Comparative Analysis of Synthesis, Biological Relevance and X-Ray Crystallization of Novel Pyrano[2,3-C]Pyrazole Derivatives

Naresh Sharma

Abstract: Two Pyrano[2,3-C]Pyrazole compounds, 6-Amino-3-methyl-4-(3,4,5-trimethoxy phenyl)-2, 4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile [Compound-I] and Ethyl 6-amino-5-cyano-4-phenyl-2,4-dihydro pyrano[2,3-*c*]pyrazole-3-carboxylate dimethyl sulphoxide monosolvate [Compound-II], were synthesized, and their crystal structures were determined by X-ray diffraction technique. The crystals of compound-I are triclinic, sp. gr. P-1, a=7.6168(6), b=9.9967(5), c=11.7888(6) Å, α=105.283(5)^o, β=99.416(5)^o, γ=92.221(5)^o and Z=2 and that of compound-II are monoclinic, sp. gr. $P2_1/c$, a=28.018(5), b=9.196(5), c=15.396(5) Å, α=90.00^o, β=93.376(5)^o, γ=90.00^o and Z=8. Crystal packing of (I) and (II) is stabilized by strong intermolecular N-H…N and N-H…O interactions. Further stabilization is possible due to the presence of C-H…π interactions in (I) and (II), which are playing their role in these two compounds.

Keywords: Pyrano[2,3-C]Pyrazole; Single-crystal X-ray; direct methods; Diffractometer.

1. Introduction

Pyrano[2,3-c]pyrazole scaffolds represent a "privileged" structural motif well distributed in bioactive natural products and pharmaceutically potent synthetic heterocycles possessing a wide range of activities such as antimicrobial [1-4], bactericidal [5], insecticidal [2], molluscicidal [4], analgesic [5], anti-inflammatory [6], hypotensive [7], hypoglycemic, and anticancer agent [8-10].

Naresh Sharma(✉)

Govt. Degree College,
Ramnagar, J&K, India
E-mail: nareshbasotra@gmail.com

Hence, investigation of the structural features of biologically relevant pyrano[2,3-c]pyrazole derivatives is of both scientific and practical interest. In continuation of efforts made by [11] to develop useful synthetic protocols for biologically significant molecules, I herein report a comparative analysis of efficient and environmentally benign synthesis and the crystal structure of the title compounds. In this communication, I wish to report the comparison of the crystal structures of 6-Amino-3-methyl-4-(3,4,5-trimethoxyphenyl)-2,4-dihydropyrano [2,3-c] pyrazole-5-carbonitrile (I) and Ethyl 6-amino-5-cyano-4-phenyl-2,4-dihydropyrano [2,3-c] pyrazole-3-carboxylate dimethyl sulphoxide monosolvate (II) synthesized via one-pot multicomponent reaction (MCR) at room temperature using commercially available urea as inexpensive and environmentally benign organo-catalyst. The structures of the title compound were elucidated by spectral methods and XRD studies.

2. Experiment

Synthesis

The synthesis of the title compounds were carried out *via* one-pot multi-component reaction in aqueous ethanol using low-cost and

environmentally benign urea as catalyst at room temperature. An oven-dried screw cap test tube was charged with a magnetic stir bar, ethyl acetoacetate (0.130 g, 1.0 mmol) and hydrazine hydrate (0.050 g, 1 mmol) [compound (I)] and with a magnetic stir bar, diethyl acetylenedicarboxylate (0.170 g, 1.0 mmol), hydrazine hydrate (0.050 g, 1 mmol)[compound (II)]. The reaction mixtures for both the compounds were stirred at room temperature for about 10 mins. After that 3,4,5-trimethoxybenzaldehyde (0.196 g, 1 mmol), malononitrile (0.066 g, 1.1 mmol), urea (0.007 g, 10 mol % as organo-catalyst), EtOH:H_2O (1:1 v/v; 4 ml)[compound (I)] and benzaldehyde (0.106 g, 1 mmol), malononitrile (0.066 g, 1.1 mmol), urea (0.007 g, 10 mol % as organo-catalyst), EtOH: H_2O (1:1 v/v; 4 ml) [compound (II)] were added in a sequential manner [11]. The reaction mixturs were then stirred vigorously at room temperature and the stirring was continued for 16 h.

