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ORIGINAL PAPER

Synthesis and Crystal Structure of New Thiazolyl-Pyrazoline Derivatives Bearing 1,2,4-Triazole Moiety

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Abstract The title compounds 1-(4-aryl-5-triazolyl-2-thiazolyl)-3,5-diaryl-2-pyrazoline derivatives (**3a–c**) were synthesized by reacting 3,5-diaryl1-thiocarbamoyl -2-pyrazoline **1** with 2-bromo-1-aryl-2-(1H-1,2,4-triazol-1-yl) ethanones **2** in boiling ethanol. Their structures were characterized by IR, ^{1}H-NMR, MS spectroscopic data and elementary analyses. The structure of compound (**3a**), $C_{26}H_{18}Cl_2N_6S$, was conclusively established with X-ray crystal structure analysis. It crystallizes in the Orthorhombic space group Pna2(1), with $a = 17.8160(5)$, $b = 18.9125(7)$, $c = 14.7926(4)$, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$and Dc = 1.379 mg/m^3 for $Z = 8$, $V = 4984.3(3)$ Å, μ(Mo–Kα) = 0.372 mm, $\lambda = 0.71070$ Å, the final $R = 0.0527$ and $wR = 0.1307$ for 43309 observed reflections with $I > 2\sigma(I)$. The structure is stabilized by weak C–H···N intramolecular hydrogen bonds and C–H···Cg p-ring intermolecular interactions and gives support to molecular packing stability in the unit cell.

Keywords 1,2,4-Triazole · Pyrazoline · Thiazole · Crystal structure

Introduction

Electron-rich nitrogen heterocyclics play an important role in diverse biological activities. 1,2,4-Triazole derivatives represent one of the most interesting and important classes of compounds, possessing a wide spectrum of biological activity such as anti-HIV, antifungal, antibacterial, COX-2 inhibitor and anticonvulsant [1–4], and some of them, for example, Fluconazole and Itraconazole, have been used clinically as antifungal agents [5, 6]. More recently, thiazolyl-pyrazoline derivatives were also reported to exhibit significant antimicrobial, antiviral and antihypertensive activities [7–9].

A literature survey shows that thiazolyl-pyrazoline derivatives containing 1,2,4-triazole moiety have never been reported so far. Encouraged by these facts and in continuation of our interest in the synthesis of chemically and biologically important heterocycles containing 1,2,4-triazole moiety[10, 11], herein, we report the synthesis and X-ray crystallographic study of some novel heterocyclic compounds including 1,2,4-triazole, pyrazoline and thiazole ring in the same molecule, which might exhibit enhanced activities owing to the incorporation of different pharmacophores into their structures R_1 = H, Cl, OCH_3

Experimental Section

Materials and Synthesis

All reagents for synthesis and analyses were purchased from commercial sources and were used as received without further purification. Melting points were recorded on a mettler FP-5 capillary melting point apparatus and are

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uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400 elemental analyzer. The IR spectra were measured on a Bruker Equinox 55 FT-IR spectrophotometer with KBr disk in the range 4000–400 cm^{-1}.The ^1H NMR spectra were recorded on a Varian Inova-400 spectrophotometer using tetramethylsilane (TMS) as internal standard and $CDCl_3$ as solvent.

1-thiocarbamoyl-3,5-bis-(4-chloro-phenyl)4,5-dihydro-1H-pyrazoline (**1**), Triazolylethanones and bromine substituted triazolylethanones (**2**) were prepared according to the reported methods [12–14].

*The Synthesis of 1-Thiocarbamoyl-3,5-bis-(4-chloro-phenyl)-4,5-Dihydro-1H-pyrazoline (**1**)*

A mixture of the appropriate chalcone (5 mmol) and thiosemicarbazide (6 mmol) was refluxed in ethanol (50 mL). After dissolution of the reactants, a solution of KOH (12.5 mmol) in water (5 mL) was added dropwise. The solution was refluxed for a further 4 h. The reaction mixture was allowed to cool, poured into crushed ice, and the solid mass separated out was filtered, washed with cold ethanol, dried, and crystallized from ethanol/water.

