**Original Research Article****DOI: 10.26479/2019.0502.72****SYNTHESIS AND CRYSTALLOGRAPHIC ANALYSIS OF 1-(2-CHLOROPHENYL)-3-METHYL-4-(P-TOLYLTHIO)-1H-PYRAZOL-5-OL**

Ronak D. Kamani¹, Rahul P. Thummar¹, Nirav H. Sapariya², Beena K. Vaghasiya¹, Jemin R Avalani³, Vishal B. Purohit³, Kirit H. Patel¹, Dipak K. Raval^{1*}

1. Department of Chemistry, Sardar Patel University, Vallabh Vidyanagar, Gujarat, India

2. Natubhai V. Patel College of Pure and Applied Sciences, Vallabh Vidyanagar, Gujarat, India

3. Shri A. N. Patel P. G. Institute of Science and Research, Anand, Gujarat, India

ABSTRACT: The synthesis of a novel tolylthiopyrazol bearing methyl has been achieved by transition metal free N-chlorosuccinimide mediated direct sulfenylation of 1-aryl pyrazolones at room temperature. The product obtained was characterized by spectroscopic techniques and finally confirmed by X-ray diffraction studies. The title compound $C_{17}H_{15}ClN_2OS$ crystallizes in Monoclinic crystal class in space group $P2_1/c$ with cell parameters $a = 9.6479(5) \text{ \AA}$, $b = 15.1233(8) \text{ \AA}$, $c = 11.4852(6) \text{ \AA}$, $\beta = 108.374(2)^\circ$, $V = 1590.4(2) \text{ \AA}^3$ and $Z = 4$. The final residual factor $R_1 = 0.0499$.

KEYWORDS: Pyrazolone, Sulfenylation, Crystal structure, Hydrogen bonding.

Corresponding Author: Dr. Dipak K. Raval* Ph.D.

Department of Chemistry, Sardar Patel University, Vallabh Vidyanagar-388120, Gujarat, India.

1. INTRODUCTION

Sulfur-containing compounds play essential role in natural products and bioactive compounds such as drugs, agrochemicals, and functional materials.[1,2,3,4] In previous years, attempts have been dedicated to develop new methods for C–S bond construction. Accordingly, novel and efficient approaches for the formation of C-S bonds is an essential issue in modern organic chemistry.

Highly efficient synthetic approach to sulfenylated pyrazoles *via* palladium,[5] iodine,[6] copper [7] and iron [8,9,10,11] catalyzed cross couplings of thiols or disulfides with aryl halides are reported. In recent years, transition metal-free syntheses for C-S bond formation *via* C-H bond sulfenylation reactions have also been intensively studied. In these transformations, various sulfenylating reagents such as aryl sulfonyl hydrazides,[12,13,14] diaryl disulfides,[15,16,17] aryl sulfonyl chlorides,[18] sulfinic acids,[19] and sodium sulfinates [20, 21] have been extensively used. Hence, directly using thiols as sulfenylation reagent appears synthetically attractive. Pyrazolones or pyrazoles have received huge attention in recent years due to their wide applications in dyes, and agrochemicals [22] The pyrazole derivatives occur in many biologically active natural and clinical products such as pyrazofurin, 4-methoxywithasomnine, and formycin,[23] crizotinib, fipronil, and celebrex,[24] respectively. The introduction of thiols into pyrazole in a regioselective fashion could enhance or alter its biological and pharmacological activity [25]. Pyrazole and its derivatives represent one of the most active classes of compounds, which exhibit broad spectrum of pharmacological activities like antimicrobial [26], anticonvulsant [27], anticancer [28], analgesic [29], anti-inflammatory [30], antitubercular [31, 32], cardiovascular [33] etc. Considering the importance of the pyrazole and thiol frameworks, together with our growing interest in sulfur-containing compounds synthesis, herein we wish to report a novel and single step reaction strategy for the construction of thiol-substituted pyrazoles C-H bond sulfenylation under transition metal free conditions (scheme 1) [34].