The progress of the reaction in both the compounds 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 which was purified just by recrystallization from ethanol without carrying out column chromatography. The structure of both the compounds was confirmed by analytical as well as spectral studies including FT-IR, ^{1}H NMR, ^{13}C NMR, and TOF-MS.

Single crystal was obtained for both the compounds 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 compound-I and compound-II is given in Figure 1 and Figure 2, respectively. The crystallographic data for both the compounds are given in Table 1.

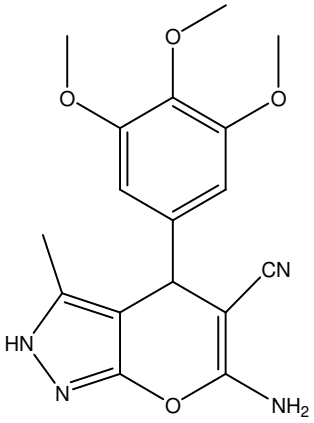

Fig. 1. The chemical structure of compound-I

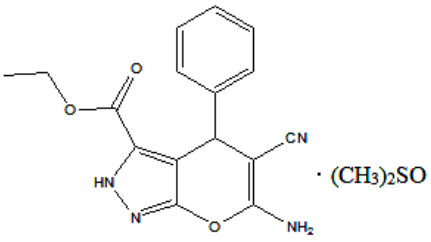

Fig. 2. The chemical structure of compound-II

Characterization

Compound-I

White solid Yield 89% Mp: 491-493 K. ^{1}HNMR (400 MHz, DMSO-d_6) δ/ppm: 12.11(1H, s, NH), 6.87 (2H, s, NH_2), 6.47 (2H, s, aromatic H), 4.59 (1H, s, CH), 3.72 (6H, s, 2 × OCH_3), 3.64 (3H, s, OCH_3), 1.87 (3H, s, CH_3). ^{13}CNMR (100 MHz, DMSO-d_6) δ/ppm: 161.39, 155.11, 153.20 (2C), 140.49, 136.55, 136.20, 121.29, 104.98 (2C), 97.74, 60.38, 57.33, 56.22 (2C), 36.87, 10.34. TOF-MS: 365.1230 $[M+Na]^+$. Elemental analysis: Calcd. (%) for $C_{17}H_{18}N_4O_4$: C, 59.64; H, 5.30; N, 16.37; found: C, 59.62; H, 5.28; N, 16.39.

Compound-II

White solid Yield 91% Mp: 521-523 K. ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 13.76 (1H, s, NH), 7.28 (2H, t, J = 7.2 Hz, aromatic H), 7.19 (1H, t, J = 7.2 Hz, aromatic H), 7.10 (2H, d, J = 7.2 Hz, aromatic H), 7.03 (2H, s, NH_2), 4.76 (1H, s, CH), 4.07 (2H, q, J = 7.2 & 6.8 Hz, CH_3), 1.03 (3H, t, J = 7.2 & 6.8 Hz, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 160.43, 158.56, 156.01, 145.31, 129.48, 128.66

(2C), 127.73 (2C), 127.04, 120.71, 104.03, 61.24, 58.32, 37.38, 14.14. TOF-MS: 333.0961 $[M+Na]^+$. Elemental analysis: Calcd. (%) for $C_{16}H_{14}N_4O_3$: C, 61.93; H, 4.55; N, 18.06; found: C, C, 61.96; H, 4.53; N, 18.04.

Crystal structure determination and refinement

The structures were solved by direct method using SHELXS97 [12]. Multisolution tangent refinement was used. All non-hydrogen atoms of the molecule were located in the best E-map and refined in anisotropic approximation. H-atom associated with N atom was located from Fourier difference map. All other H atoms were geometrically fixed and allowed to ride on their parent atoms with N-H=0.91 Å [compound (I)], N-H=0.86 Å [compound (II)], C-H=0.93-0.98 Å, and U_{iso}(H)=1.5 Ueq of the attached C atoms for methyl groups and 1.2 U_{eq}(N, C) for other H atoms. The geometry of the molecules was calculated using the WinGX [13], PARST [14] and PLATON [15] software.