*The Synthesis of 1-(4-aryl-5-triazolyl-2-thiazolyl)-3,5-diaryl-2-Pyrazoline derivatives (**3a–c**)*

General Procedure a mixture of 3,5-Bis-(4-chloro-phenyl)-4,5-dihydro-1H -pyrazole-1-carbothioamide **1** (0.5 mmol) and 2-bromo-1-(4-substituted phenyl)-2-(1H-1,2,4-triazol-1-yl) ethanone **2** (0.5 mmol) in ethanol (30 mL) was heated under reflux for 0.5 h. The progress of reaction was monitored on TLC. Then the crystalline solid product separated by filtered, washed by cold ethanol and dried. The crude compound was recrystallized from ethanol to obtained **3a–c**.

3a White crystals, Yield 80.3%; m.p. 204–205 °C. IR (KBr)ν/cm^{-1}:1631 (C=N); 1HNMR(CDCl3 + DMSO-d6, 400 MHz ppm):δ 8.06,8.16 (2H, 2 s, Triazole-H), 6.82–7.70 (13H, m, phenyl-H), 5.69(dd, 1H, C5-Hx, Jax = 11.93 Hz, Jbx = 5.97 Hz), 3.94(dd, 1H, C4-Ha, Jax = 11.93 Hz, Jab = 17.60 Hz), 3.32(dd, 1H, C4-Hb, Jbx = 5.97 Hz, Jab = 17.60 Hz).MS(EI)m/z(%): 516 (M+), 91, 77; Anal.Calcd. (%) for C26H18Cl2N6S : C, 16.24; H, 3.51; N, 60.35; Found (%): C, 16.27; H, 3.62; N, 60.42.

3b White crystals, Yield 76.3%;.m.p. 256–258 °C. IR (KBr)ν/cm^{-1}:1632 (C=N); 1HNMR (CDCl3 + DMSO-d6, 400 MHz ppm): δ8.06, 8.16(2H,2 s,Triazole-H), 6.75–7.70 (12H, m, phenyl-H), 5.71(dd, 1H, C5-Hx, Jax = 11.95 Hz, Jbx = 5.99 Hz), 3.90(dd, 1H, C4-Ha, Jax = 11.95 Hz, Jab = 17.60 Hz), 3.29(dd, 1H, C4-Hb, Jbx = 5.99 Hz, Jab = 17.60 Hz).MS(EI)m/z(%): 552(M+), 91, 77; Anal. Calcd. (%) for C26H17 Cl3 N6 S: C, 15.23; H, 3.10; N, 60.35; Found (%): C, 15.26; H, 3.12, N, 60.35.

3c White crystals, Yield 83.6%; m.p. 214–215 °C. IR (KBr) ν/cm^{-1}: 1634 (C=N); 1H NMR(CDCl3 + DMSO-d6, 300 MHz, ppm):δ8.06,8.16(2H, 2s, Triazole-H), 6.73–7.69(12H,m,phenyl-H), 5.70(dd, 1H, C5-Hx, Jax = 12.00 Hz, Jbx = 6.39 Hz), 3.92(dd, 1H, C4-Ha, Jax = 12.00 Hz, Jab = 17.60 Hz), 3.76(3H,s,CH3O), 3.30(dd, 1H, C4-Hb, Jbx = 6.39 Hz, Jab = 17.60 Hz). MS(EI)m/z(%): 552 (M+), 91, 77; Anal. Calcd. (%) for C27H20Cl2N6OS: C, 15.35; H,3.68; N.59.24; Found (%): C, 15.33; H, 3.64; N, 59.25.

Crystal Structure Determination

The selected crystal with approximate dimensions of 0.41 × 0.29 × 0.14 mm^3 was mounted thin glass fiber with the aid of an epoxy resin. The XRD data were collected with multi-scan mode at 293(2) K on a Bruker Smart AXSCCD with a graphite monochromatic Mo–Kα radiation (λ = 0.71073 Å). APEX2 software was used for data reduction and multi-scan absorption correction. [15] A total of 21,794 reflections ($2\theta_{max}$ = 52.38) were collected, of which 5,871 unique reflections (R_{int} = 0.0525) were used to structural elucidation. The structures were solved by direct methods using SHELXS97 [16] and refinement was carried out by the full-matrix least-squares technique on F2 using SHELXL97 [16]. The function $Rw = |\sum w(|F_0|^2 - |F_c^2|/\sum| w(f_0)^2|^{1/2}$was minimized, where $w = [1/\sigma^2(F_0)^2 + (aP_0)^2 + bP]$, ($P = [F_0^2 + 2F_c^2]/3$. The final R_1 and wR_2 values 0.0115 and 0.0211 are for 1,138 independent reflections [$I > 2\sigma(I)$]. All non-hydrogen atoms were assigned anisotropic displacement parameters in the refinement. All hydrogen atoms were added atcalculated positions and refined usin a riding model, with C–H distances in the range 0.93 Å and with their U_{iso}'s set at 1.2 (1.4 for methyl groups) times the *Ueq* values of the appropriate carrier atoms. Molecular structure was checked using PLATON [17]. Data collection details and structure determination results are summarized in Table 1**.** Some selected bond distances and angles quoted in Table 2. CCDC-800971 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at http://www.ccdc.cam.ac.uk/conts/ retrieving.html.

