

Article

Synthesis, Characterization and Crystal Structures of 3,5-Bis(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazole-1-carboxamide and 3,5-Bis(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide

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Received: 28 June 2012; in revised form: 19 July 2012 / Accepted: 24 July 2012 /

Published: 15 August 2012

Abstract: Two new pyrazoline derivatives, 3,5-bis(4-fluorophenyl)-4,5-dihydropyrazole-1-carboxamide (**1**) and 3,5-bis(4-fluorophenyl)-4,5-dihydropyrazole-1-carbothioamide (**2**), were synthesized by reacting 4,4'-difluoro chalcone with semicarbazide hydrochloride and thiosemicarbazide in ethanolic sodium hydroxide solution. Both the compounds were confirmed by single crystal X-ray diffraction data and supported by IR, NMR, and mass spectral data. In **1**, crystal packing is stabilized by N–H...O hydrogen bonds and weak N–H...N, N–H...F and C–H...F intermolecular interactions. In **2**, only weak N–H...F and N–H...S intermolecular interactions are observed. Crystal data: C₁₆H₁₃F₂N₃O, (**1**), $M_r = 301.29$, monoclinic, $C2/c$, $a = 17.6219(6)$ Å, $b = 10.8735(3)$ Å, $c = 15.3216(5)$ Å, $\beta = 102.864(3)^\circ$, $V = 2862.11(16)$ Å³, $Z = 8$, $T = 173$ K, $R(F) = 0.0511$, $wR(F^2) = 0.1333$; C₁₆H₁₃F₂N₃S, (**2**), $M_r = 317.35$, monoclinic, $P2_1/c$, $a = 14.339(2)$ Å, $b = 11.1478(17)$ Å, $c = 9.541(2)(5)$ Å, $\beta = 107.007(18)^\circ$, $V = 1458.5(5)$ Å³, $Z = 4$, $T = 173$ K, $R(F) = 0.0413$, $wR(F^2) = 0.0959$.

Keywords: pyrazoline derivatives; X-ray crystal structure; hydrogen bonds; weak intermolecular interactions

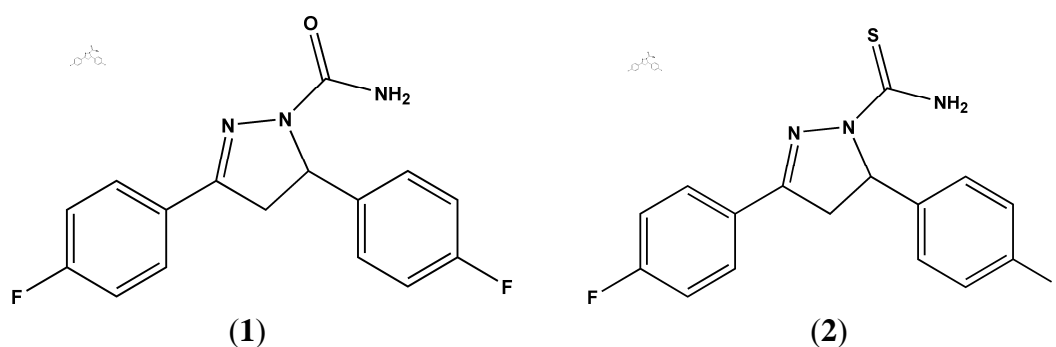
1. Introduction

Pyrazolines are well known, and important nitrogen-containing five-membered heterocyclic compounds and various methods have been reported for their synthesis [1,2]. Substituted pyrazolines are useful in pharmaceutical and agrochemical research. They display various biological activities such as antitumor, antibacterial, antifungal, antiviral, antiparasitic, anti-tubercular and insecticidal [3–5]. Some of these compounds have also antioxidant, anti-inflammatory and analgesic properties [6,7]. Due to these interesting activities of diversely substituted pyrazolines as biological agents, considerable attention has been focused on this class. In addition, pyrazolines have played a crucial part in the development of the theory in heterocyclic chemistry and also used extensively in organic synthesis [8].