Table 1. Crystallographic data for compound-I and compound-II

Crystallographic data	**Compound-I**	**Compound-II**
System, sp. gr., *Z*	Triclinic, P-1, 2	Monoclinic, $P2_1/c$, 4
Empirical formula	$C_{17}H_{18}N_4O4$	$C_{16}H_{14}N_4O_3.C_2H_6OS$
a, b, c Å	7.6168(6), 9.9967(5), 11.7888(6)	28.018(5), 9.196(5), 15.396(5)
α, β, γ deg	105.283(5), 99.416(5), 92.221(5)	90.00, 93.376(5), 90.00
V, $Å^3$	851.05(9)	3960(3)
Density, Mgm-3	1.336	1.303
Radiation, λ, Å	Mo*K*α, 0.71073	Mo*K*α, 0.71073
μ, mm^{-1}	0.098	0.194
T, K	293(2)	293(2)
Sample size, mm	0.30 X 0.30 X 0.20	0.30 X 0.30 X 0.20
Diffractometer	X'calibur system – Oxford diffraction make, U.K	X'calibur system – Oxford diffraction make, U.K
Scan mode	ω scan	ω scan
Absorption correction	Multi-scan	Multi-scan
θ range for entire data collection, deg	-3.51 < θ < 26.0	-3.43 < θ < 25.00
h, k, l ranges	-9< h<4, -12< k<12, -14< l <14	-31< h<33, -6<k<10, -18<l <9
Reflections collected / unique	6228/3344	13653/6946
Reflections observed (I > 2σ(I))	2201	3460
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Number of refined parameters	242	510
Final R	0.0473	0.0677
Goodness-of-fit on F^2	1.000	0.995
$\Delta\rho_{max}/\Delta\rho_{min}$, e/$Å^3$	-0.215 / 0.218	-0.235 / 0.320
Programs	SHELXS97 [12], SHELXL97 [12]	SHELXS97 [12], SHELXL97 [12]

3. Results and discussion

An ORTEP view [16] of the compound-I and compound-II with atomic labeling are shown in Figure 3 and Figure 4, respectively. In the crystal structure of (I), there is only one molecule in the asymmetric unit cell whereas in compound (II), there exists two crystallographically independent molecules. The geometry of both the compounds is similar in terms of their bond lengths and bond angles and is in good agreement with the standard values [17] and also corresponds to those observed in related structures [18-19]. The six C-C bond lengths in the benzene ring range from 1.380(3) to 1.390(4) Å with an average value of 1.385(3) Å. The bond angles in this benzene ring vary from 119.6(2) to 120.4(2)^o with an average value of 119.98(2)^o[compound (I)], and in

[compound (II)] the six C-C bond lengths in the phenyl ring lie in the wide range: 1.344(11) Å-1.390(10) Å [average being 1.375(8) Å for molecule-A], and 1.333(11) Å–1.431(8) Å [average being 1.376(8) Å for molecule-B]. The average value of bond angles in the phenyl ring for both the molecules is 119.98(5)°, which coincides almost with the theoretical value of sp^2-hybridization. The length of the double bond C13=O13 [1.212(5) Å for molecule-A and 1.210(5) Å for molecule-B] [compound (II)], confirmed the C=O double bond character and is slightly longer than that observed for carbonyl bonds [1.19 2 Å], probably because atom O13 is involved in intermolecular N-H…O hydrogen bond.

