



STRUCTURE OF 2-AMINO-4-(3-BROMOPHENYL)-7,7-DIMETHYL-5-OXO-5,6,7,8-TETRAHYDRO-4H-CHROMENE-3-CARBONITRILE

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Keywords: Crystal structure, direct methods, hydrogen interactions.

The title compound, 2-amino-4-(3-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (C₁₈H₁₇BrN₂O₂), was synthesized, in 86% yield, by one-pot multicomponent reaction of 3-bromobenzaldehyde, malononitrile and dimedone using 10 mol % urea as an organo-catalyst at room temperature. It crystallizes in the monoclinic space group C 2/c with the unit-cell parameters: a= 23.557(2), b= 9.2963(7), c= 15.7502(12) Å, β = 93.430(8)° and Z = 8. The crystal structure was solved by direct methods using single-crystal X-ray diffraction data collected at room temperature and refined by full-matrix least-squares procedures to a final R-value of 0.0585 for 1411 observed reflections. The packing between the molecules within the unit cell is stabilized by N-H...O and N-H...N type of intermolecular hydrogen interactions.

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Introduction

4H-Pyran-annulated heterocyclic scaffolds represent a “privileged” structural motif well distributed in naturally occurring compounds¹⁻³ with a broad spectrum of significant biological activities.⁴⁻⁷ Recently, a series of synthetic 2-amino-3-cyano-4H-pyrans have been evaluated to possess potent anticancer,⁸⁻¹¹ antibacterial and antifungal,^{12,13} and anti-rheumatic¹⁴ properties. In this communication, we wish to report on one-pot facile synthesis of a novel 4H-pyran-annulated heterocyclic compound, namely 2-amino-4-(3-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile via multi-component reaction (MCR) at room temperature using commercially available urea as inexpensive and environmentally benign organo-catalyst, and determination of its crystal structure. The structure of the title compound was elucidated by spectral methods and XRD studies.

Experimental

Synthesis

An oven-dried screw cap test tube was charged with a magnetic stir bar, 3-bromobenzaldehyde (0.183 g, 1 mmol), malononitrile (0.066 g, 1.1 mmol), urea (0.007 g, 10 mol % as organo-catalyst), and EtOH:H₂O (1:1 v/v; 4 mL) in a sequential manner; the reaction mixture was then stirred vigorously at room temperature for about 20 min. After that, dimedone (0.140 g, 1 mmol) was added to the stirred reaction mixture, and the stirring was continued for 6 h.¹⁵ The progress of the reaction was monitored by TLC. On completion of the reaction, a solid mass precipitated out that

was filtered off followed by washing with aqueous ethanol to obtain crude product. It was purified just by re-crystallization from ethanol without carrying out column chromatography. The structure of title compound was confirmed by analytical as well as spectral studies including FT-IR, ¹H NMR, ¹³C NMR, and TOF-MS.

Unit crystal was obtained from DMSO as a solvent. For crystallization 50 mg of compound dissolved in 5 mL DMSO and left for several days at ambient temperature which yielded white block shaped crystals. The chemical structure of the title compound is given in Figure 1.

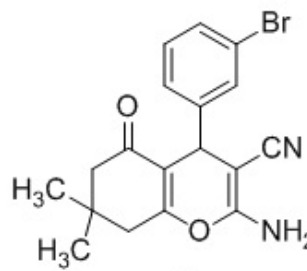


Figure 1. Chemical diagram of title compound

Characterisation

Infrared spectra were recorded using a Shimadzu (FT-IR 8400S) spectrophotometer using KBr disc. ¹H and ¹³C NMR spectra were obtained at 400 and 100 MHz, respectively, using a Bruker DRX-400 spectrometer and DMSO-*d*₆ as the solvent. Mass spectra (TOF-MS) were measured on a QTOF Micro mass spectrometer. Elemental analyses were performed with an Elementar Vario EL III Carlo Erba 1108 micro analyzer instrument. The melting point was recorded on a Chemiline CL-725 melting point apparatus and is uncorrected. Thin layer chromatography (TLC) was performed using silica gel 60 F254 (Merck) plates.