Crystal structures of some 3,5-diaryl-4,5-dihydropyrazoles substituted at position 1 with carboxamide or carbothioamide groups, viz., 4,5-dihydro-3-methyl-5-(4-methylphenyl)-1*H*-pyrazole-1-carboxamide [9] and 3-(4-bromophenyl)-5-[4-(dimethylamino)phenyl]-4,5-dihydro-1*H*-pyrazole-1-carbothioamide [10] have been reported.

In view of the importance of pyrazolines and in continuation of our work on synthesis of various derivatives of 4,4'-difluoro chalcones [11–18], we report the synthesis and crystal structures of new 3,5-bis(4-fluorophenyl)-4,5-dihydropyrazoles substituted at position 1 with carboxamide or carbothioamide groups (Figure 1).

Figure 1. The molecular structures of (1) $C_{16}H_{13}F_2N_3O$ and (2) $C_{16}H_{13}F_2N_3S$.



2. Results and Discussion

The IR spectrum of compound **1** (Figure S1) showed a forked band at 3452 cm^{-1} corresponding to NH_2 group and a band at 1681 cm^{-1} assigned to the carbonyl group. While, the IR spectrum of compound **2** (Figure S2) demonstrated a forked band at 3475 cm^{-1} corresponding to a NH_2 - group and a band at 1365 cm^{-1} corresponding to a $\text{C}=\text{S}$ group. The IR spectra of both the compounds showed a $-\text{C}=\text{N}$ -stretch at 1577 & 1599 cm^{-1} , which confirmed the formation of the pyrazoline moiety. In the ^1H NMR spectra of pyrazolines (Figures S3 and S4), protons H_A and H_B are geminal protons at the C4 carbon. They appeared in the region 3.03 – 3.12 ppm and 3.75 – 3.84 ppm as a doublet of doublets for both the compounds. The CH proton at C5 also appeared as a doublet of doublets in the region of

5.38–5.89 ppm, due to vicinal coupling with two non-equivalent geminal protons of the C4 carbon. Beside these signals, the amino protons appeared as broad singlet signal at δ 6.5 in compound **1** and as two singlet signals at δ 7.95 & 8.02 in compound **2**. LCMS (Figures S5 and S6) and elemental analysis also gave satisfactory results for both of the compounds.

In the crystal structures, the dihedral angle between the pyrazole ring and the two benzene rings is 1.9(1) Å and 55.9(6) Å in **1** (Figure 2) and 15.1(1) Å and 80.9(8) Å in **2** (Figure 3), respectively.

Figure 2. Molecular structure of **1** showing the atom labeling scheme and 50% probability displacement ellipsoids.

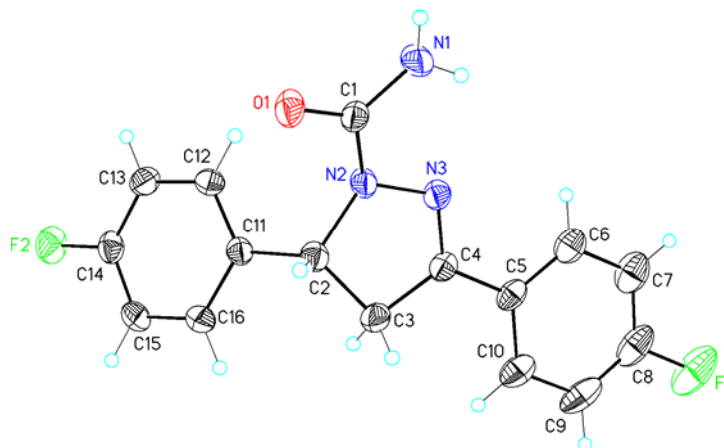
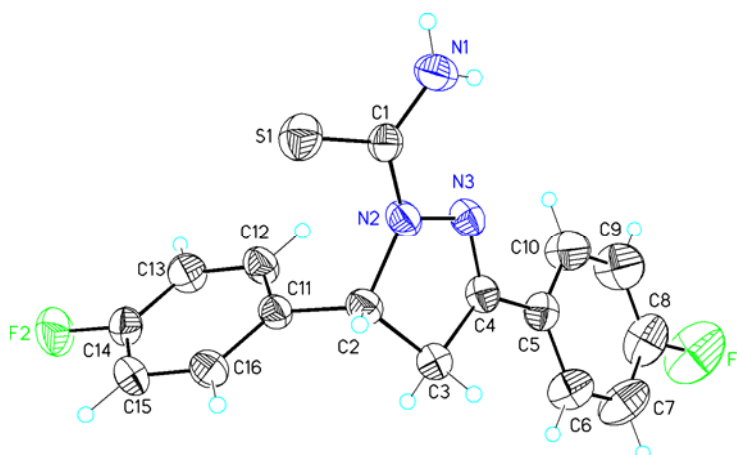


Figure 3. Molecular structure of **2** showing the atom labeling scheme and 50% probability displacement ellipsoids.