2. MATERIALS AND METHODS

2.1 Materials and instrumentation

All the chemicals were purchased from commercial suppliers and used without further purification. All the reactions were monitored by thin layer chromatography (TLC). ¹H NMR and ¹³C-NMR spectra were determined in DMSO-*d*₆ on Bruker Avance 400 MHz and 100 MHz spectrometer respectively and reported in δ ppm. The following abbreviations were used; s = singlet; d = doublet; t = triplet; m = multiplet; dd = doublets of doublet; J, coupling constant (Hz). IR spectra were obtained with a FTIR PerkinElmer Spectrum 100 spectrometer in KBr pellets with absorption in cm⁻¹. Melting points were measured using the capillary method on μ ThermoCa110 (Analab Scientific Pvt. Ltd.) melting point apparatus and are uncorrected. IKA RV 10 control rotary evaporator was used to remove the solvents under vacuum. X-ray diffraction crystal structure analysis was obtained on the RIGAKU SCX mini X-ray Diffractometer. All measurements were made on a Rigaku SCX mini Diffractometer using graphite monochromated Mo-K α radiation.

Structure Solution and Refinement was solved by direct methods [35] and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement [36] on F² was based on 3647 observed reflections and 199 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of: $R1 = \sum ||F_o| - |F_c|| / \sum |F_o| = 0.0499$ and $wR2 = [\sum (w(F_o^2 - F_c^2)^2) / \sum w(F_o^2)^2]^{1/2} = 0.1496$. The standard deviation of an observation of unit weight was 1.07. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.54 and -0.45 e-/Å³, respectively. Neutral atom scattering factors were taken from Cromer and Waber [37]. Anomalous dispersion effects were included in F_{calc} [38]; the values for Δf' and Δf'' were those of Creagh and McAuley [39]. The values for the mass attenuation coefficients are those of Creagh and Hubbell [40]. All calculations were performed using the Crystal Structure crystallographic software package except for refinement, which was performed using SHELXL-97 [41].

2.2 Synthesis of 1-(2-chlorophenyl)-3-methyl-4-(p-tolylthio)-1H-pyrazol-5-ol

In a round bottom flask, a mixture of aryl thiols (1.0 mmol) and N-chlorosuccinimide (NCS) (1.2 mmol) was magnetically stirred in 2 mL of dichloromethane (DCM) for 30 min. 1-aryl pyrazolones (1.0 mmol) was added to it. Stirring was continued for further 15-30 min at room temperature and the reaction was monitored by TLC. After completion, the reaction mixture was poured into 20 mL of saturated sodium bicarbonate solution and extracted with dichloromethane. The remaining organic phase was dried with anhydrous Na₂SO₄ and the solvent was distilled off under reduced pressure. The resulting residues were purified by a simple wash with n-hexane to afford the target products. The method employed for synthesis is shown in Scheme 1.

FT-IR (KBr): 3341 (-OH stretching), 3025 (C-H stretching, Asymmetric), 2935 (C-H stretching, symmetric), 1587, 1480, 1329, 1319, 1229, 1156, 1127, 1012, 831, 710 (C-S stretching) cm⁻¹.

¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 2.09 (s, 3H), 2.23 (s, 3H), 6.98 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.46-7.56 (m, 3H), 7.66 (dd, *J* = 7.6 Hz; 1.6 Hz, 1H), 11.09 (s, 1H).

¹³C NMR DEPT-135 (100 MHz, DMSO-*d*₆) δ (ppm): 136.0, 130.6, 130.3, 130.2, 130.1, 129.6, 127.9, 124.9, 20.3, 12.34.

