X-RAY STUDIES OF METHYL 6-AMINO-5-CYANO-2-METHYL-4-(3-NITROPHENYL)-4*H*-PYRAN-3-CARBOXYLATE

Suresh Sharma[a], Goutam Brahmachari[b], Bubun Banerjee[b], Rajni Kant[a] and Vivek K. Gupta[a] *

Keywords: crystal structure, direct methods, hydrogen bond.

The title compound, methyl 6-amino-5-cyano-2-methyl-4-(3-nitrophenyl)-4*H*-pyran-3-carboxylate ($C_{15}H_{13}N_3O_5$), was synthesized, in 92 % yield, by one-pot multicomponent reaction of 3-nitrobenzaldehyde, malononitrile and methyl acetoacetate using 10 mol% urea as an organo-catalyst at room temperature.. It crystallizes in the triclinic space group P -1 with the unit-cell parameters: a= 8.1780(4), b= 8.3787(4), c= 11.8005(6) Å, α = 75.703(4)º, β = 86.017(4)º, γ = 72.983(4)º and Z = 2. 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 0.0538 for 1896 observed reflections. The molecules within the unit cell are stabilized by C-H…O, N-H…O and N-H…N type of hydrogen bonding. In addition π-π interactions are also observed in the crystal structure.

*Corresponding Authors
Tel: +91 9419102467
E-Mail: vivek_gupta2k2@hotmail.com
[a] X-ray Crystallography Laboratory, Post-Graduate Department of Physics & Electronics, University of Jammu, Jammu Tawi - 180 006, India
[b] Laboratory of Natural Products & Organic Synthesis, Department of Chemistry, Visva-Bharati (a Central University), Santiniketan – 731235, West Bengal, India.

Introduction

Substituted-pyran scaffolds represent key structural motifs in significant natural bioactive molecules[1-5] and this has led to the synthesis of a huge number of synthetic analogs of such promising *O*-heterocycle with a broad range of biological activities including anticancer,[6-9] antibacterial and antifungal[10,11] and anti-rheumatic.[12] In this communication, we wish to report on one-pot facile synthesis of a novel 4*H*-pyran, namely methyl 6-amino-5-cyano-2-methyl-4-(3-nitrophenyl)-4*H*-pyran-3-carboxylate *via* multicomponent reaction (MCR) at room temperature using commercially available urea as inexpensive and environmentally benign organocatalyst, and 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-nitrobenzaldehyde (0.151 g, 1 mmol), malononitrile (0.066 g, 1.1 mmol), urea (0.007 g, 10 mol % as organo-catalyst), and EtOH:H_2O (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, methyl acetoacetate (0.116 g, 1 mmol) was added to the stirred reaction mixture, and the stirring was continued for 8h.[13] 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 recrystallization from ethanol without carrying out column chromatography. The structure of methyl 6-amino-5-cyano-2-methyl-4-(3-nitrophenyl)-4*H*-pyran-3-carboxylate was confirmed by analytical as well as spectral studies including FT-IR, ^{1}H NMR, ^{13}C 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 title compound is shown in Figure 1.

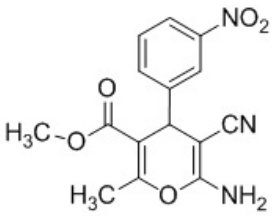

Figure 1. Chemical structure of title compound

White solid. Yield 92%. Mp: 204-206 ºC. IR (KBr) ν_{max}/cm^{-1}: 3391, 3323, 3207, 3159, 3076, 2945, 2908, 2349, 2183, 1684, 1678, 1601, 1580, 1529, 1423, 1265, 1182, 1067, 906, 835, 787, 729, 683, 623, 523. ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 8.11 (1H, d, *J* = 7.2 Hz, aromatic H), 7.97 (1H, s, aromatic H), 7.65 (2H, d, *J* = 7.6 Hz, aromatic H), 7.10, (2H, s, N*H*$_2$), 4.52 (1H, s, C*H*), 3.53 (3H, s, OC*H*$_3$), 2.35 (3H, s, C*H*$_3$). ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 166.11, 159.11, 158.41, 148.31, 147.66, 134.43, 130.62, 122.42, 121.90, 119.76, 106.59, 56.79, 52.05, 38.91, 18.83. TOF-MS: 338.0756 [M + Na]$^+$. Elemental analysis: Calcd. (%) for $C_{15}H_{13}N_3O_5$: C, 57.14; H, 4.16; N, 13.33; found: C, 57.16; H, 4.15; N, 13.37.