Result and Discussion

The synthetic routes leading to the desired compounds are shown in Schemes 1.

The IR spectral, mass spectra and ^1H NMR spectral data gave strong evidence for the structure of **3a–c**. The IR spectra of **3a–c** exhibit bands at 1631–1632 cm^{-1}(C=N).

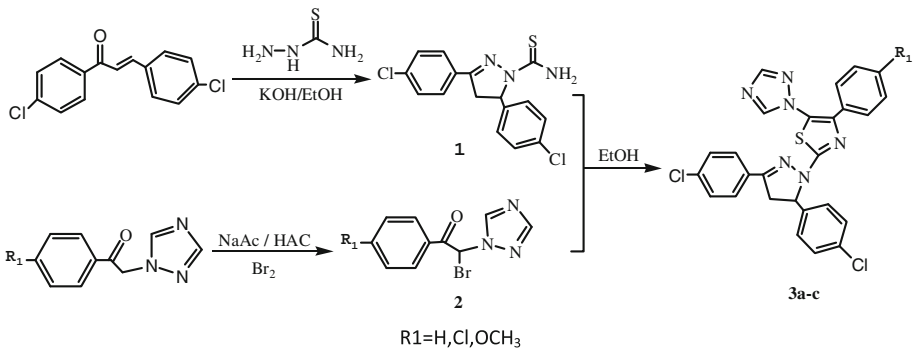
Table 1 Crystal data and structure refinement

Formula	$C_{26}H_{18}C_{12}N_6S$	V (Å^3)	4984.3(3)
Crystal color	Colorless	Crystal size (mm)	0.36 × 0.26 × 0.19
Formula weight	517.43	Crystal system	Orthorhombic
Temperature	293(2) K	Space group	Pna2(1)
a (Å)	17.8160(5)	γ (°)	90
b (Å)	18.9125(7)	*Z*	8
c (Å)	14.7926(4)	*D*c (mg/m^3)	1.379
α (°)	90	θ range (°)	3.14–27.48
β (°)	90	μ/mm	0.372
Data/restraints/parameters	11066/1/632	Reflections collected	43309
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0527$, $wR_2 = 0.1307$	*R* indices (all data)	$R_1 = 0.1094$, $wR_2 = 0.1639$

Table 2 Selected bond lengths (Å), bond angels (°) and torsion angles (°) of compounds

N(7)–C(35)	1.283(5)	N(8)–C(42)	1.369(5)	C(43)–C(46)–C(47)–C(52)	119.0(5)
N(7)–N(8)	1.379(4)	N(8)–C(33)	1.479(5)	N(11)–N(10)–C(43)–C(46)	−73.1(5)
C(33)–C(34)	1.553(5)	C(32)–C(33)	1.506(6)	C(27)–C(28)–C(29)–Cl(3)	−179.1(3)
C(34)–C(35)	1.510(5)	C(35)–C(36)	1.447(5)	C(44)–N(10)–C(43)–C(46)	105.9(6)
S(2)–C(42)	1.738(4)	C(43)–C(46)	1.360(5)	C(31)–C(30)–C(29)–Cl(3)	178.2(4)
N(10)–C(43)	1.412(5)	C(46)–C(47)	1.473(5)	C(43)–S(20–C(42)–N(9)	−0.1(3)
C(38)–C(39)–Cl(4)	119.4(3)	C(40)–C(39)–Cl(4)	119.6(4)	C(41)–C(40)–C(39)–Cl(4)	−178.9(4)
N(12)–C(45)–N(11)	116.9(5)	N(8)–C(42)–S(2)	119.7(3)	N(7)–N(8)–C(42)–N(9)	178.7(4)
C(30)–C(29)–Cl(3)	119.0(5)	N(9)–C(42)–S(2)	117.9(3)	N(7)–C(35)–C(36)–C(41)	2.8(6)
C(28)–C(29)–Cl(3)	118.9(5)	C(45)–N(11)–N(10)	101.0(4)	C(46)–N(9)–C(42)–S(2)	0.1(2)