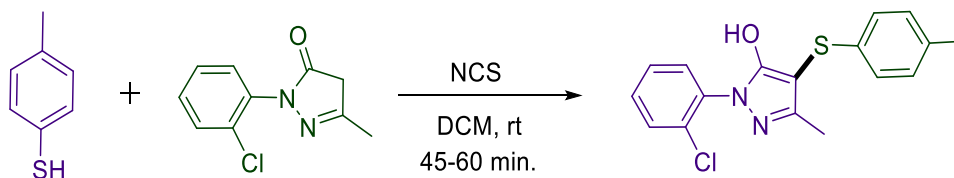
MS (m/z): 330.83

2.3 Method of Crystallization

The pure 1-(2-chlorophenyl)-3-methyl-4-(p-tolylthio)-1H-pyrazol-5-ol (0.12 g) was dissolved in 20 mL of ethyl acetate. The resulting solution was warmed with charcoal on a water bath and 1–3

drops of DMF were added to the solution. The solution was filtered while hot through Whatmann 2 filter paper. The solution was kept in a stopper conical flask slightly opened. Crystals grew after 8-10 days due to thin layer evaporation. They were filtered and washed with chilled n-hexane.

3. RESULTS AND DISCUSSION



Scheme 1: Synthetic protocol for 1-(2-chlorophenyl)-3-methyl-4-(p-tolylthio)-1H-pyrazol-5-ol

Table 1. Crystal Data and structure refinement

Empirical Formula	C ₁₇ H ₁₅ ClN ₂ OS
Formula Weight	330.83
Temperature	20 ± 1 °C
Space group	P2 ₁ /c
Crystal Color, Habit	Colorless, block
Crystal Dimensions	0.540 X 0.490 X 0.320 mm
Crystal System	Monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 9.6479(5) Å b = 15.1233(8) Å c = 11.4852(6) Å β = 108.374(2)°
Volume	1590.4(2) Å ³
Space Group	P2 ₁ /c (#14)
Z	4
Density (calculated)	1.382 g/cm ³
F ₀₀₀	688.00
Reflections collected	15922
Independent reflections	3647 were unique (R _{int} = 0.0238)
Refinement method	Full-matrix least-squares on F ²
Theta range for data collection	2.0°-55.0°
μ (MoKα)	3.735 cm ⁻¹
Reflections/variables	3647/199
Reflection ratio	18.33
Final R indices [I>2.00σ(I)]	Final R indices [I>2.00σ(I)]
0.0499 (R _I)	0.0499 (R _I)
R indices (all data)	R indices (all data)
R=0.0570 and wR ₂ =0.01496	R=0.0570 and wR ₂ =0.01496
Largest diff. peak and hole	0.540 and -0.450 e Å ⁻³

A colorless block crystal of $C_{17}H_{15}ClN_2OS$ having approximate dimensions of 0.540 x 0.490 x 0.320 mm was mounted on a glass fiber. The data were collected at a temperature of $20 \pm 1^\circ\text{C}$ to a maximum 2θ value of 55.0° . The crystal-to-detector distance was 52.00 mm and readout was performed in the 0.146 mm pixel mode given the total of 540 oscillation images and its collection. A sweep of data was done using ω oscillations from -120.0 to 60.0° in 1.0° steps, in which the exposure rate and detector swing angle was 8.0 [sec./ $^\circ$], -30.80° respectively. Data were collected and processed using Crystal-clear (Rigaku), In which the total 15922 reflections were collected, out of them 3647 were unique ($R_{\text{int}} = 0.0238$) and equivalent reflections. The linear absorption coefficient, μ , for Mo-K α radiation is 3.735 cm^{-1} . Empirical absorption correction was applied which resulted in transmission factors ranging from 0.700 to 0.887. The details of crystal data and refinement are given in Table 1.

