J Chem Crystallogr (2011) 41:742–746
DOI 10.1007/s10870-010-9966-5

ORIGINAL PAPER

Synthesis and Crystal Structure of 2-Amino-4,6,6-trimethyl-cyclohex-2-en-1,1,3,4(*S*)-tetracarbonitrile

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Received: 13 August 2009 / Accepted: 31 December 2010 / Published online: 11 January 2011

Abstract Crystal structure analysis of the novel 2-amino-4,6,6-trimethyl-cyclohex-2-en-1,1,3,4(*S*)-tetracarbonitrile, obtained in 70% yield, by the $Bi(OTf)_3$ catalyzed reaction of acetone and malononitrile, at room temperature, is described. For the first time $Bi(OTf)_3$–Et_3N has been used in this inverse electron demand Diels–Alder cycloaddition reaction involving the participation of carbonitrile π-bond. The structure of the molecule was established by spectral analysis and X-ray diffraction studies. The compound crystallizes in the monoclinic space group $P2_1/n$ with unit cell parameters: $a = 8.0580$ (17), $b = 13.038$ (3), $c = 12.641$ (3) Å, $\beta = 101.883$ (4)°, $Z = 4$. The crystal structure was solved by direct methods and refined to $R = 0.0506$ for 2,456 observed reflections. The cyclohexene ring of the molecule adopts a distorted sofa conformation. The molecules in the unit cell are arranged in layers. The crystal structure in stabilized by C–H···N and N–H···N interactions.

Keywords Bismuth triflate-triethylamine · Inverse electron demand Diels–Alder reaction · Crystal structure · Sofa · Direct methods · Hydrogen bonding

Introduction

Cyclohexenes are ubiquitous in nature. A large number of polysubstituted cyclohexanes are associated with bioactivity [1–3]. Polyfunctionalized cyclohexanes, especially bearing nitrogen functionalities serve as important synthons for the preparation of bioactive nitrogen heterocyclic compounds. The most popular method for the preparation of cyclohexenes is the transition metal catalyzed Diels–Alder cycloaddition reaction [4, 5]. Although, this reaction has been carried out with a variety of substrates, including electron rich dienes and dienophiles [6–9], the direct participation of conjugated carbonitrile π-bonds in the cycloaddition reaction has not been reported so far.

Earlier, the versatility of Bi(III) salts in bringing about single-pot tandem reactions leading to polysubstituted nitrogen heterocycles has been demonstrated in our laboratory [10–13]. Herein, we report the Bi(III) triflate-triethylamine catalyzed one-pot tandem reaction of acetone and malononitrile, at room temperature, to afford novel 2-amino-4,6,6-trimethyl-cyclohex-2-en-1,1,3,4(*S*)-tetracarbonitrile. The reaction may involve the intermolecular inverse electron demand Diels–Alder reaction [6], with the participation of carbonitrile π-bonds, of conjugated dicarbonitriles, formed in situ.

Experimental

Synthesis

A mixture of acetone and malononitrile (1×10^{-2} mol each) in acetonitrile (10 mL) and $Bi(OTf)_3$ (20 mol.%) and Et_3N (1×10^{-2} mol, 1 mL) was stirred at room temperature (25–28 °C). On completion of the reaction (TLC)

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(24 h), the solvent was evaporated under reduced pressure. The residue was taken in ethyl acetate and filtered. The filtrate on distillation of the solvent afforded colorless crystalline product **1**. It was purified by flash chromatography on silica gel using CH_2Cl_2–EtOAc (9:1 v/v) as solvent system. The compound was re-crystallized from hot methanol (yield 70%). Single crystals for X-ray analysis were obtained by slow evaporation of the acetone solution.

