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Metal- and oxidant-free highly regioselective synthesis and structure analysis of 3-methyl-1-phenyl-4-(*p*-tolylthio)-1*H*-pyrazol-5-amine

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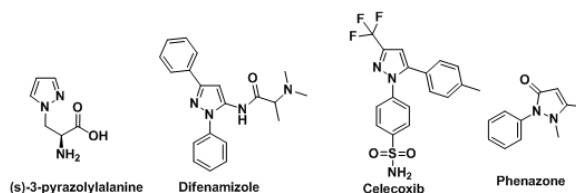
Abstract: 3-Methyl-1-phenyl-4-(*p*-tolylthio)-1*H*-pyrazol-5-amine was synthesized by reacting 3-methyl-1-phenyl-1*H*-pyrazol-5-amine and 4-methylthiophenol in the presence of *N*-chlorosuccinimide mediated sulfenylation. A highly chemoselective C⁴ sulfenylation of pyrazole delivered in excellent yield (95%). The target compound was characterized by spectroscopic techniques and confirmed by X-ray crystallographic studies. The crystallographic analysis suggests that the title compound crystallizes in the monoclinic space group P21/c (#14) with cell parameters $a = 12.466(2) \text{ \AA}$, $b = 5.9276(9) \text{ \AA}$, $c = 21.389(3) \text{ \AA}$, $\beta = 101.530(4)^\circ$, $V = 1548.6(4) \text{ \AA}^3$ for $Z = 4$. The structure has been confirmed by direct methods and refined to $R1 = 0.0495$ for 3,543 observed reflections and 190 variable parameters and converged.

Keywords: Metal-free, oxidant-free, chemoselective, X-Ray analysis, pyrazole

Introduction

Pyrazole skeleton, a diverse class of natural products [1], possess are well known to exhibit a wide range of biological properties, such as anti-inflammatory [2-3] antimicrobial [4] antioxidant [5] anticancer [6] antiviral [7] and Hepatitis C virus [8]. Pyrazole derivatives can be utilized as immuno modulators and for the prophylaxis and treatment of different diseases of diabetes, psoriasis, connective tissues, ulcerous colitis anti-viral and chronic hepatitis. Pyrazole ring containing natural products and

drug like skeleton consisting, for example (*S*)-3-pyrazolyl alanine, Difenamizole, Celecoxib and Phenazone have therapeutic potentials.



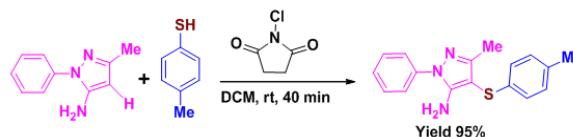
In continuation of the search for such potent molecules and as a part of our ongoing research, we planned to synthesize the hybrid

structure consisting the lipophilic functionality on the pyrazole ring. We have introduced sulfur substitution at the C⁴ via electrophilic substitution reaction in pyrazole nucleus [9-11]. We have also reported the synthesis of chromeno-pyrazoles in the presence of Zn[L-Proline]₂ catalyst via microwave-assisted strategy [12]. We herein describe a one-step method of sulfenylation of 5-amino pyrazole using *in situ* generated sulfenyl chlorides from a 4-methylthiophenol using *N*-chlorosuccinimide proceeded at ambient-temperature with an excellent yield. The current work highlights the synthesis as well as the crystallographic studies of the therapeutically important pyrazoles motif. The structure of the title compound was confirmed by FTIR, ¹H-NMR, ¹³C-NMR and X-ray crystallography.

Preparation and General Characterization

The melting point was determined in an open capillary melting point apparatus. The IR was recorded on Shimadzu FTIR-8400 spectrometer (KBr Pellet method, 400–4000 cm⁻¹). ¹H and ¹³C NMR spectrum was recorded on a Bruker AC 400 MHz using TMS as an internal standard and DMSO-*d*₆ as solvent (chemical shifts are in ppm and coupling constant (*J*) in Hz). Mass spectrum was obtained using a Jeol SX 102/DA-6000 spectrometer (for FAB). Differential-Scanning Calorimetry (DSC) experiments were performed on a Pyris 1 (PerkinElmer) differential scanning calorimeter with an attached intercooler. The DSC was calibrated using indium and leads celebrants'. Samples were analyzed in closed aluminum pans under a dry nitrogen atmosphere (35 mL/min) and heated between from 25 °C up to 600 °C at heating rate of 10 °C/min (114.27 °C). TLC was performed on 0.25 mm pre-coated silica gel plates (Merck 60 F254) by using ethyl acetate/hexane (1:9) as the eluents.