Table 2. Bond lengths (Å) and Bond angles ($^\circ$)

Bond lengths (Å)		Bond angles ($^\circ$)			
Atom	Distance	Atom	Angle	Atom	Angle
C11-C12	1.725(3)	C2-S1-C4	101.97(10)	C2-S1-C4	101.97(10)
S1-C4	1.786(3)	N2-N1-C11	121.23(17)	N2-N1-C11	121.23(17)
N1-N2	1.380(3)	N1-N2-C1	108.37(17)	N1-N2-C1	108.37(17)
N1-C11	1.422(3)	N2-C1-C21	120.7(2)	N2-C1-C2	109.48(19)
C1-C2	1.381(4)	S1-C2-C1	127.60(17)	C2-C1-C21	129.80(19)
C2-C3	1.423(3)	C1-C2-C3	107.57(17)	S1-C2-C3	124.59(17)
C4-C9	1.388(4)	O1-C3-C2	133.12(19)	O1-C3-N1	121.96(19)
C6-C7	1.387(5)	S1-C4-C5	118.15(19)	N1-C3-C2	104.91(19)
C7-C10	1.510(5)	C5-C4-C9	118.8(2)	S1-C4-C9	123.08(16)
C11-C12	1.389(3)	C5-C6-C7	121.5(3)	C4-C5-C6	120.2(3)
C12-C13	1.387(4)	C6-C7-C10	121.8(3)	C6-C7-C8	117.6(3)
C14-C15	1.371(4)	C7-C8-C9	121.5(3)	C8-C7-C10	120.6(3)
S1-C2	1.7406(19)	N1-C11-C12	120.84(17)	C4-C9-C8	120.4(3)
O1-C3	1.251(3)	C12-C11-C16	119.72(19)	N1-C11-C16	119.42(19)
N1-C3	1.380(3)	C11-C12-C13	119.53(18)	C11-C12-C11	120.64(17)
N2-C1	1.327(3)	C12-C13-C14	119.9(3)	C11-C12-C13	119.8(2)
C1-C21	1.487(4)	C14-C15-C16	120.4(3)	C13-C14-C15	120.5(3)
C4-C5	1.388(3)	N2-N1-C3	109.66(17)	C11-C16-C15	119.7(3)
C5-C6	1.387(4)	C3-N1-C11	127.43(19)	N2-C1-C2	109.48(19)
C7-C8	1.387(4)	N2-C1-C21	120.7(2)	C2-C1-C21	129.80(19)
C8-C9	1.383(4)	O1-C3-N1	121.96(19)	S1-C2-C3	124.59(17)
C11-C16	1.379(3)	N1-C3-C2	104.91(19)		
C13-C14	1.365(4)				
C15-C16	1.383(4)				

Cell constants and an orientation matrix for data collection corresponded to a primitive monoclinic cell with dimensions: $a = 9.6479(5) \text{ \AA}$, $b = 15.1233(8) \text{ \AA}$, $c = 11.4852(6) \text{ \AA}$, $\beta = 108.374(2)^\circ$, Volume = $1590.4(2) \text{ \AA}^3$, $Z = 4$, F.W. = 330.83 and the calculated density is 1.382 g/cm^3 . The reflection conditions $h0l: l = 2n$ and $0k0: k = 2n$ uniquely determine the space group to be: $P2_1/c$ (#14). The value of bond angles and bond lengths were described in Table 2. In which, the C–S and C–O bond distances 1.740 \AA and 1.251 \AA are in good agreement with literature values of 1.744 \AA [42] and 1.255 \AA [43], respectively. The C–S bond length and bond angle of C2–S1–C4 (101.97°) also confirmed the bond formation of C2–S1–C4 (Table 2).

Table 3. Torsion Angles ($^\circ$)

