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Synthesis, Characterization and Crystal Structure of 1-[3,5-Bis(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl]propan-1-one

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ABSTRACT

*The title compound, 1-[3,5-bis(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl]propan-1-one (**2**), is synthesized by the reaction of 4,4'-difluoro chalcone (**1**) and hydrazine hydrate in propionic acid. The synthesized compound (**2**) is well characterized by IR, ^{1}H-NMR, ^{13}C-NMR, LCMS data and elemental analysis. The proposed structure is further confirmed by determining its single crystal XRD data. The compound crystallizes in the monoclinic space group $P2_1/c$, with a = 9.9470 (1) Å, b = 14.7200 (2) Å, c = 12.7390 (2) Å, β = 122.0700(4)°, V = 1580.61 (4) Å^3, Z = 4, S = 0.95, R[$F^2 > 2\sigma(F^2)$] = 0.085, wR(F^2) = 0.247. The pyrazole ring adopts an envelope conformation and makes the dihedral angles of 2.8(2) and 81.9(3)°, respectively, with the two fluoro-substituted benzene rings. The dihedral angle between the two fluoro-substituted benzene rings is 79.6(3)°. The crystal packing is stabilized by C—H...O hydrogen bonds, forming zigzag C(7) chains along [001].*

Keywords: 4,4'-Difluoro chalcone, Pyrazoline derivative, Crystal structure, C—H...O Hydrogen bonds.

INTRODUCTION

Pyrazolines are well-known nitrogen-containing five-membered heterocyclic compounds having various pharmaceutical applications. In particular, they are used as antitumor, antibacterial, antifungal, antiviral, antiparasitic, anti-tubercular and insecticidal agents [1-3]. Some of these compounds have also anti-inflammatory, anti-diabetic, anaesthetic and analgesic properties [4-6]. In addition, pyrazolines have played a crucial part in the development of theory in heterocyclic chemistry and also used extensively in organic synthesis [7]. In view of the importance of pyrazoline derivatives and in continuation of our work on synthesis of various derivatives of 4,4'-

diflouro chalcone [8-16], the title compound (**2**) is synthesized and its crystal structure is reported here.

MATERIALS AND METHODS

Melting point was taken in open capillary tube and was uncorrected. The purity of the compound was confirmed by thin layer chromatography using Merck silica gel 60 F254 coated aluminium plates. IR spectrum was recorded on Shimadzu-FTIR Infrared spectrometer in KBr (mmax in cm^{-1}). ^1H (400 MHz) NMR spectrum was recorded on a Bruker AMX 400 spectrometer, with 5 mm PABBO BB -1H TUBES and ^{13}C (100 MHz) NMR spectrum was recorded for approximately 0.03 M solutions in DMSO-d_6 at 100 MHz with TMS as internal standard. LCMS was obtained using Agilent 1200 series LC and Micromass zQ spectrometer. Elemental analysis was carried out by using VARIO EL-III (Elementar Analysensysteme GmBH).

Synthesis of 1-[3,5-Bis(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl]propan-1-one

A mixture of 4,4'-difluoro chalcone **1** (2.44 g, 0.01 mol) and hydrazine hydrate (0.5 ml, 0.01 mol) in 25 ml propionic acid was refluxed for 8 h. The reaction mixture was cooled and poured into 50 ml ice-cold water. The precipitate was collected by filtration and purified by recrystallization from ethanol. The pale-yellow block-like crystals were grown from DMF by slow evaporation method and yield of the compound was 83%.

Melting point: 104–106 °C.

IR (KBr): νmax (cm^{-1}), 3078 (Ar-H), 2960, 2937, 2873 (C-H aliphatic), 1658 (C=O), 1602, 1512 (C=C aromatic), 1222 (C-F).

^1H NMR (400 MHz, DMSO-d_6): δ/ppm, 1.02 (t, 3H, CH_3), 2.67-2.74(q, 2H, $COCH_2$), 3.10-3.16 (dd, 1H, CH_2-H_A, J_{AB} =18.13 Hz, J_{AX} = 4.37 Hz), 3.79-3.86 (dd, 1H, CH_2-H_B, J_{BA} =18.13 Hz, J_{BX} = 11.97 Hz), 5.52-5.56 (dd, 1H, pyrazoline 5C-H, J_{XB} = 11.79, J_{XA} = 4.38 Hz), 7.11-7.84(m, 8H, Ar-H).