Scheme 1 Preparation of 3-methyl-1-phenyl-4-(*p*-tolylthio)-1*H*-pyrazol-5-amine



Under ambient temperature, a solution of *N*-chlorosuccinimide (**3**) (2.0 g, 15 mmol) and 4-methylthiophenol (**2**) (1.87 g, 15 mmol) was stirred in dichloromethane (15 mL) for 20 min. 3-Methyl-1-phenyl-1*H*-pyrazol-5-amine (**1**) (1.73 g, 10.0 mmol) was added under inert atmosphere and the reaction mixture was stirred for 20 min at same temperature. After completion of reaction as indicated by TLC, the mixture was quenched with sat. NaHCO₃ solution and the product were extracted with dichloromethane (20 mL × 2). The combined organic layer was washed with water (20 mL × 2) and brine (10 mL × 1) and dried with anhydrous Na₂SO₄. The solvent was removed at reduced pressure to leave the crude product which was purified by silica-gel column chromatography eluting with (EtOAc/Hexane, 1/9) yielded 3-methyl-1-phenyl-4-(*p*-tolylthio)-1*H*-pyrazol-5-amine (**4**) (2.75 g, 95%) as yellow solid, m. p. 112-114 °C.

Spectral data of 3-methyl-1-phenyl-4-(*p*-tolylthio)-1*H*-pyrazol-5-amine (**4**)

IR (KBr, cm⁻¹): 3302.13br(v (NH₂)), 3155.54s(v (CH, alkynes (terminal))), 1897.95v, 1805.37br, 1620.21s, 1489.05br, 1018.41br, 702.09 br, 532.35s, 432.05s.

¹H NMR (400 MHz, DMSO-*d*₆): δ 2.05 (3H, s), 2.22-2.27 (3H, d, *J* = 18 Hz), 5.64 (2H, s), 6.96-6.98 (2H, d, *J* = 8.16 Hz), 7.08-7.10 (2H, d, *J* = 8.40 Hz), 7.31-7.35 (1H, t, *J* = 7.40 Hz), 7.47-7.51 (2H, t, *J* = 8.24 Hz), 7.59-7.61 (2H, m).

¹³C NMR (100 MHz, DMSO-*d*₆): δ 12.1, 20.4, 86.2, 122.7, 125.2, 126.4, 129.2, 129.6, 134.2, 135.0 139.0, 150.0, 151.5.

In DEPT-90 ¹³C experiments, all the carbons exhibited upward (+ve) signals indicating the presence of only -CH₃ carbons. As there was no

downward (-ve) signal in DEPT 90.

EI-MS (*m/z*): 295.

Crystal Structure Determination and Refinements

A yellow prism crystal of $C_{17}H_{15}N_3S$ having approximate dimensions of $0.790 \times 0.420 \times 0.300$ mm was mounted on a glass fiber. All measurements were made on a Rigaku SCX mini diffractometer using graphite monochromated Mo-K α radiation. The crystal to detector distance is fixed at 52 mm with a detector. The data were collected at a temperature of $20 \pm 1^\circ\text{C}$ to a maximum 2θ value of 55.0° . A total of 540 oscillation images were collected. A sweep of data was done using ω oscillations from -120.0 to 60.0° in 1.0° steps. The exposure rate was 10.0 [sec./ $^\circ$]. The detector swing angle was -30.80° . A second sweep was performed using ω oscillations from -120.0 to 60.0° in 1.0° steps. The exposure rate was 10.0 [sec./ $^\circ$]. The detector swing angle was -30.80° . Another sweep was performed using ω oscillations from -120.0 to 60.0° in 1.0° steps. The exposure rate was 10.0 [sec./ $^\circ$]. The detector swing angle was -30.80° . The crystal-to-detector distance was 52.00 mm. Readout was performed in the 0.146 mm pixel mode.