Atom 1	Atom 2	Atom 3	Atom 4	Torsion angle	Atom 1	Atom 2	Atom 3	Atom 4	Torsion angle
C2	S1	C4	C5	-165.36(17)	C2	S1	C4	C9	14.1(3)
C4	S1	C2	C1	-98.32(18)	C4	S1	C2	C3	75.27(19)
N2	N1	C3	O1	-179.68(18)	N2	N1	C3	C2	0.9(2)
C3	N1	N2	C1	-1.4(2)	N2	N1	C11	C12	99.0(2)
N2	N1	C11	C16	-82.4(3)	C11	N1	N2	C1	-167.65(16)
C3	N1	C11	C12	-64.7(4)	C3	N1	C11	C16	114.0(3)
C11	N1	C3	O1	-14.5(4)	C11	N1	C3	C2	166.07(19)
N1	N2	C1	C2	1.3(3)	N1	N2	C1	C21	-178.11(15)
N2	C1	C2	S1	173.71(16)	N2	C1	C2	C3	-0.8(3)
C21	C1	C2	S1	-6.9(4)	C21	C1	C2	C3	178.6(2)
S1	C2	C3	O1	5.9(4)	S1	C2	C3	N1	-174.76(14)
C1	C2	C3	O1	-179.4(3)	C1	C2	C3	N1	-0.1(3)
S1	C4	C5	C6	-179.58(17)	S1	C4	C9	C8	-179.11(17)
C5	C4	C9	C8	0.3(4)	C9	C4	C5	C6	1.0(4)
C4	C5	C6	C7	-1.3(5)	C5	C6	C7	C8	0.2(5)
C5	C6	C7	C10	-179.9(3)	C6	C7	C8	C9	1.1(5)
C10	C7	C8	C9	-178.8(3)	C7	C8	C9	C4	-1.4(5)
N1	C11	C12	C11	-2.6(4)	N1	C11	C12	C13	176.77(19)
N1	C11	C16	C15	-177.3(2)	C12	C11	C16	C15	1.3(4)
C16	C11	C12	C11	178.8(2)	C16	C11	C12	C13	-1.9(4)
C11	C12	C13	C14	-179.71(19)	C11	C12	C13	C14	0.9(4)
C12	C13	C14	C15	0.6(5)	C13	C14	C15	C16	-1.1(5)
C14	C15	C16	C11	0.1(5)					

In the title compound the pyrazole ring shows the pentagonal-planer conformation with perpendicular to the phenyl rings was also confirmed by the value of torsion angle between the atoms of C3–N1–N2–C1 = $-1.4(2)^\circ$, N1–N2–C1–C2 = $1.3(3)^\circ$, N2–N1–C3–C2 = $0.9(2)^\circ$, N2–C1–C2–C3 = $-0.8(3)^\circ$ and C1–C2–C3–N1 = $-0.1(3)^\circ$ (Table 3). The torsion angle about C2–S1–C4–C5 being $-165.36(17)^\circ$ and that about N1–C11–C12–C13 is $176.77(3)^\circ$ shows anti-periplanar conformation.