^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm, 8.94 (CH_3), 26.91 (C-4 of pyrazole), 41.88 (C-5 of pyrazole), 59.02 (CH_2), 115.25 (d), 115.72 (d), 127.53 (q), 128.93 (d), 138.61 (d), 153.15, 160.08, 162.02 (d), 164.94, 170.85 (C=O).

LCMS: *m/z* = 314.9 (M^+).

Elemental analysis: Calculated for $C_{18}H_{16}F_2N_2O$, C, 68.78%, H, 5.13%, N, 8.91%; Found: C, 68.76%, H, 5.16%, N, 8.87%.

X-ray Data Collection and Structure Refinement

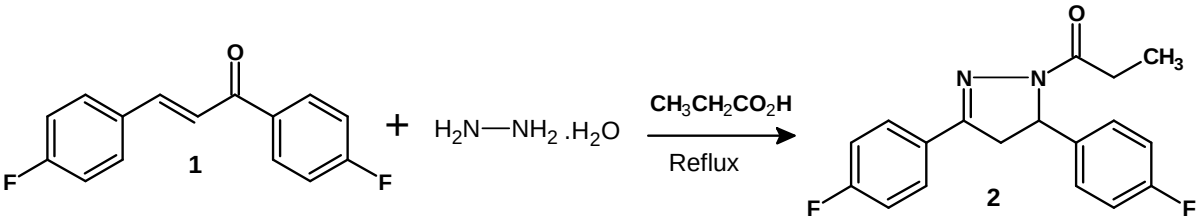
A suitable crystal was selected for structure determination by single-crystal X-ray diffraction. Diffraction data collection was performed on a Rigaku R-AXIS RAPID-S diffractomer equipped with a MoKα radiation (λ = 0.71073 Å) at 294(2) K. The data were processed using CrystalClear. An empirical absorption correction was applied using XABS2 [25].

A summary of the experimental details for compound **2** is given in Table 1. The structure was solved by direct methods using SIR-97 [26]. H atoms were placed in their calculated positions (C—H = 0.93-0.98 Å) and refined using a riding model with $U_{iso}(H) = 1.2$ or $1.5U_{eq}(C)$. Owing to the poor diffraction quality of the crystal, the ratio of observed to unique reflections is low (33%). The structure was refined by full-matrix least-squares with SHELX-97 [27], refining on F^2.

RESULTS AND DISCUSSION

One of the most convenient method for the synthesis of pyrazolines is the reaction of α,β-unsaturated ketones with hydrazine hydrate and its derivatives. The title compound (**2)** is synthesized by the reaction of 4,4'-difluoro chalcone (**1**) with hydrazine hydrate in propionic acid under reflux condition [17].

Scheme 1. Synthesis of 1-[3,5-bis(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl]propan-1-one.



The purity of the compound is checked by single-spot TLC, and the compound is characterized on the basis of spectral data (IR, NMR and LCMS) and elemental analysis. Spectral data of the synthesized compound **2** is in full agreement with its proposed structure. In the IR spectrum absorption bands at 2960, 2937, 2873 cm^{-1} are due to aliphatic CH groups and an absorption band at 1658 cm^{-1} is due to carbonyl group. In ^{1}H-NMR spectrum, the signals of the respective protons of the title compound are verified on the basis of their chemical shifts, multiplicities, and coupling constants. The formation of pyrazoline ring is confirmed by the appearance of ABX system in ^{1}H NMR due to geminal-vicinal coupling between protons H_A and H_B at C-4 and H_X at C-5. H_A which appeared as doublet of doublet at δ 3.10-3.16 ppm is the proton trans to H_X and geminal to H_B (J_{AB} =18.13 Hz, J_{AX} = 4.37 Hz). H_B is the proton cis and vicinal to H_X and appeared as doublet of doublet at δ 3.79-3.86 ppm (J_{BA} =18.13 Hz, J_{BX} = 11.97 Hz). While, H_X appeared as doublet of doublet at δ 5.52-5.56 ppm (J_{XB} = 11.79, J_{XA} = 4.38 Hz) [18]. Beside these signals, the protons of ethyl group appeared as a triplet and quartet at δ 1.02 and 2.67 ppm respectively. The ^{13}C-NMR spectrum shows peak at δ 170.85 ppm for a carbonyl carbon. Due to the *para*-fluoro substituents in two phenyl rings, six phenyl carbon signals of these two rings are split into doublets by 1, 2 and 3 bond coupling with ^{19}F. The mass spectrum shows the presence of a peak at *m/z* 314.9 (M^+) in accordance with the molecular formula. Elemental analysis also gives satisfactory results for the title compound.