Data Reduction of the 14636 reflections that were collected, 3543 were unique ($R_{\text{int}} = 0.0273$), equivalent reflections were merged. Data were collected and processed using Crystal Clear [13]. The linear absorption coefficient μ , for Mo K α radiation is 2.054 cm^{-1} . An empirical absorption correction was applied which resulted in transmission factors ranging from 0.747 to 0.940. The data were corrected for Lorentz and polarization effects. Structure Solution and Refinement, The structure was solved by direct methods [14] 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 [15] on F^2 was based on 3543 observed reflections and

190 variable parameters and converged. The standard deviation of an observation of unit weight [16] was 1.03. Unit weights were used. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.30 and $-0.34\text{ e}^-/\text{\AA}^3$, respectively. Neutral atom scattering factors were taken from Cromer and Waber [17]. Anomalous dispersion effects were included in F Calculation [18] the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley [19]. The values for the mass attenuation coefficients are those of Creagh and Hubbell [20]. All calculations were performed using the CrystalStructure [21]. Crystallographic software package except for refinement, which was performed using SHELXL-97 [22]

Results and Discussion

The crystals of 4 crystallize in monoclinic space group P21/c (#14). The bond lengths and bond angles in all the compounds are in excellent agreement with the expected values for the corresponding dimensions selected bond distances and angles have been listed in Table 2 and Table-3. The X-ray crystal structure determination shows that the interatomic distances 1.735(2) Å for S1-C8 is near to that of a typical Aromatic C-S bond (1.741). The bond length for 1.376(3) Å for C7-C8 and 1.412(3) Å for C8-C9 are near to that of a typical C-C Aromatic double bond (1.34). The bond angles for N1-C1-C2, C2-C1-C6 N2-C9 -C10 which illustrate that $120.01(17)^\circ$, $120.02(19)^\circ$, $121.66(18)^\circ$ C1, C2, C6, C9, N1, N2 all adopt sp^2 hybrid orbit to form C=C and C=N double bonds. The bond angles for C8-S1-C11 is $103.63(10)^\circ$ which illustrate that C8, S1, C11 all adopt sp^2 hybrid orbit to form C-S-C Single bond. In this molecule N1-C7-C8-C9-N2 of the pyrazole core is planar. A study of torsion angles of C8/S1/C11/C12 is $170.84(12)^\circ$.

Table 1 Crystal data and Structure Refinement Table

CCDC Deposition Number	CCDC 1054817
Empirical Formula	$C_{17}H_{15}N_3S$
Formula Weight	293.39

Crystal Color, Habit	yellow, prism	Ω oscillation Range	-120.0 - 60.0°
Crystal Dimensions	0.790 × 0.420 × 0.300 mm	Exposure Rate	10.0 sec./°
Crystal System	monoclinic	Detector Swing Angle	-30.80°
Lattice Type	Primitive	Detector Position	52.00 mm
Lattice Parameters	a = 12.466(2) Å b = 5.9276(9) Å c = 21.389(3) Å β = 101.530(4) Å V = 1548.6(4) Å ³	Pixel Size	0.146 mm
Space Group	P2 ₁ /c (#14)	2 Φ max	55.0o
Z value	4	No. of Reflections	Total: 14636
D _{calc}	1.258 g/cm ³	Measured	Unique: 3543 (R _{int} = 0.0273)
F ₀₀₀	616.00	Corrections	Lorentz-polarization
μ (MoK α)	2.054 cm ⁻¹		Absorption
Diffractometer	SCX mini	R indices	(trans. factors: 0.747 - 0.940)
		Largest diff. peak and hole(e. Å ⁻³)	0.0495, 0.1484
		Goodness of Fit	0.30, -0.34
Radiation	MoK α (λ = 0.71075 Å) graphite monochromated		1.030

Table 2 Bond Lengths (Å)

	Atom	Atom	Distance	Atom	Atom	Distance
Voltage, Current	S1	C8	1.735(2)	S1	C11	1.779(2)
Temperature	N1	N2	1.387(2)	N1	C1	1.416(3)
Detector Aperture	N1	C7	1.351(3)	N2	C9	1.317(3)
	N3	C7	1.376(3)	C1	C2	1.385(3)
Data Images	C1	C6	1.379(3)	C2	C3	1.380(3)
Ω oscillation Range	C3	C4	1.372(4)	C4	C5	1.371(4)
Exposure Rate	C5	C6	1.383(4)	C7	C8	1.376(3)
Detector Swing Angle	C8	C9	1.412(3)	C9	C10	1.487(4)
Ω oscillation Range	C11	C12	1.393(3)	C11	C16	1.382(3)
Exposure Rate	C12	C13	1.375(3)	C13	C14	1.381(3)
Detector Swing Angle	C14	C15	1.391(3)	C14	C17	1.505(4)
	C15	C16	1.378(3)			