White solid, yield 86 %. m.p. 227-228 °C. IR (KBr): cm⁻¹: 3331, 3304, 3128, 3035, 2945, 2326, 2189, 1670, 1664, 1601, 1583, 1373, 1364, 1231, 1144, 1034, 876, 862, 631 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆) δ/ppm: 7.39 (1H, d, *J* = 8.4 Hz, aromatic H), 7.31 (1H, t, *J* = 1.6 Hz, aromatic H), 7.27 (1H, t, *J* = 8.0 & 7.6 Hz, aromatic H), 7.16 (1H, d, *J* = 7.6 Hz, aromatic H), 7.09 (2H, s, NH₂), 4.21 (1H, s, CH), 2.53 (2H, s, CH₂), 2.26 (1H, d, *J* = 16.4 Hz), 2.13 (1H, d, *J* = 16.0 Hz), 1.04 (3H, s, CH₃), 0.96 (3H, s, CH₃). ¹³C NMR (100 MHz, DMSO-*d*₆) δ/ppm: 196.16, 163.30, 158.95, 147.87, 131.05, 130.34, 129.95, 126.77, 121.97, 119.92, 112.51, 58.07, 50.33, 35.75, 32.25 (2C), 28.73, 27.19. TOF-MS: 395.0364 (M+Na)⁺. Elemental analysis: Calcd. (%) for C₁₈H₁₇BrN₂O₂: C, 57.92; H, 4.59; N, 7.51; found: C, 57.88; H, 4.56; N, 7.53.

X-Ray Structure determination

X-ray intensity data of 6665 reflections (of which 3385 unique) were collected on *X'calibur* CCD area-detector diffractometer equipped with graphite monochromated MoK α radiation (λ = 0.71073 Å). The crystal used for data collection was of dimensions 0.30 x 0.20 x 0.20 mm. The cell dimensions were determined by least-squares fit of angular settings of 1379 reflections in the θ range 3.58° to 24.51°. The intensities were measured by ω scan mode for θ ranges 3.46° to 26.00°. 1411 reflections were treated as observed ($I > 2\sigma(I)$). Data were corrected for Lorentz, polarization and absorption factors. The structure was solved by direct methods using SHELXS97.¹⁶ All non-hydrogen atoms of the molecule were located in the best E-map. Full-matrix least-squares refinement was carried out using SHELXL97.¹⁶ The final refinement cycles converged to an $R = 0.0585$ and $wR(F^2) = 0.1056$ for the observed data. Residual electron densities ranged from $-0.528 < \Delta\rho < 0.491 \text{ e}\text{\AA}^{-3}$. 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.

Results and Discussion

An ORTEP17 view of the compound with atomic labelling is shown in Figure 2. The geometry of the molecule was calculated using the WinGX,¹⁸ PARST¹⁹ and PLATON²⁰ software. Packing view of the molecules in the unit cell viewed down the *b*-axis is shown in Figure 3.

The title compound comprises of three rings A, B and C in which ring A is pyran ring, ring B is cyclohexane ring and ring C is phenyl ring. The mean plane of phenyl ring C makes the dihedral of 88.86(14)° and 83.77(15)° with the mean planes of pyran ring A and cyclohexane ring B respectively. The pyran ring A deviates significantly from planarity and adopts boat conformation with one mirror plane passing through the atoms O1 and C4 and the other bisecting the bonds C2-C3 and C5-C6 with asymmetry parameters $\Delta C_s(O1) = 3.706$, $\Delta C_2(C2-C3) = 14.00$. Cyclohexane ring B adopts flattened sofa conformation with mirror plane passing through the atoms C3 and C8 with asymmetry parameters $\Delta C_s(C3) = 9.987$. Phenyl ring C is planar as reflected from small values of torsion angles. The