Scheme 1 The synthesis of title compounds



Also, their ^{1}H NMR spectra revealed multiplet between δ 7.79 and 6.73 ppm due to the protons of aromatic rings, the signal for 1,2,4-trizole and methoxyl appeared at δ 8.19–8.06 ppm and δ 3.82–3.74 ppm, respectively. Three distinct double doublets of the ABX system (a CH proton and two anisochronous protons of a CH2) appeared at δ 5.71–3.29 ppm, as has been observed in pyrazoline ring. The EI mass spectra of compounds **3a–c** revealed the existence of the molecular ion peaks and anticipant fragmentation peaks, which were in good accordance with the given structures of products. For example, the mass spectrum of **3a** had the molecular ion peaks at *m*/*z* 448 (100%).

The structure of the crystal **3a** is displayed in Fig. 1**.** The C(33), C(34), C(35), N(7) and N(8) atoms form a five-membered ring, X-ray analysis reveals that the five-membered ring of pyrazoline adopts an envelope conformation with the atom C(33) deviating from the plane defined by the atoms C(34), C(35), N(7) and N(8) of 0.2753 Å. The N7–N8 and N8–C33 bond distances of 1.379(4) and 1.479(5) Å are showing they belong to single bond. However, the C35=N7 bond distance of 1.283(5) Å is falling into the C=N double bond distance region. Because of the existence of conjugate system of C35=N7 and phenyl ring (C36–C41), the distance of C(35)–C(36)

(1.447 Å) is shorter than the normal C–C single bond (1.53 Å). The torsion angles of N7–C35–C36–C41, N8–C33–C32–C27 and N7–N8–C4–N9 are 2.8(6)°, 119.4(4)°, and 169.9(4)°, respectively. The plane of C(34)–C(35)–N(7)–N(8) is nearly parallel with the phenyl ring of C(36)–C(41) and thiazole ring, forming a dihedral angle of 4.0(2)° and 10.7(2)°, respectively, while it is nearly perpendicular with the phenyl ring C(27)–C(32), forming a dihedral angle of 86.7(2)°.

The thiazole ring is planar with maximum deviations of 0.01(4) and −0.01(3) Å for the S2 and C42 atoms, respectively. The smaller bond length of the N(8)–C(42) (1.369 Å) than a typical C–N single bond(1.47–1.50 Å), [18] clearly indicates the double bond nature of the N(8)=C(42) bond due to the conjugation of N(8) with thiazole ring. The dihedral angles of thiazole plane forms with the triazole and the phenyl ring of C47–C52 are 101° and 20.7°, respectively.

Globally, the molecule has a distinctive curved conformation. In the crystal structure, there is no classic hydrogen bonds. The crystal structure is stabilized by weak C–H···N intramolecular hydrogen bonds and C–H···Cg intermolecular interactions (Table 3). The bond lengths of C(8)–H8···Cg(7), C(31)–H(31A)···Cg(8)and C(48)–H(48A)···Cg(9) correspond to 2.75, 2.65, and 2.86 Å, respectively. Additionally, the ∏–∏ stacking interactions were observed with the centroid–centroid separation of Cg(1)–Cg(8) = 5.189(2) Å, Cg(1)–Cg(10) = 5.312(3) Å, Cg(1)–Cg(12) = 4.186(3) Å, which link the two independent molecule. [Cg(1) is center of gravity of ring (S1, N3, C16, C17, C21); Cg(10) is the center of gravity of ring (C27, C28, C29, C30, C31, C32) and Cg(12) is the center of gravity of ring (C47, C48, C49, C50, C51, C52)]. The perpendicular distance between Cg(1)–Cg(8), Cg(1)–Cg(10) and Cg(1)–Cg(12) are 2.3840(16), 1.2066(14) and 3.3036(15) Å, respectively.