Bond lengths are in normal ranges for **1** and **2** [19]. Selected bond lengths and angles for both molecules are listed in Table 1.

Table 1. Selected atom distances [Å] for **1** and **2**.

Atoms 1	Distance 1	Atoms 2	Distance 2
C1—O1	1.2300(19)	C1—S1	1.6818(16)
C1—N1	1.340(2)	C1—N1	1.331(2)
N2—N3	1.3929(17)	N2—N3	1.3924(17)
N2—C2	1.4754(19)	N2—C2	1.4761(19)
N3—C4	1.2804(19)	N3—C4	1.283(2)

Table 1. Cont.

Atoms 1	Distance 1	Atoms 2	Distance 2
C2—C3	1.544(2)	C2—C3	1.538(2)
C3—C4	1.498(2)	C3—C4	1.501(2)
C8—F1	1.358(2)	C8—F1	1.356(2)
C14—F2	1.3658(18)	C14—F2	1.3665(19)

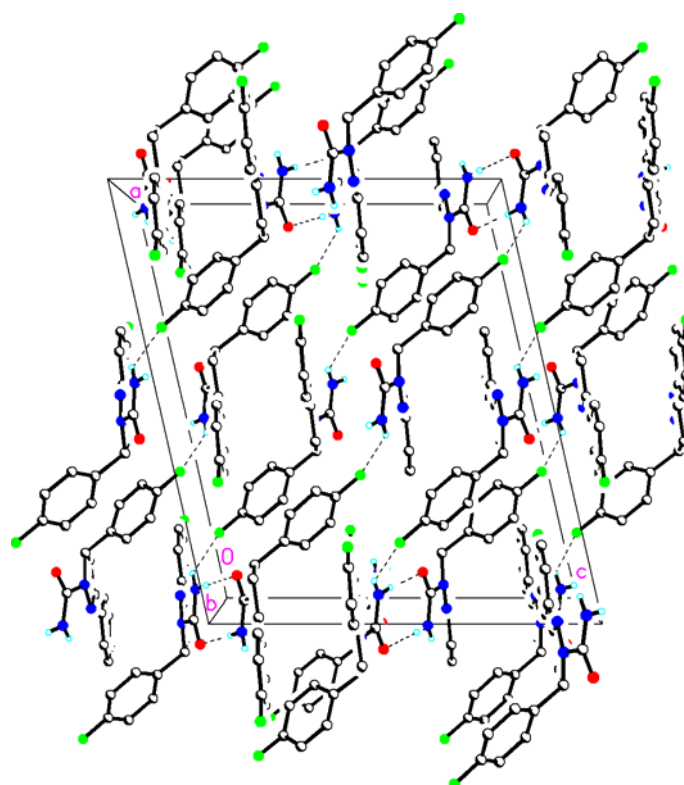
In **1**, the molecules in the crystal form an inversion dimer through a pair of N—H...O, hydrogen bonds. These dimers are further linked through weak N—H...F and C—H...F intermolecular interactions (Table 2) into a sheet-like structure in the *ac*-plane (Figure 4). In addition, weak π — π intermolecular interactions (Cg1...Cg2; 3.9841(11) Å; $1-x, 1-y, 1-z$, and Cg1...Cg3; 3.8319(9) Å, x, y, z where Cg1 = centroid for N2/N3/C4/C3/C2, Cg2 = centroid for C5—C10, Cg3 = centroid for C11—C16) are observed which help stabilize crystal packing.

Table 2. Hydrogen bonds for **1**, C₁₆H₁₃F₂N₃O [Å and °].