Compound **1** was analyzed for $C_{13}H_{13}N_5$ (calculated C 65.27, H 5.47, N 29.28%; found C 65.14, H 5.35, N 29.16%). It exhibited the following spectral data. IR (KBr): υ_{max} cm^{-1} 3354 (NH_2), 2214 ($C\equiv N$), 1588 (–C=C–). ^1H NMR (JEOL FT-NMR AL-300 MHZ, $CDCl_3$): δ_H 1.35 (d, $J = 1.7$ Hz, 6H, gem. $CH_3 \times 2$), 1.39 (s, 3H, CH_3), 1.95 (s, 2H, CH_2), 5.31 (s br, 2H, exch. D_2O, NH_2); ^{13}C-NMR (125 MHZ, $CDCl_3$): δ_C 20.4, 25.1, 26.8, 27.0, 27.9, 40.1, 46.9, 95.7, 112.3, 112.9, 113.4, 114.5, 166.8. HRMS (JEOL inst.) rel. int.): *m/z* (%) 239.1123 (100) (M^+), 213 (42), 183 (33), 113 (58), 93 (45), 56 (34). For the scale up of the reaction, 1.25 mol each of acetone and malononitrile was reacted under identical reaction conditions when 12.0 g (approx. 70%) of the product **1** was obtained.

Crystal Structure Determination and Refinement

X-ray intensity data of 8,206 reflections (of which 3,130 unique) were collected at room temperature on Bruker CCD area-detector diffractometer equipped with graphite monochromated Mo $K\alpha$ radiation ($\lambda = 0.71073$ Å). The crystal used for data collection was of dimensions 0.3 × 0.2 × 0.1 mm. The cell dimensions were determined by least-square fit of angular settings of 2,484 reflections in the θ range 2.76°–28.14°. The intensities were measured by ϕ and ω scan mode for θ ranges 2.27°–28.33°. 2,456 reflections were treated as observed ($I > 2\sigma(I)$). Data were corrected for Lorentz and polarisation factors. The structure was solved by direct methods using SHELXS97 [14]. All non-hydrogen atoms of the molecule were located in the best E-map. Full-matrix least-squares refinement was carried out using SHELXL97 [14]. All the hydrogen atoms were located on a difference electron density map and their positional and isotropic thermal parameters were included in the refinement. The final refinement cycles converged to an $R = 0.0506$ and $wR(F^2) = 0.1204$ for the observed data. Residual electron densities ranged from −0.225 to 0.350 e $Å^{-3}$. Atomic scattering factors were taken from International Tables for X-ray Crystallography (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4). The crystallographic data are summarized in Table 1. CCDC-733563 contains the supplementary crystallographic data for this paper.

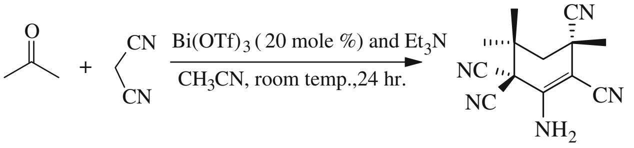
Table 1 Crystal data and other experimental details

CCDC number	733563
Crystal description	Colorless rectangular
Crystal size	0.3 × 0.2 × 0.1 mm
Empirical formula	$C_{13}H_{13}N_5$
Formula weight	239.28
Radiation, wavelength	Mo $K\alpha$, 0.71073 Å
Unit cell dimensions	$a = 8.0580$ (17), $b = 13.038$ (3), $c = 12.641$ (3) Å $\beta = 101.883$ (4)°
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell volume	1299.6 (5) $Å^3$
Number of molecules per unit cell, *Z*	4
Temperature	100 (2) K
Absorption coefficient	0.079 mm^{-1}
F(000)	504
θ range for entire data collection	$2.27° < \theta < 28.33°$
Reflections collected/unique	8206/3130
Reflections observed ($I > 2\sigma(I)$)	2456
Refinement	Full-matrix least-squares on F^2
Number of parameters refined	215
Final *R* factor	0.0506
$wR(F^2)$	0.1204
Weight	$1/[\sigma^2(F_o^2) + (0.0715P)^2 + 0.2790P]$ where $P = [F_o^2 + 2F_c^2]/3$
Goodness-of-fit	1.001
$(\Delta/\sigma)_{max}$	0.001 (for y H521)
Final residual electron density	$-0.225 < \Delta\rho < 0.350$ e $Å^{-3}$

Results and Discussion

The reaction of equimolar mixture of acetone and malononitrile, at room temperature, in the presence of $Bi(OTf)_3$ and triethylamine afforded novel 2-amino-4,6,6-trimethylcyclohex-2-en-1,1,3,4(*S*)-tetracarbonitrile **1** (Scheme 1).