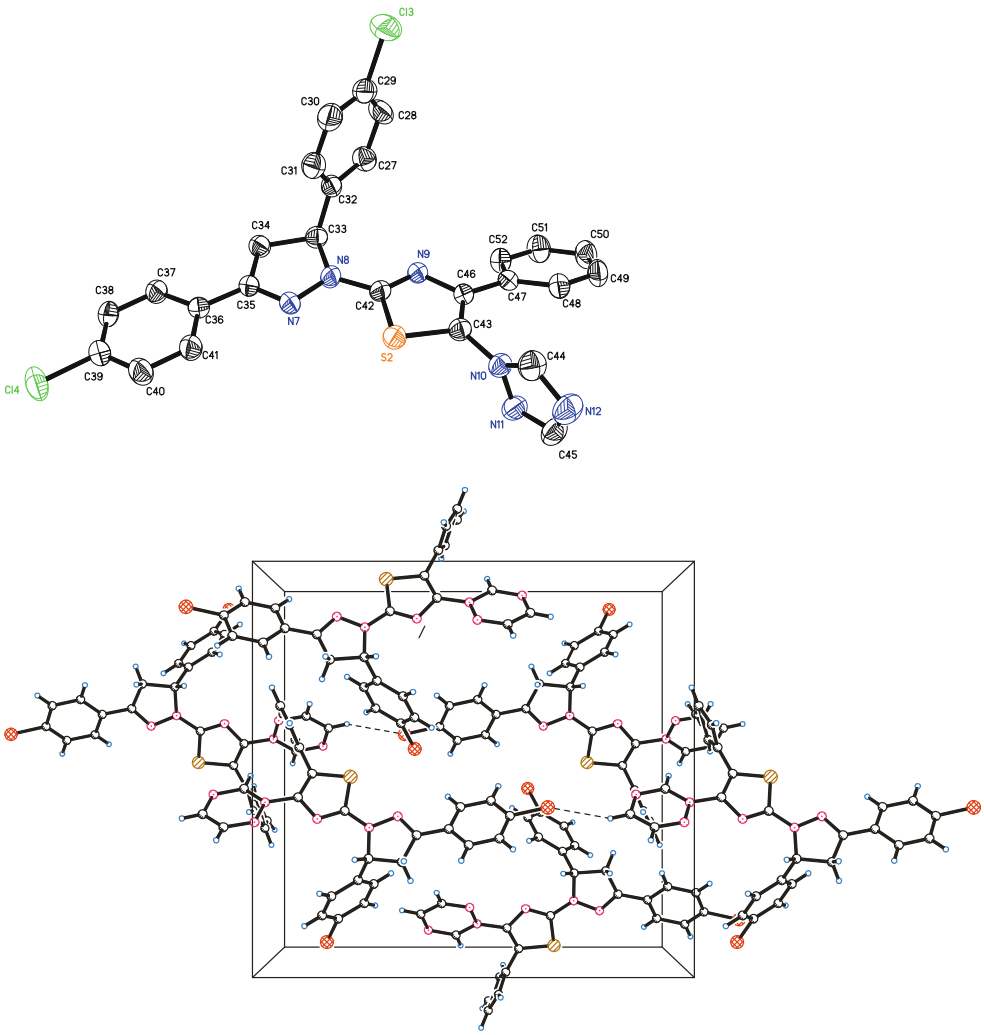


Fig. 1 ORTEP view and packing diagram of molecular structure of compound **3a**

Table 3 intra- and inter-molecular interaction

Intramolecular interactions (A°)				
D–H···A	D–H	H···A	D···A	D–H···A
C(48)–H(48A)···N(10)	0.93	2.58	3.137(5)	119
C(52)–H(52A)···N(9)	0.93	2.49	2.819(5)	101
Intermolecular interactions (A°)				
D–H···A	H···A	D···A	D–H···A	Symmetry code
C(8) –H(8B)···Cg(7)[a]	2.75	3.072(5)	133	$2 - x, 1 - y, ½ + z$
C(31)–H(31A)···Cg(8)[b]	2.65	2.818(5)	100	x, y, z
C(48)–H(48A)···Cg(9)[c]	2.86	3.558(4)	133	x, y, z

[a] Cg7 = S2–C43–C46–N9–C42

[b] Cg(8) = N7–N8–C33–C34–C35

[c] Cg9 = N10–N11–N12–C44–C45

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