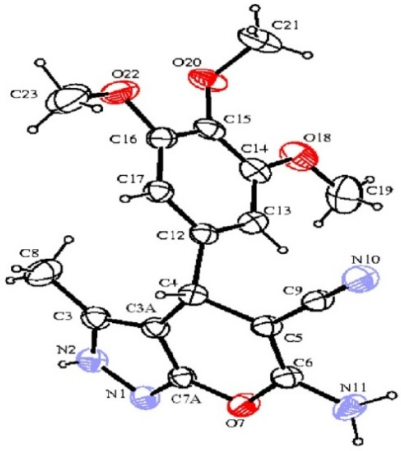

Fig. 3. The ORTEP view of compound-I

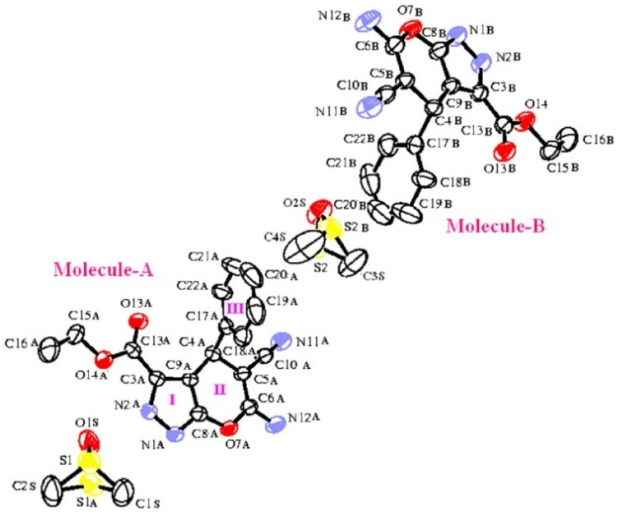

Fig. 4. The ORTEP view of compound-II

The values of the C-O bonds, [C7A-O7=1.371(3) Å, C6-O7=1.369(3) Å] [compound (I)] and (C6A-O7A=1.363(5) Å, C8A-O7A=1.379(4) Å) [molecule-A] and (C6B-O7B=1.362(5) Å, C8B-O7B=1.379(4) Å) [molecule-B] [compound (II)], in the pyran ring are in agreement with the C-O distance17. The S atoms are disordered over two sets of sites with occupancy ratios of 0.679(4):0.321(4) [molecule-A] and 0.546(6):0.454(6) [molecule-B] [compound (II)]. The bond length (C9-N10)=1.151(3) Å and bond angle (C5-C9-N10)=179.2(3)° [compound (I)] and the bond lengths (C10A-N11A)=1.145(5)Å [molecule (A)] and (C10B-N11B)=1.147(5)Å [molecule-B] and bond angles (C5A-C10A-N11A)=178.7(4)° [molecule-A] & (C5B-C10B-N11B)=178.2(4)° [molecule-B] [compound (II)], are almost similar in both the compounds and shows the linear character of the carbonitrile group, a feature observed in carbonitrile compounds [20]. Further, the values of dihedral angle between benzene ring and pyran ring being 88.26(6) [compound (I)], 89.8(1) [molecule-A] and 88.7(1)° [molecule-B] [compound (II)], are almost same in both the compounds and shows that benzene ring is almost perpendicular to pyran ring. In the crystal structure of 6-amino-3-methyl-4-(3,4,5-trimethoxyphenyl)-2,4-dihydropyrano [2,3-c] pyrazole-5-carbonitrile, he pyran moiety adopts a strongly flattened boat conformation with one mirror plane passing through the atoms C4 and O7 and the other bisecting the bonds C3A-C7A and C5-C6 [asymmetry parameters ΔCs(C4)=2.40, ΔC2(C3A-C7A)=1.72] and in the crystal structure of Ethyl 6-amino-5-cyano-4-phenyl-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate dimethyl sulphoxide monosolvate, the pyran ring adopts a flattened sofa conformation in molecule-A and a flattened boat conformation in molecule-B, with asymmetry parameters [ΔCs(C4)=2.73 for molecule-A and ΔCs(C4)=1.03, ΔC2(C4-C5)=1.14 for molecule-B] [21]. The Phenyl ring and pyrazole ring in both the compounds are planar. The predicted biological activities like antianginal, antiischemic, antihypertensive, angiogenesis inhibitor and antimitotic, etc. are common in the two compounds.