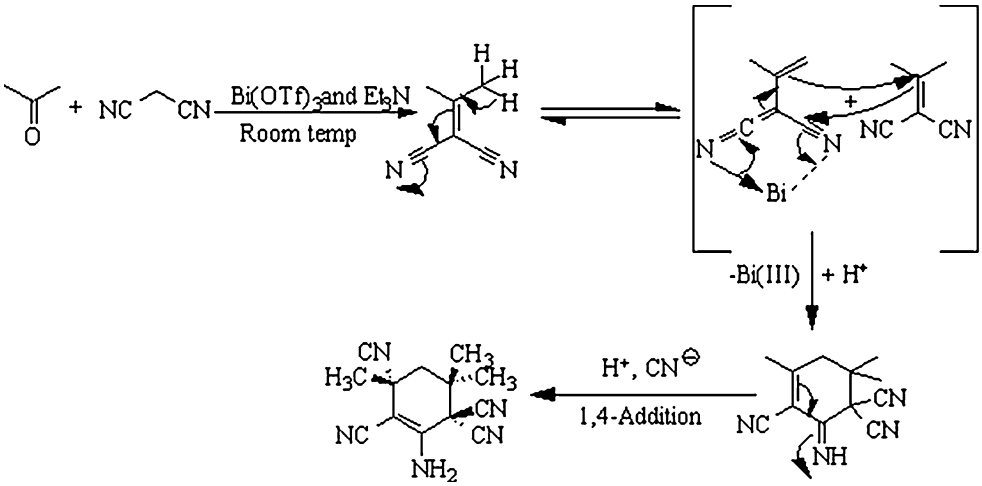
The reaction has been scaled up to multi-gram preparation of compound **1** (see "Experimental" section) with almost 70% yield.



1

Scheme 1 Preparation of 2-amino-4,6,6-trimethyl-cyclohex-2-en-1,1,3,4(*S*)-tetracarbonitrile

Scheme 2 Rationalization of formation of compound **1**



Mechanistically the reaction may be rationalized as to involve initial condensation of acetone and malononitrile to form an electron-rich alkene, 2-methyl-prop-1-en-1,1-dicarbonitrile. This intermediate compound may undergo tautomeric change followed by intermolecular inverse electron demand Diels–Alder reaction involving C≡N bond (Scheme 2) to afford compound **1**.

This is the first report on the direct preparation of aminocyclohexene carbonitriles by tandem reaction of acetone and malononitrile involving the inverse electron demand Diels–Alder reaction with the participation of C≡N bond in the cycloaddition. Further study on the scope and limitation of the reaction is in progress.

Selected bond distances, bond angles and torsion angles are listed in Table 2. An ORTEP view of the title compound with atomic labeling is shown in Fig. 1 [15]. The geometry of the molecule was calculated using the WinGX [16] and PARST [17] softwares. Bond lengths and bond angles of the title compound are comparable to the theoretical values as reported by Allen et al. [18]. The cyano groups mean bond length is 1.143 (2) Å, which is similar to those in cyano-substituted organic ligands [1].