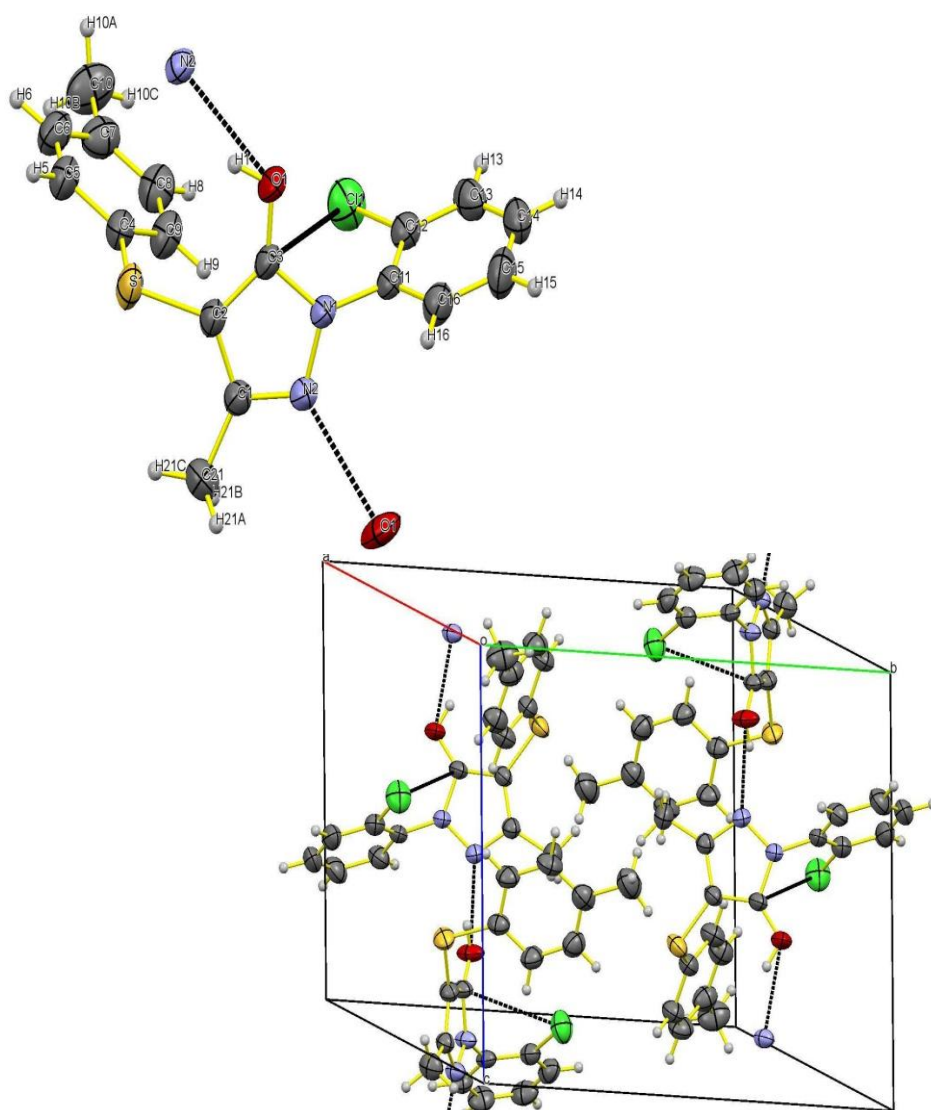
The atoms C3–N1–C11–C12 and C1–C2–S1–C4 gives syn-clinal conformation with a value of $-64.7(4)^\circ$ and $-98.32(18)^\circ$, respectively. Subsequent refinements were carried out with equivalent thermal parameters for non-hydrogen atoms and isotropic temperature factors for the hydrogen atoms which were placed at chemically acceptable positions. The hydrogen atoms were allowed to ride on their parent atoms (Table 4).

Table 4. Atomic coordinates and equivalent thermal parameters of the non-hydrogen atoms

Atom	x	y	z	Beq
C11	0.66727(7)	0.05292(5)	0.47096(7)	5.05(2)
S1	0.59025(7)	0.36797(4)	0.27472(5)	3.72(2)
O1	0.8377(2)	0.2085(1)	0.3446(2)	4.18(4)
N1	0.8345(2)	0.2229(1)	0.5432(2)	2.96(3)
N2	0.7647(2)	0.2753(1)	0.6058(2)	2.89(3)
C1	0.6806(3)	0.3326(2)	0.5273(2)	2.84(4)
C2	0.6908(3)	0.3178(2)	0.4117(2)	2.97(4)
C3	0.7903(3)	0.2467(2)	0.4210(2)	2.92(4)
C4	0.4520(3)	0.2873(2)	0.2103(2)	3.32(4)
C5	0.3707(3)	0.2952(2)	0.0873(2)	3.92(5)
C6	0.2616(3)	0.2345(2)	0.0335(3)	4.51(6)
C7	0.2325(3)	0.1639(2)	0.0994(3)	4.32(5)
C8	0.3162(3)	0.1561(2)	0.2217(3)	4.31(5)
C9	0.4234(3)	0.2171(2)	0.2771(3)	3.98(5)
C10	0.1140(4)	0.0974(3)	0.0413(4)	6.03(7)
C11	0.9096(3)	0.1447(2)	0.5966(2)	2.75(4)
C12	0.8443(3)	0.0623(2)	0.5678(2)	3.19(4)
C13	0.9223(3)	-0.0135(2)	0.6163(3)	4.00(5)
C14	1.0622(4)	-0.0066(2)	0.6934(3)	4.44(5)
C15	1.1260(3)	0.0747(2)	0.7243(3)	4.57(6)
C16	1.0502(3)	0.1508(2)	0.6761(2)	3.70(4)
C21	0.5948(3)	0.4000(2)	0.5694(3)	4.12(5)

$$B_{eq} = 8/3 \pi^2 (U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha)$$