D—H...A	d (D—H)	d (H...A)	d (D...A)	< (DHA)
N1—H1NA...O1 ^{#1}	0.88(2)	2.06(2)	2.928(2)	171(2)
N1—H1NB...F2 ^{#2}	0.88(2)	2.38(2)	3.129(2)	143(2)
C13—H13A...F1 ^{#3}	0.93	2.54	3.386(2)	151

Symmetry transformations used to generate equivalent atoms: ^{#1} $-x + 1, -y + 2, -z + 1$; ^{#2} $x - 1/2, -y + 3/2, z - 1/2$; ^{#3} $-x + 1, y + 1, -z + 3/2$.

Figure 4. Packing diagram of **1** viewed along the *b* axis. Dashed lines indicate N—H...O hydrogen bonds forming an inversion dimer. Additional weak N—H...F and C—H...F intermolecular interactions further link the molecules into a sheet-like structure in the *ac*-plane. Remaining H atoms have been removed for clarity.



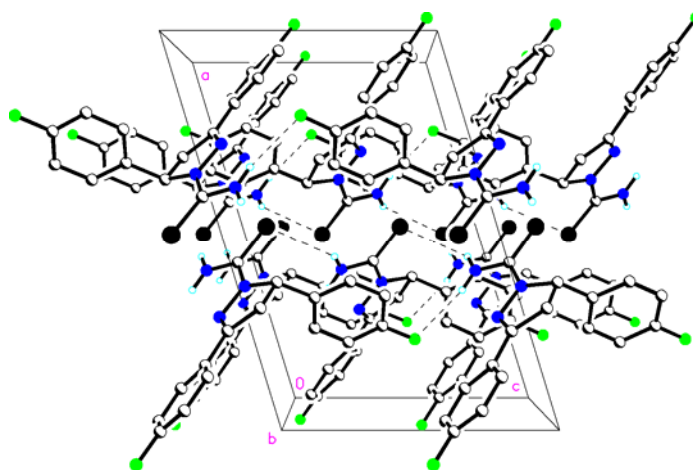
In **2**, N–H...F and N–H...S hydrogen bonds are observed creating an infinite 1-D chain along (001) which along with weak C–H...Cg π -ring intermolecular interactions (Table 3) strongly influence crystal packing (Figure 5).

Table 3. Hydrogen bonds for **2**, C₁₆H₁₃F₂N₃S [Å and °].

D–H...A	d (D–H)	d (H...A)	d (D...A)	< (DHA)
N1–H1NB...F2 ^{#1}	0.87(2)	2.41(2)	3.258(2)	164(2)
N1–H1NA...S1 ^{#2}	0.84(2)	2.85(2)	3.525(2)	138(2)

Symmetry transformations used to generate equivalent atoms: ^{#1} $x, y, z-1$; ^{#2} $x, -y + 3/2, z - 1/2$.

Figure 5. Packing diagram of **2** viewed along the b axis. Dashed lines indicate N–H...F and N–H...S hydrogen bonds forming chains along (001). Remaining H atoms have been removed for clarity.

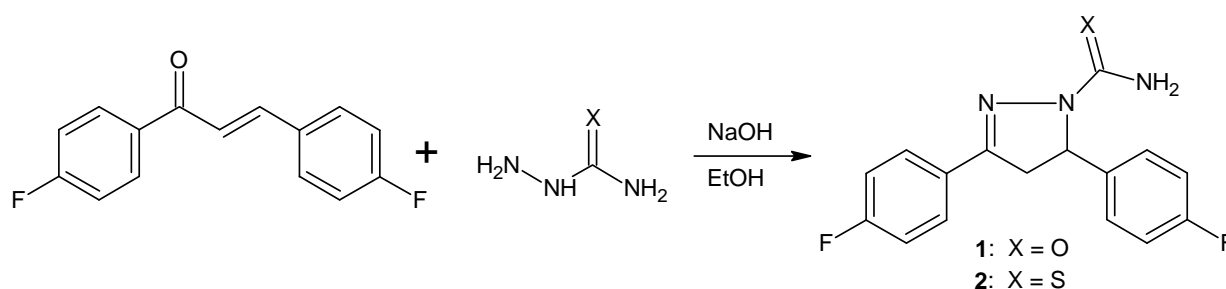


3. Experimental Section

3.1. General

The synthesis of the target compounds is outlined in Scheme 1. 4,4'-Difluoro chalcone was reacted with semicarbazide HCl or thiosemicarbazide in ethanolic NaOH to afford 3,5-bis(4-fluorophenyl)-4,5-dihydropyrazole-1-carboxamide (**1**) and 3,5-bis(4-fluorophenyl)-4,5-dihydropyrazole-1-carbothioamide (**2**) respectively.