X-ray structure determination

X-ray intensity data of 8981 reflections (of which 2942 unique) were collected on *X'calibur* CCD area-detector diffractometer equipped with graphite monochromated MoKα 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 3730 reflections in the θ range 3.49° to 29.14°**.** The intensities were measured by 'ω scan' mode for θ ranges 3.50° to 26.00°. 1896 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.[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] The final refinement cycles converged to an R = 0.0538 and wR (F^2) = 0.1255 for the observed data. Residual electron densities ranged from -0.205 < $\Delta\rho$ < 0.239 eÅ^{-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.

Table 1. Crystal data and other experimental details

CCDC Number	**1059815**
Crystal description	Block
Crystal size	0.30 x 0.20 x 0.20 mm
Empirical formula	$C_{15}H_{13}N_3O_5$
Formula weight	315.28
Radiation, Wavelength	Mo *K*α, 0.71073 Å
Unit cell dimensions	*a*= 8.1780(4)Å *b*= 8.3787(4) Å *c*= 11.8005(6) Å α= 75.703(4)° β = 86.017(4)° γ= 72.983(4)°
Crystal system, Space group	triclinic , P-1
Unit cell volume	749.23(6) Å^3
No. of molecules per unit cell, Z	2
Absorption coefficient	0.107 mm^{-1}
F(000)	328
θ range for entire data collection	3.50 <θ< 26.00
Reflections collected / unique	8981/ 2942
Reflections observed I > 2σ(I))	1896
Range of indices	*h*= -9 to 10 *k*=-10 to 10 *l*= -14 to 14
No. of parameters refined	209
Final R-factor	0.0538
w*R*(*F*2)	0.1255
R_{int}	0.0407
R_σ	0.0509
Goodness-of-fit	1.017
Final residual electron density	-0.205 < $\Delta\rho$ < 0.239 eÅ^{-3}

Result and discussions

An ORTEP[15] view of the compound with atomic labeling is shown in Figure 2. The geometry of the molecule was calculated using the WinGX,[16] PARST[17] and PLATON[18] software. Packing view of the molecules is shown in Figure 3.