The ORTEP of the molecule with thermal ellipsoids drawn at 50% probability is shown in Fig. 2. The structure exhibits inter-molecular hydrogen bonds of the type O–H-----N. O1–H1-----N2 has a length of 2.619(3) Å with an angle of 148.64° along with the symmetry codes X, -Y+1/2, Z+1/2-1 respectively (Fig. 1). The stability of the crystal structure can be accounted for by these hydrogen bonds.



Possible hydrogen bonds (Å):

Donor	H	Acceptor			
O1	H1	N2 ¹			
D----	A	D-H	H---A	D-H---	A
2.619(3)	0.82	1.88	148.64		

Symmetry Operators:

$X, -Y+1/2, Z+1/2-1$

Figure 1: Possible hydrogen bonds, Symmetry Operators and crystal packing arrangement view along the b-axis showing N-H---O hydrogen bonds.

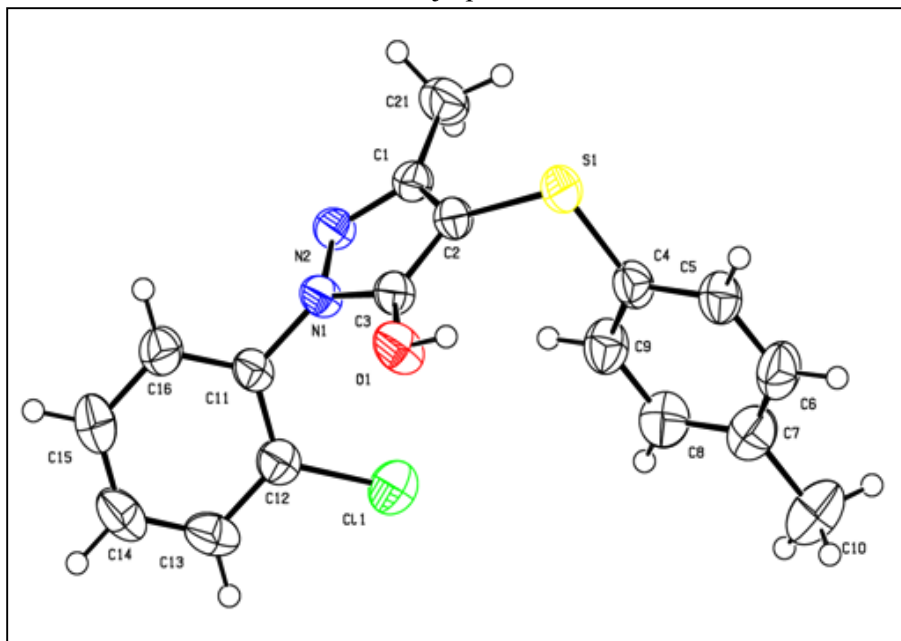


Figure 2. ORTEP diagram with thermal ellipsoids drawn at 50% probability (CCDC: 1561633)

4. CONCLUSION

In conclusion, we have developed an efficient and simple protocol for the synthesis of N-chlorosuccinimide mediated sulfenylated pyrazoles at room temperature. N-chlorosuccinimide was demonstrated to facilitate this transformation possibly by generating more reactive phenyl hypochlorothioite in situ from thiophenols. The synthesized product was characterized by spectroscopic techniques and X-ray diffraction studies. The X-ray studies shows that the inter-molecular hydrogen bonding of the type O-H-----N and the pyrazole ring gives pentagonal-planer conformation perpendicular to the phenyl rings.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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