Table 2 Selected bond lengths (Å), bond angles (°) and torsion angles (°) for non hydrogen atoms (esd's are given in *parentheses*)

C2–C3	1.3662 (17)	C2–N5	1.3391 (16)
C7–N1	1.1415 (19)	C8–N2	1.1395 (19)
C9–N3	1.1515 (17)	C10–N4	1.1434 (18)
N5–C2–C3	124.58 (11)	N5–C2–C1	115.95 (11)
N1–C7–C1	178.20 (15)	N2–C8–C1	176.72 (15)
N3–C9–C3	178.87 (14)	N4–C10–C4	176.19 (15)
C1–C2–C3–C4	−7.48 (18)	C2–C3–C4–C5	11.84 (17)
C3–C4–C5–C6	−39.86 (15)	C4–C5–C6–C1	60.67 (14)
C5–C6–C1–C2	−52.90 (13)	C6–C1–C2–C3	28.75 (16)

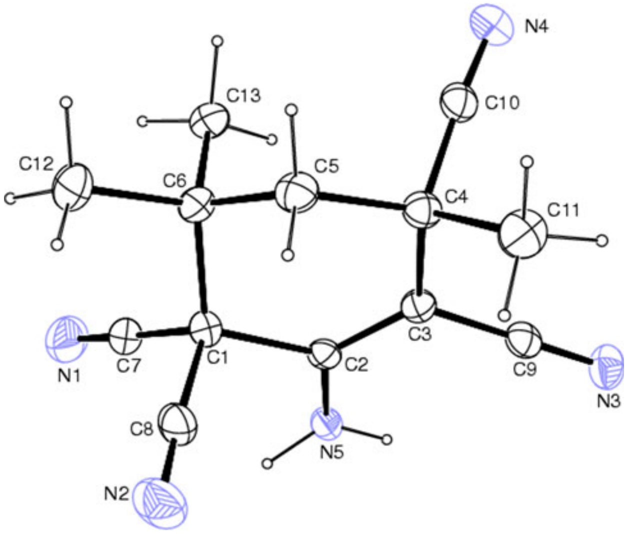


Fig. 1 *ORTEP* view of the molecule, showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii

In cyclohexene ring, the C2–C3 distance of 1.366 (2) Å confirms the localization of a double bond at this position. The presence of double bond at C2–C3 imposes a distorted 6*β*-*sofa* conformation, with asymmetry parameter ΔC_s (C3–C6) = 8.26, ΔC_2 (C2–C3) = 15.07 [19]. Atom C6 deviates by 0.673 (1) Å from the mean plane through the atoms C1–C5. The absolute stereochemistry at chiral centre C4 is decided on the basis of the slightly enhanced bond length of the C4–C9 indicating that the methyl group occupies the equatorial position at C4.

Packing view of the molecules in the unit cell viewed down the *a*-, *b*- and *c* axis is shown in Figs. 2, 3 and 4, respectively. Molecules in the unit cell are packed together to form well defined layers. Molecules within the layers are arranged in an antiparallel manner. In the crystal the molecules are linked by two different N–H···N intermolecular hydrogen bonds between amino hydrogen atoms and carbonitrile nitrogen atoms. In addition, the crystal