Scheme 1. The synthesis of **1** and **2**.



Melting points were taken in open capillary tubes and were uncorrected. The purity of the compounds was confirmed by thin layer chromatography using Merck silica gel 60 F254 coated aluminum plates. IR spectra were recorded on Shimadzu-FTIR Infrared spectrometer in KBr (mmax in cm^{-1}). ^1H (400 MHz) NMR spectra were recorded on a Bruker AMX 400 spectrometer, with 5 mm PABBO BB -1H TUBES with TMS as internal standard. LCMS was obtained using Agilent 1200 series LC and Micromass zQ spectrometer. Elemental analyses were carried out by using VARIO EL-III (Elementar Analysensysteme GmbH).

3.2. Synthesis of 3,5-Bis(4-fluorophenyl)-4,5-dihydro-1H-pyrazole-1-carboxamide (1)

A mixture of 4,4'-difluoro chalcone (1.22 g, 0.005 mol), semicarbazide HCl (0.6 g, 0.005 mol) and NaOH (0.5 g, 0.0125 mol) was heated under reflux in absolute ethanol (12.5 mL) for 12 h. The reaction mixture was cooled and poured into ice cold water. The solid separated was filtered, dried and recrystallized from ethanol. The single crystals were grown from DMF by slow evaporation method and yield of the compound was 78%. (m.p. 435 K).

IR (KBr, cm^{-1}): 3452, 3211 (NH_2), 1681 ($\text{C}=\text{O}$), 1599 ($\text{C}=\text{N}$), 1224 ($\text{C}-\text{F}$); ^1H NMR (400 MHz, DMSO) δ ppm 3.03 (dd, 1H, H_A , $J = 5.2$ Hz), 3.75 (dd, 1H, H_B , $J = 12$ Hz), 5.38 (dd, 1H, H_X , $J = 5.60$ Hz), 6.50 (br s, 2H, NH_2), 7.11–7.85 (m, 8H, Ar-H); LCMS: m/z 301.9 (M^+); Analytical data: Found (Cald): C%: 63.72 (63.78); H%: 4.34 (4.35); N%: 13.91 (13.95).

3.3. Synthesis of 3,5-Bis(4-fluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (2)

A mixture of 4,4'-difluoro chalcone (1.22 g, 0.005 mol), thiosemicarbazide (0.46 g, 0.005 mol) and NaOH (0.5 g, 0.0125 mol) was heated under reflux in absolute ethanol (12.5 mL) for 16 h. The reaction mixture was cooled and poured into ice cold water. The solid separated was filtered, dried and recrystallized ethanol. The single crystals were grown from DMF by slow evaporation method and yield of the compound was 72%. (m.p. 526 K).

IR (KBr, cm^{-1}): 3475, 3354 (NH_2), 1577 ($\text{C}=\text{N}$), 1365 ($\text{C}=\text{S}$), 1213 ($\text{C}-\text{F}$). ^1H NMR (400 MHz, DMSO) δ ppm 3.12 (dd, 1H, H_A , $J = 3.6$ Hz), 3.84 (dd, 1H, H_B , $J = 11.6$ Hz), 5.89 (dd, 1H, H_X , $J = 3.6$ Hz), 7.11–7.94 (m, 8H, Ar-H), 7.95 & 8.02 (two s, 2H, NH_2); LCMS: m/z 317.9 (M^+); Analytical data: Found (Cald): C%: 60.52 (60.55); H%: 4.15 (4.13); N%: 13.22 (13.24).