Table 1. Crystal data and other experimental details

CCDC Number	1444488
Crystal description	Block
Crystal size	0.30 x 0.20 x 0.20 mm
Empirical formula	C ₁₈ H ₁₇ BrN ₂ O ₂
Formula weight	373.25
Radiation, Wavelength	Mo K α , 0.71073 Å
Unit cell dimensions	$a = 23.557(2)$ Å $b = 9.2963(7)$ Å $c = 15.7502(12)$ Å $\alpha = 90.00^\circ$ $\beta = 93.430(8)^\circ$ $\gamma = 90.00^\circ$
Crystal system, Space group	monoclinic, C 2/c
Unit cell volume	3443.0(5) Å ³
No. of molecules per unit cell, Z	8
Absorption coefficient	2.398 mm ⁻¹
$F(000)$	1520
θ range for entire data collection	3.58 < θ < 24.51
Reflections collected / unique	6665 / 3385
Reflections observed $I > 2\sigma(I)$	1411
Range of indices	$h = -28$ to 16 $k = -11$ to 11 $l = -17$ to 19
No. of parameters refined	210
Final R-factor	0.0585
$wR(F^2)$	0.1056
Rint	0.0617
Rsigma	0.1252
Goodness-of-fit	0.934
Final residual electron density	$-0.528 < \Delta\rho < 0.491 \text{ e}\text{\AA}^{-3}$

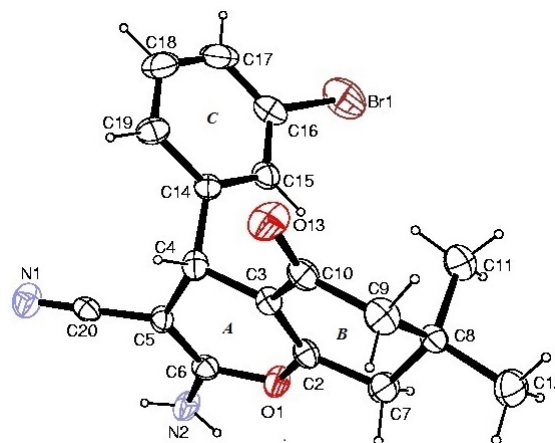
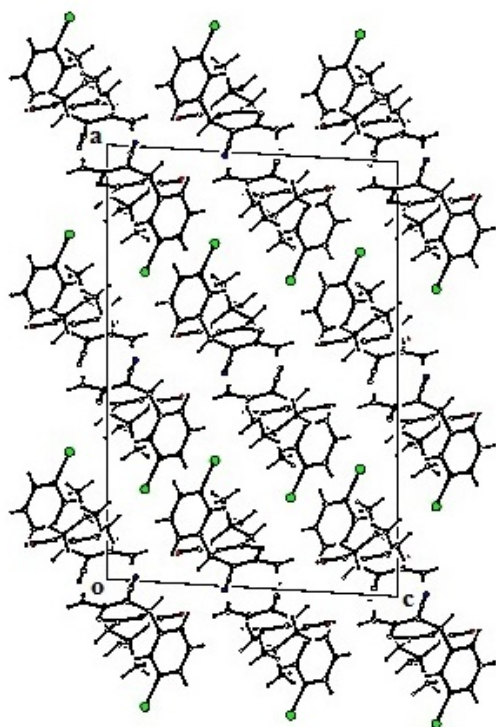
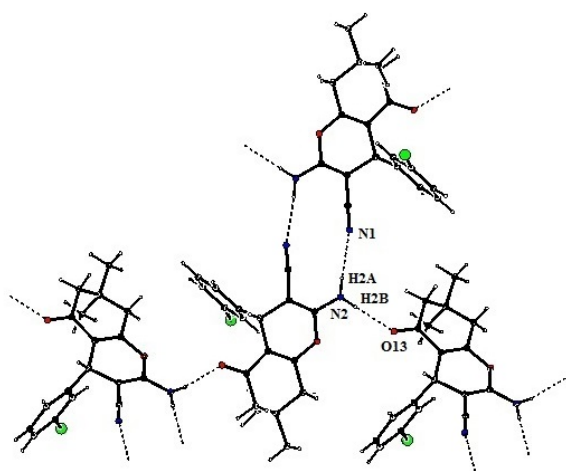