Crystal Structure Determination

In the title molecule **2**, (Fig. 1), all the bond lengths and angles are consistent with those of our similar compounds previously reported [12, 19, 20]. Selected bond lengths and bond angles of **2** are listed in Table 2. The pyrazole ring (N(1)/N(2)/C(7)–C(9)) has an envelope conformation

[puckering parameters [21]: q_2 = 0.118(6) Å and ϕ = 259(3) °] with the C(9) atom bonded to the fluorophenyl group at the flap.

The pyrazole ring makes the dihedral angles of 2.8(2) and 81.9(3)°, respectively, with the two fluoro-substituted benzene rings (C(1)–C(6) and C(10)–C(15)) which they form dihedral angles of 5.6 (2) and 75.7 (3)°, respectively, with the plane [r.m.s. deviation = 0.006 Å] defined by the O(1), N(1), N(2), C(9) and C(16)–C(18) atoms.

Figure 1. The title molecule (2) showing the atom labeling scheme. Displacement ellipsoids for non-H atoms are drawn at the 30% probability level.

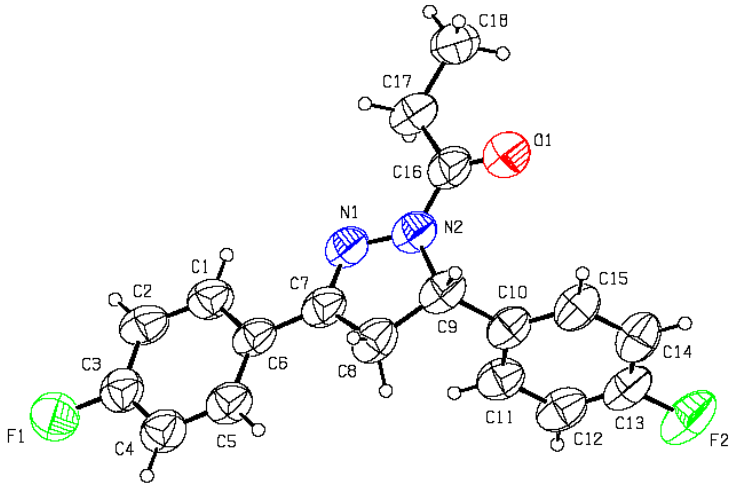


Table 1. Crystallographic Data and Structure Refinement Details for 2

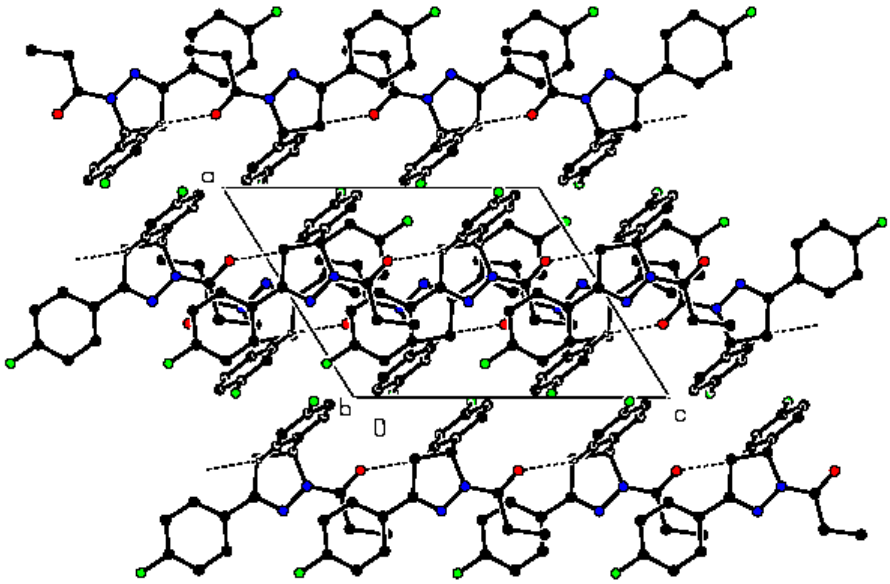
Empirical formula	$C_{18}H_{16}F_2N_2O$
Formula weight	314.33
Crystal size (mm^3)	0.20 × 0.20 × 0.20
Crystal system	Monoclinic
Space group	$P2_1/c$
a (A)	9.9470 (1)
b (A)	14.7200 (2)
c (A)	12.7390 (2)
β (°)	122.0700(4)
V (A^3)	1580.61 (4)
Z	4
D_c ($g \cdot cm^{-3}$)	1.321
μ (mm^{-1})	0.10
F(000)	656
θ range for data collection (°)	2.3, 26.4
independent reflections	3214
Observed reflections ($I > 2\ \sigma(I)$)	1055
Parameters	210
R/*wR* ($I > 2\ \sigma(I)$)	0.085/0.247
S on F^2	0.95