3.4. Data Collection and Refinement

Crystallographic data for both **1** and **2** were collected on an Agilent Gemini CCD-Diffractometer with monochromatic Mo- $K\alpha$ radiation ($\lambda = 0.71073$ Å) and an EOS detector [20]. The structures were solved by direct methods [21], full-matrix least-squares refinement [21] on F^2 with 313 **1** or 219 **2** parameters. In both **1** and **2**, H1NA, and H1NB, were located in a difference map and refined isotropically. All of the remaining H atoms were placed in their calculated positions and then refined using the riding model with C–H lengths of 0.93 or 0.98 Å (CH) or 0.97 Å (CH_2). The isotropic displacement parameters for these atoms were set to 1.19 to 1.20 (CH , CH_2), times U_{eq} of the parent atom.

Crystal data for **1**: colorless chunk, $0.22 \times 0.21 \times 0.20$ mm, $\text{C}_{16}\text{H}_{13}\text{F}_2\text{N}_3\text{O}$, $M_r = 301.29$, monoclinic $C2/c$, $a = 17.6219(6)$ Å, $b = 10.8735(3)$ Å, $c = 15.3216(5)$ Å, $\beta = 102.864(3)^\circ$ and $V = 2862.11(16)$ Å³,

$Z = 8$, $F(000) = 1248$, $T = 173(2)$ K, $\rho_{\text{calc}} = 1.398 \text{ g}\cdot\text{cm}^{-3}$, $\mu = 0.108 \text{ mm}^{-1}$, 12815 reflections measured ($-22 \leq h \leq 23$, $-14 \leq k \leq 13$, $-20 \leq l \leq 19$; $3.2974 \leq \theta \leq 32.3351$), $R_{\text{int}} = 0.0220$, 3684 merged reflections, $I > 2\sigma(I)$, 205 parameters, 2 restraints, $\text{GOF} = 1.011$, $R(F) = 0.0511$, $wR(F^2) = 0.1333$, $w = 1/\sigma^2(F_o^2) + 0.0541P^2$, where $P = (F_o^2 + 2F_c^2)/3$, min./max. $\Delta\rho = -0.38, +0.37 e \text{ \AA}^3$. Cambridge Database deposition number: CSD-888442.

Crystal data for **2**: colorless chunk, $0.20 \times 0.16 \times 0.12 \text{ mm}$, $\text{C}_{16}\text{H}_{13}\text{F}_2\text{N}_3\text{S}$, $M_r = 317.35$, monoclinic $P2_1/c$, $a = 14.339(2) \text{ \AA}$, $b = 11.1478(17) \text{ \AA}$, $c = 9.541(2) \text{ \AA}$, $\beta = 107.007(18)^\circ$ and $V = 1458.5(5) \text{ \AA}^3$, $Z = 4$, $F(000) = 656$, $T = 173(2)$ K, $\rho_{\text{calc}} = 1.445 \text{ g}\cdot\text{cm}^{-3}$, $\mu = 0.243 \text{ mm}^{-1}$, 13239 reflections measured ($-18 \leq h \leq 18$, $-14 \leq k \leq 14$, $-11 \leq l \leq 12$; $2.9651 \leq \theta \leq 30.0998$), $R_{\text{int}} = 0.0331$, 3483 merged reflections, $I > 2\sigma(I)$, 205 parameters, 2 restraints, $\text{GOF} = 1.004$, $R(F) = 0.0413$, $wR(F^2) = 0.0959$, $w = 1/\sigma^2(F_o^2) + 0.0541P^2$, where $P = (F_o^2 + 2F_c^2)/3$, min./max. $\Delta\rho = -0.216, +0.213 e \text{ \AA}^3$. Cambridge Database deposition number: CSD-888534.

4. Conclusions

The crystal and molecular structures of 3,5-bis(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazole-1-carboxamide (**1**) and 3,5-bis(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide (**2**), and spectroscopic supporting data are reported. These data represent crystallographically characterized compounds of two new pyrazoline derivatives which are potentially useful in pharmaceutical and agrochemical research. The effects of hydrogen bonding and weak intermolecular interactions observed in both molecules influence crystal packing as described.

Acknowledgements

BN thanks the UGC SAP for financial assistance for the purchase of chemicals. SS thanks Mangalore University for research facilities. JPJ acknowledges the NSF--MRI program (grant No.CHE1039027) for funds to purchase the X-ray diffractometer.

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