Figure 2. ORTEP view of the title molecule with displacement ellipsoids drawn at 50% probability level. H atoms are shown as small spheres of arbitrary radii.

bond distance Br1-C16 has the value 1.888(6) Å, close to literature value.²¹ The bond distances C10-O13 and N1-C20 are 1.215(5) Å and 1.137(5) Å respectively and agree well with the corresponding values in related structures.^{22,23} The bond angle N1-C5-C20 is 176.7(5)° confirms the linear character of carbonitrile group. The bond angles O13-C10-C3, O13-C10-C9 and C3-C10-C9 are 120.4(4)°, 122.9(4)° and 116.6(4)° respectively, are close to 120° and thus suggest the planar geometry about carbon atom C10.

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

Bond distances(Å)		Bond angles(°)		Torsion angles(°)	
O1-C2	1.366(5)	C2-O1-C6	118.5(3)	C6-O1-C2-C7	168.7(4)
O1-C6	1.370(5)	C3-C2-O1	122.8(4)	C4-C3-C10-O13	-0.1(7)
N1-C20	1.137(5)	O13-C10-C3	120.4(4)	Br1-C16-C17-C18	179.2(4)
N2-C6	1.338(5)	O13-C10-C9	122.9(4)	C14-C15-C16-Br1	-179.9(3)
C5-C20	1.419(6)	C3-C10-C9	116.6(4)	C2-O1-C6-N2	-170.0(4)
C16-Br1	1.888(6)	N1-C20-C5	176.7(5)	C20-C5-C6-N2	1.2(8)
C10-O13	1.215(5)	N2-C6-C5	127.6(4)	C19-C14-C15-C16	1.0(7)
C8-C11	1.534(7)	N2-C6-O1	110.8(4)	O1-C2-C7-C8	161.2(4)

**Figure 3.** Packing view of molecules down to b-axis**Figure 4.** Partial view of intermolecular hydrogen interactions between the molecules.**Table 3.** Geometry of intermolecular hydrogen bonds

D-H...A	D-H (Å)	H...A (Å)	D...A (Å)	∠[D-H...A] (°)
N2-2A...N1 ⁱ	0.86	2.17	3.019(5)	168
N2-H2B-O13 ⁱⁱ	0.86	2.05	2.871(5)	159

Symmetry codes: i. -x,-y+1,-z+1, ii. x,-y, z+1/2

Selected bond lengths, bond angles and torsion angles are given in Table 2. The dihedral angle C20-C5-C6-N2 with value 1.2(8)° suggest the coplanarity of amino and carbonitrile groups. The packing view of molecules is shown in Figure 2. Analysis of the crystal packing of title compound shows the presence of intermolecular C-H...N and N-H...O hydrogen bonds in the structure (Table 3). The oxygen atom O13 of carbonyl group form hydrogen interactions with H2B attached to N2 of amino group. In addition H2A attached to N2 form intermolecular hydrogen interaction with the N1 atom of carbonitrile group. The N-H...O interactions link the molecules to form chain like structure whereas the adjacent chains are linked together by a pair of N-H...N hydrogen interactions to form dimeric structure as shown in Figure 4. In addition to these the crystal packing is also stabilized by weak Van der Waals interactions

Acknowledgments

GB is thankful to the SERB-DST, New Delhi for financial support [Grant No. EMR/2014/1220].

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Received: 07.02.2016.

Accepted: 19.02.2016.