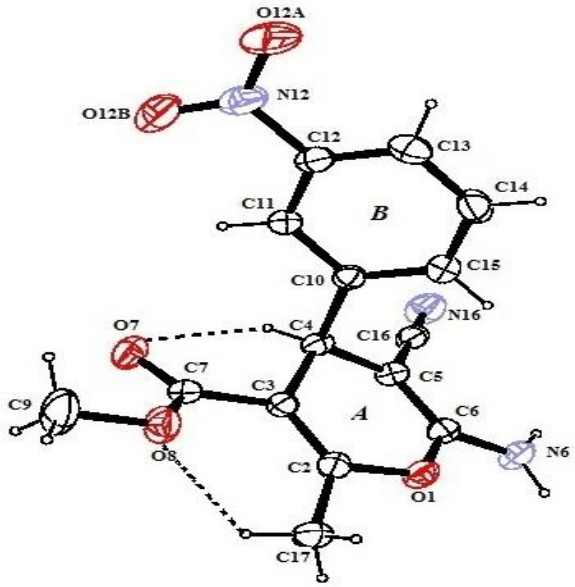

Figure 2. ORTEP view of the molecule with displacement ellipsoids drawn at 40 %

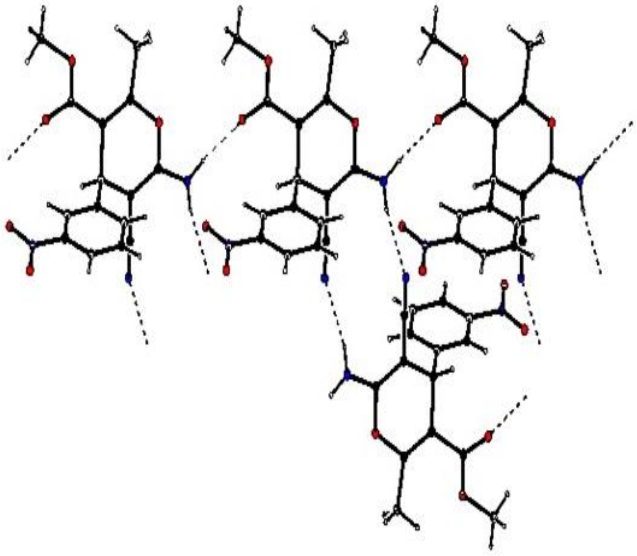

Figure 3. Partial view of hydrogen interactions between the molecules

The title compound comprises of two rings in which phenyl ring (ring-*B*) is planar and pyran ring (ring-*A*) deviates significantly from planarity as reflected from the large values of torsion angles in it. It adopts boat conformation with asymmetry parameters ΔC_s(O1-C4) = 7.56 and ΔC_2(C2-C3) = 10.17. The maximum deviation from the mean plane of pyran ring is observed for atom C4 which lies above the mean plane by 0.1648 Å. The bond distances O1-C6 and O1-C2 are 1.368(2) Å and 1.385(2) Å, are close to each other and agree well with the literature values.[19]

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

Bond distances(Å)		Bond angles(°)		Torsion angles(°)	
O1-C6	1.368(2)	O12B-N12-O12A	122.8(2)	C16-C5-C6-N6	4.9(4)
O1-C2	1.385(2)	O12B-N12-C12	118.7(2)	C17-C2-C3-C7	-1.0(4)
C7-O7	1.203(2)	O12A-N12-C12	118.5(3)	C2-C3-C7-O7	-153.2(2)
C7-O8	1.326(3)	O8-C7-C3	115.79(18)	C11-C12-N12-O12A	-171.8(3)
O8-C9	1.458(3)	C7-O8-C9	115.66(19)		
N12-O12B	1.207(3)	N16-C16-C5	178.0(2)		
N12-O12A	1.211(3)	C3-C4-C10	110.12(15)		
C4-C10	1.528(3)	C5-C4-C10	113.06(17)		

Table 3. Geometry of intramolecular and intermolecular hydrogen bonds

D-H…A	D-H (Å)	H…A (Å)	D…A (Å)	θ[D-H…A (º)]
C4-H4...O7	0.98	2.457(1)	2.807(2)	100.55(13)
C17-H17C...O8	0.96	2.250(2)	2.898(3)	123.99(16)
N6-H6A...N16^{i}	0.86	2.167(2)	3.008(2)	165.65(14)
N6-H6B...O7^{ii}	0.86	2.023(2)	2.877(3)	171.67(14)
C9-H9C-O12B^{iii}	0.96	2.493(3)	3.405(4)	158.70(20)

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

Table 4. Geometry of π-π hydrogen interactions

CgI-CgJ	CgI-CgJ(Å)	CgI...P(Å)	α(º)	β(º)	Δ(Å)
Cg2-Cg2^{i}	3.8139(13)	3.589	0.02	19.80	1.29

Symmetry code: i. –x, 1-y, 1-z; Here C_{g2} represents the centre of gravity of phenyl ring-*B*.

The bond distance C16-N16 is 1.148(2) Å, verifies its triple bond character. The bond distances N12-O12B and N12-O12A are 1.207(3) Å and 1.211(3) Å, are reasonable. The mean value of endocyclic bond angles in the phenyl ring is close to 120º as expected. The bond angles O12B-N12-O12A, O12B-N12-C12 and O12A-N12-C12 are 122.8(2)º, 118.7(2)º and 118.5(3)º respectively, signifies the planar geometry of nitro group. There is significant deviation of angles C3-C7-O8 and C7-O8-C9 with values 115.79(18)º and 115.66(19)º from the ideal value of 120º and such deviations are also observed in similar structure[20]. The bond angle N16-C16-C5 with value 178.0(2)º signifies the linear character of carbonitrile group. The dihedral angle C17-C2-C3-C7 has the value -1.0(4)º, reflects that the methyl and carboxylate groups are almost coplanar. The carbonitrile and amino groups are deviated from coplanarity as reflected from the value of torsion angle C16-C5-C6-N6 with value 4.9(4)º. Some important bond lengths, bond angles and torsion angles are listed in Table 2. All other geometrical parameters of the title compound are normal and agree well with the related structure.[20]

The crystal packing is stabilized by both intra and inter molecular hydrogen interactions. The intramolecular hydrogen interactions lead to formation of two virtual rings [Figure 2]. Both the hydrogen atoms of amino group are involved in intermolecular hydrogen interactions in which N6-H6B…O7 generates a chain like structure and other is responsible for the formation of dimmer. The adjacent chains are linked to each other by N6-H6A…N16 hydrogen interactions [Figure 3]. In addition crystal structure is also stabilized by π-π hydrogen interactions. The geometry of hydrogen interactions is given in Table 3 and Table 4.