$(\Delta/\sigma)_{max}$	<0.0001
$\Delta\rho_{max}$ (e $Å^{-1}$)	0.17
$\Delta\rho_{min}$ (e $Å^{-1}$)	-0.19

In the crystal structure, molecules are linked via C(11)—H(11)...O(1)^{i} [symmetry code: (i) x, 1/2-y, -1/2+z; H...*A* = 2.42 Å, *D*...*A* = 3.190 (7) Å, *D*—H...*A* = 141°] hydrogen bonds, forming zigzag C(7) chains [22, 23] along [001], (see Fig. 2 drawn by using PLATON [24]).

Table 2. Selected Bond Lengths (Å) and Bond Angles (°) for observed unit cell Molecule 2 (Standard deviations in parentheses)

Designation	Parameter
F(1)—C(3)	1.368 (7)
F(2)—C(13)	1.370 (7)
O(1)—C(16)	1.221 (8)
N(1)—N(2)	1.391 (8)
N(1)—C(7)	1.276 (10)
N(2)—C(9)	1.484 (9)
N(2)—C(16)	1.365 (10)
N(2)—N(1)—C(7)	108.1 (6)
N(1)—N(2)—C(9)	113.8 (5)
N(1)—N(2)—C(16)	122.2 (6)
C(9)—N(2)—C(16)	124.0 (6)
F(1)—C(3)—C(2)	118.7 (7)
F(1)—C(3)—C(4)	118.1 (7)
N(1)—C(7)—C(6)	121.1 (7)
N(1)—C(7)—C(8)	113.5 (6)
N(2)—C(9)—C(8)	100.5 (5)
N(2)—C(9)—C(10)	111.0 (5)
F(2)—C(13)—C(12)	119.5 (6)
F(2)—C(13)—C(14)	117.0 (7)
O(1)—C(16)—N(2)	120.3 (8)
O(1)—C(16)—C(17)	123.1 (7)
N(2)—C(16)—C(17)	116.5 (6)

Figure 2. View of the packing diagram and hydrogen bonding of 2 viewed down the b axis. H atoms not involved in hydrogen bonds have been omitted for clarity.



CONCLUSION

A pyrazoline derivative, *1-[3,5-bis(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl]propan-1-one,* was synthesized and well characterized by IR, ^{1}H-NMR, ^{13}C-NMR, LCMS and single crystal XRD data.

Supplementary Materials

CCDC 827252 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk.

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