3 d, the starting material completely dissolved in the reaction mixture and from this point on, the conversion was monitored by TLC (hexane/ethyl acetate/triethylamine 92:7:1). Excess ethyl formate was evaporated to give a slightly yellow oil (640 mg, 64%). The material was recrystallized from acetone. M.p. 178.0–179.6°C and then recrystallized from a mixture of dichloromethane/acetonitrile. M.p. 180–185°C (DSC) to yield crystals suitable for X-ray crystallography.

^{1}H NMR ($CDCl_3$): δ = 3.04–3.09 (m, 2H), 3.03 (d, J = 13.2 Hz, 1H), 3.50–3.51 (m, 2H), 3.58–3.61 (m, 2H), 3.68 (d, J = 12.6 Hz, 1H), 3.76 (d, J = 15 Hz, 1H), 3.83 (d, J = 13.8 Hz, 1H), 3.94 (d, J = 4.2 Hz, 1H), 4.05 (d, J = 13.2 Hz, 1H), 4.14 (dd, J = 5.4, 9.0 Hz, 2H), 4.34 (d, J = 16.2 Hz, 1H), 4.65 (d, J = 16.2 Hz, 1H), 5.26 (d, J = 15 Hz, 1H), 6.82 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 13.8 Hz, 2H), 7.04 (d, J = 7.8 Hz, 2H), 7.09–7.12 (m, 4H), 7.16 (d, J = 8.4 Hz, 2H), 7.33–7.44 ppm (m, 12H) ; ^{13}C NMR ($CDCl_3$): δ = 47.8, 48.8, 50.2, 50.9, 51.6, 56.2, 57.1, 59.4, 74.7, 76.5, 119.9, 120.7, 121.0, 121.3, 121.4, 129.0, 129.4, 130.0, 130.1, 130.5, 131.0, 131.2, 131.3, 131.6, 131.6, 131.7, 137.2, 137.8, 138.1, 138.4, 139.0, 141.3, 158.8 ppm; FTIR (solid film): $\tilde{\nu}$ = 3296, 3027, 2847, 1639 cm^{-1}; MS: m/z: 1179, 1181, 1183, 1185, 1186, 1187, 1188.

Crystallographic analysis: A single crystal of **10** (X = Br) was attached to a glass fiber, with epoxy glue, and transferred to a Bruker SMART APEX CCD X-ray diffractometer equipped with a graphite monochromator. The system was controlled by a pentium-based PC running the SMART software package.[18a] Data were collected at room temperature using $Mo_{K\alpha}$ radiation (λ = 0.71073 Å). Immediately after collection, the raw data frames were transferred to a second PC computer for integration and reduction by the SAINT program package.[18b] The structure was solved and refined by the SHELXTL software package.[18c]



Scheme 2. Suggested mechanism for the rearrangement of **1**.

CCDC-771431 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Keywords: cage compounds · hexabenzylhexaazaisowurtzitane · high-energy materials · rearrangement

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