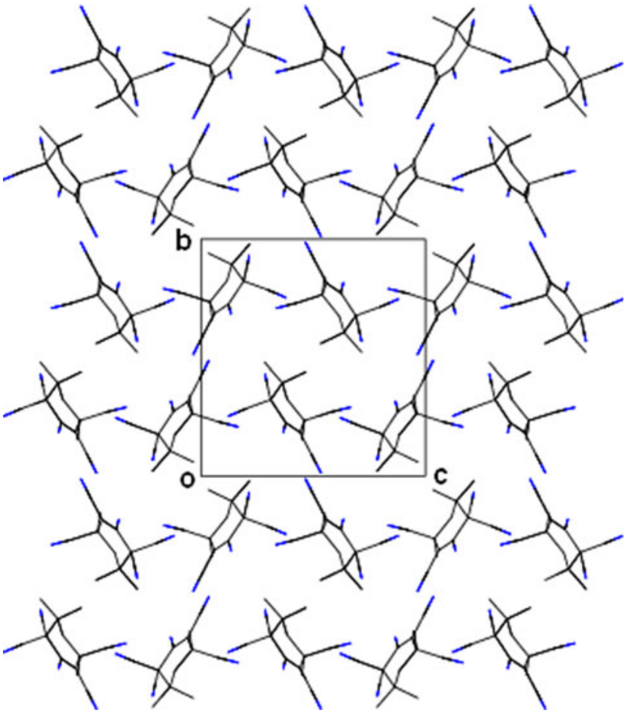


Fig. 2 The crystal packing projected on to the *bc* plane

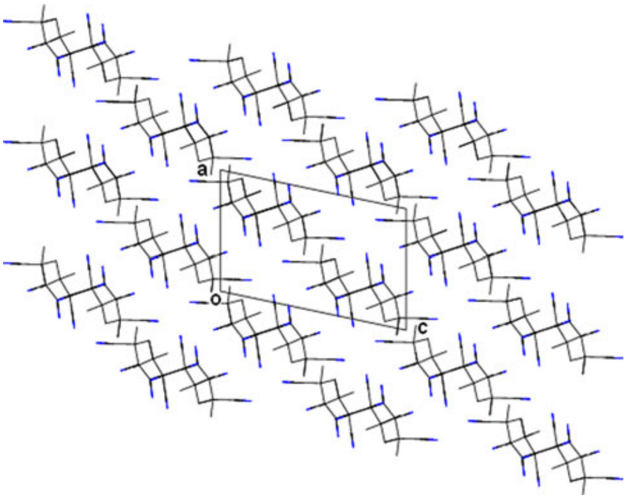


Fig. 3 The crystal packing projected on to the *ac* plane

packing exhibits one C–H···N interaction between the methyl hydrogen and carbonitrile nitrogen atom. The geometry of N–H···N and C–H···N interactions is given in Table 3.

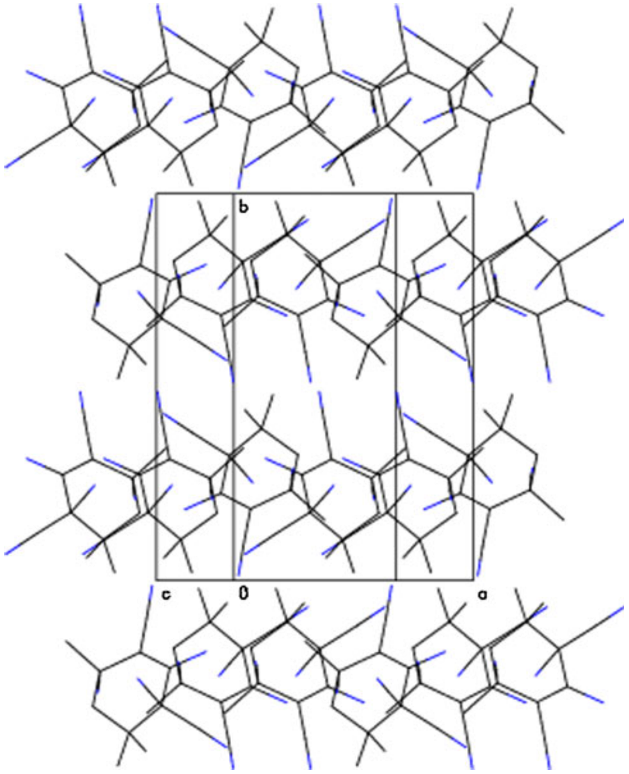


Fig. 4 The crystal packing projected on to the *ab* plane

Table 3 Hydrogen-bonding geometry (esd's in *parentheses*)

D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (°)
N5–H511···N4^{i}	0.92 (2)	2.12 (2)	3.015 (2)	163 (1)
N5–H521···N3^{ii}	0.88 (2)	2.18 (2)	3.049 (2)	168 (1)
C12–H121···N3^{iii}	0.99 (2)	2.59 (2)	3.462 (2)	147 (1)

Symmetry code: (i) $-1/2 + x$, $1/2 - y$, $1/2 + z$ (ii) $-x$, $-y$, $1 - z$ (iii) $1/2 + x$, $1/2 - y$, $1/2 + z$

Supplementary Material

CCDC-733563 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.

Acknowledgment The authors are thankful to Prof. P. K. Bharadwaj, Department of Chemistry, IIT, Kanpur, India, for the use of the data collection facility.

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