Acknowledgments

GB is thankful to the CSIR, New Delhi for financial support [Grant No. 02(0110)/12/EMR-II]. BB is grateful to the UGC, New Delhi for awarding him a Senior Research Fellowship.

References

[1]Dean, F. M., *Naturally Occurring Oxygen Ring Compounds;* Butterworths: London, **1963**, p. 176.

[2]Raj, T., Bhatia, R. K., Kapur, A., Sharma, M., Saxena, A. K. and Ishar, M. P. S., *Eur. J. Med. Chem.* **2010**, *45*, 790.

[3]Flavin, M. T., Rizzo, J. D., Khilevich, A., Kucherenko, A., Sheinkinan, A. K., Vilavchack, V., Lin, L., Chen, W., Mata, E., Pengsuparp, T., Pezzuto, J. M., Hughes, S. H., Flavin, T. M., Cibulski, M., Boulanger, W. A., Shone, R. L. and Xu, Z.-Q., *J. Med. Chem.* **1996**, *39*, 1303

[4]Morgan, L.R., Jursic, B.S., Hooper, C.L., Neumann, D.M., Thangaraj, K., Leblanc, B., *Bioorg. Med. Chem. Lett.*, **2002**, *12*, 3407.

[5]Kumar, A., Maurya, R. A., Sharma, S. A., Ahmad, P., Singh, A. B., Bhatia, G. and Srivastava, A. K., *Bioorg Med Chem Lett* . **2009**, *19*, 6447.

[6]Skommer, J., Wlodkowic, D., Matto, M., Eray, M. And Pelkonen, J., *Leuk. Res*, **2006**, *30*, 322.

[7]Kasibhatla, S., Gourdeau, H., Meerovitch, K., Drewe, J., Reddy, S., Qiu, L., Zhang, H., Bergeron, F., Bouffard, D., Yang, Q., Herich, J., Lamothe, S., Cai, S. X. and Tseng, B., *Mol Cancer Ther*. **2004**, *3*, 1365.

[8]Kemnitzer, W., Drewe, J., Jiang, S., Zhang, H., Zhao, J., Grundy, C. C., Xu, L., Lamothe, S., Gourdeau, H., Denis, R., Tseng, B., Kasibhatla, S. and Cai, S. X., *J. Med. Chem.*, **2007**, *50*, 2858.

[9]Bhavanarushi, S., Kanakaiah, V., Yakaiah, E., Saddanapu, V., Addlagatta, A. and Rani,V.J., *Med. Chem. Res.* **2013**, *22*, 2446.

[10]Paliwal, P., K., Jetti, S. R. and Jain, S., *Med. Chem. Res.*, **2013**, *22*, 2984.

[11]Kumar, D., Reddy, V.B., Sharad, S., Dube, U. and Kapur, S. *Eur. J. Med. Chem.*, **2009**, *44*, 3805.

[12]Smith, C. W., Bailey, J. M., Billingham, M. E. J., Chandrasekhar, S., Dell, C. P., Harvey, A. K., Hicks, C. A., Kingston, A. E. and Wishart, G. N., *Bioorg. Med. Chem.* Lett. **1995**, *5*, 2783.

[13]Brahmachari, G. and Banerjee, B., *ACS Sustainable Chem. Eng.*, **2014,** 2, 411.

[14]Sheldrick, G.M., *Acta Cryst.*, **2008,** *A64*, 112.

[15]Farrugia, L.J. *J Appl Cryst.*, **1997,** *30*, 565.

[16]Farrugia, L.J., *J Appl Cryst.*,**1999,** *32*, 837.

[17]Nardelli, M., *J Appl Cryst*., **1995,** *28*, 659.

[18]Spek, A.L., *Acta Cryst*., **2009,** *D65*, 148.

[19]Allen, F. H., Kennard,O., Watson,D.G., Brammer,L., Orpen,A.G., and Taylor,R. *J. Chem.Soc., Perkin Trans-II.*, **1987**, S1.

[20]Li, Y., Wang, X., Zeng, Z., Shi, D., Wei, X. and Zong, Z., *Acta Cryst. E* **2005**, *E61*, o1115.

Received: 24.04.2015.
Accepted: 04.06.2015.