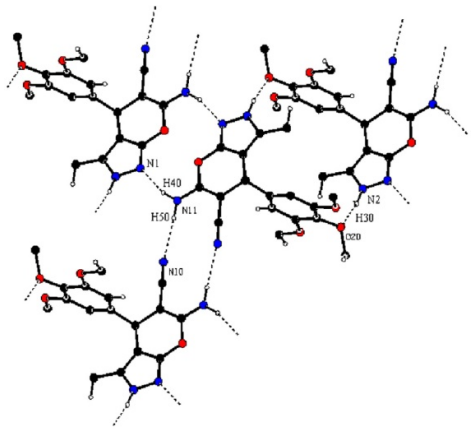

Fig. 5. A partial view of hydrogen interactions in compound-I

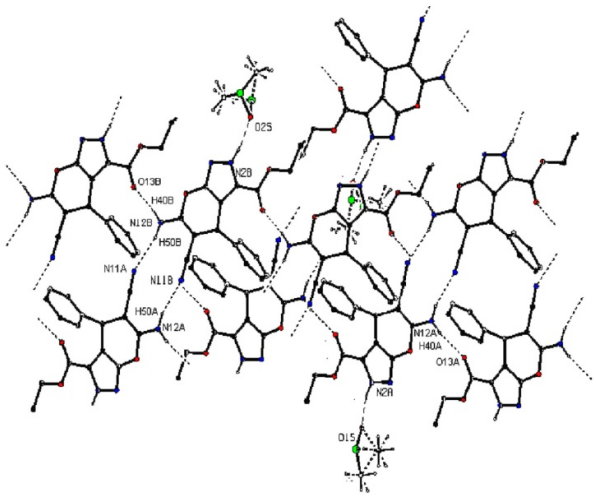

Fig. 6. A partial view of hydrogen interactions in compound-II

A partial view of hydrogen interactions in both the compounds is shown in Figure 5 and Figure 6 respectively. The geometry of inter and intra molecular hydrogen bonding in both the compounds is given in Table 2. The crystal structures of the title compounds are dictated by N-H…N and N-H…O intermolecular interactions. Intermolecular interactions are responsible for the stability of molecules within the unit cell. A pair of intermolecular N11-H40…N1, N11-H50…N10 and N2-H30…O20 hydrogen bonds link the molecules into inversion dimers generating (12) graph-set motifs for N-H…N and (20) graph-set motif for N-H…O interactions [22-23] (Figure 5) [compound-I] and intermolecular N-H...N hydrogen bonds link the molecules into inversion dimers generating (12) graph-set motifs [22-23] and C(9) graph-set motif for N-H…O interactions (Figure 6) [compound (II)] . These dimers are arranged in a manner to form chains of rings parallel to the (110) direction [compound-I] and [010] [compound-II]. Further stabilization is possible due to the presence of C-H…π interactions in (I) and (II), which are playing their role in these two compounds.

Table 2. Geometry of intermolecular hydrogen bonds in compound-I and compound-II

Compound-I: N-H…O, C-H...N, N-H…N and C-H...π hydrogen bonding geometry. Cg3 represent the center of gravity of the ring (C12/C13/C14/C15/C16/C17).

D-H…A	D-H(Å)	H…A(Å)	D…A(Å)	D-H…A(°)
N2-H30…O20^{i}	0.94(2)	1.96(2)	2.882(2)	165(2)
C19-H19B…N1^{ii}	0.96(3)	2.52	3.455(4)	165
N11-H40...N1^{iii}	0.95(2)	2.11(2)	3.030(3)	163(2)
N11-H50...N10^{iv}	0.91(2)	2.25(2)	3.156(3)	172(2)
C21- H21A…Cg3^{v}	0.96	2.85	3.55	130

Symmetry code: (i) –x+1,-y, -z+1, (ii) -x, -y, -z+1 (iii) -x, -y+1, -z+1 (iv) -x, -y+1, -z+2, (v) –x+1, -y, -z+2

Compound-II: N-H…N, N-H...O and C-H...π hydrogen bond geometry. Cg2 represent the center of gravity of the ring (N1B/N2B/C3B/C9B/C8B).

D-H…A	D-H(Å)	H…A(Å)	D…A(Å)	D-H…A(°)
N12A-H50A…N11B^{i}	0.86	2.19	3.024(5)	164
N12A-H40A…O13A^{ii}	0.86	2.11	2.958(4)	170
N12B-H50B…N11A^{iii}	0.86	2.23	3.072(5)	165
N12B-H40B…O13B^{iv}	0.86	2.10	2.945(4)	168
C16B- H16A... Cg2^{v}	0.96	2.95	3.854	156

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

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