Table 3 Bond angles (°)

Atom	Atom	Atom	Angle	Atom	Atom	Atom	Angle
C8	S1	C11	103.63(10)	N2	N1	C1	120.21(15)
N2	N1	C7	111.58(16)	C1	N1	C7	128.01(15)
N1	N2	C9	104.56(15)	N1	C1	C2	120.01(17)
N1	C1	C6	119.95(18)	C2	C1	C6	120.02(19)
C1	C2	C3	119.72(19)	C2	C3	C4	120.2(3)
C3	C4	C5	120.0(3)	C4	C5	C6	120.4(3)
C1	C6	C5	119.5(2)	N1	C7	N3	123.17(17)
N1	C7	C8	106.83(15)	N3	C7	C8	129.95(17)
S1	C8	C7	125.61(14)	S1	C8	C9	129.16(16)
C7	C8	C9	105.22(17)	N2	C9	C8	111.79(17)
N2	C9	C10	121.66(18)	C8	C9	C10	126.5(2)
S1	C11	C12	117.61(15)	S1	C11	C16	123.53(16)
C12	C11	C16	118.85(19)	C11	C12	C13	120.11(18)
C12	C13	C14	121.89(19)	C13	C14	C15	117.2(2)
C13	C14	C17	121.74(19)	C15	C14	C17	121.06(19)
C14	C15	C16	121.87(19)	C11	C16	C15	120.02(19)

Table 2 and Table 3 give the list of Bond Lengths and Bond Angles of non-hydrogen atoms, respectively. The bond lengths and bond angles are in excellent conformity with the standard values. Fig. 1 represents the ORTEP of the molecule with thermal ellipsoids drawn at 50% probability. Fig. 2 depicts the packing of the molecules when viewed down the b axis.

Fig. 1 ORTEP diagram of the molecule with thermal ellipsoids drawn at 50% probability

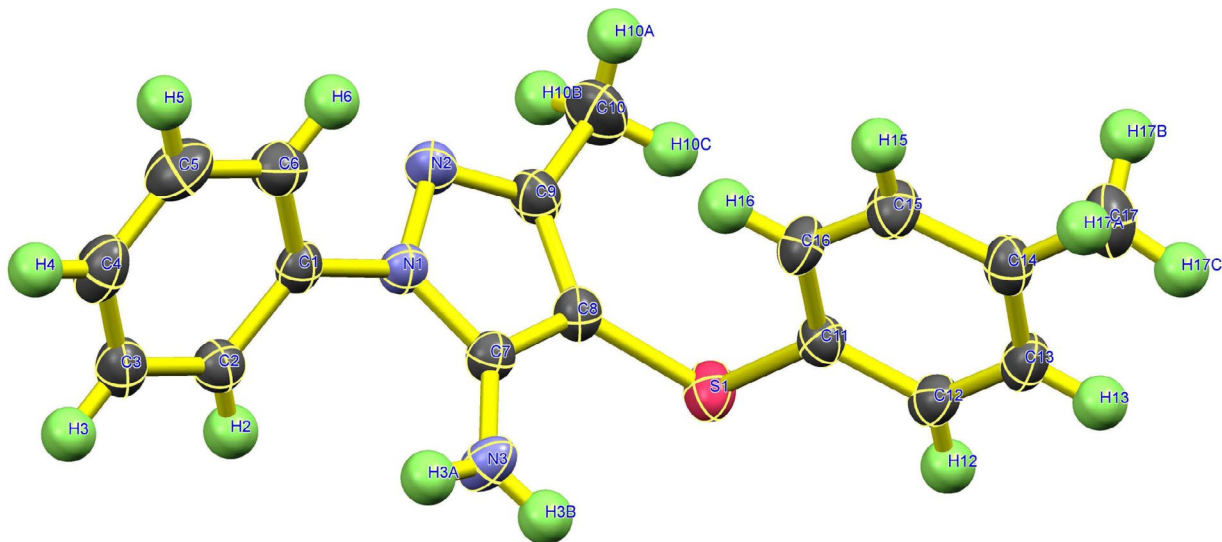


Fig. 2 Packing diagram of the molecules when viewed down the b axis. The dashed lines represent the hydrogen bonds

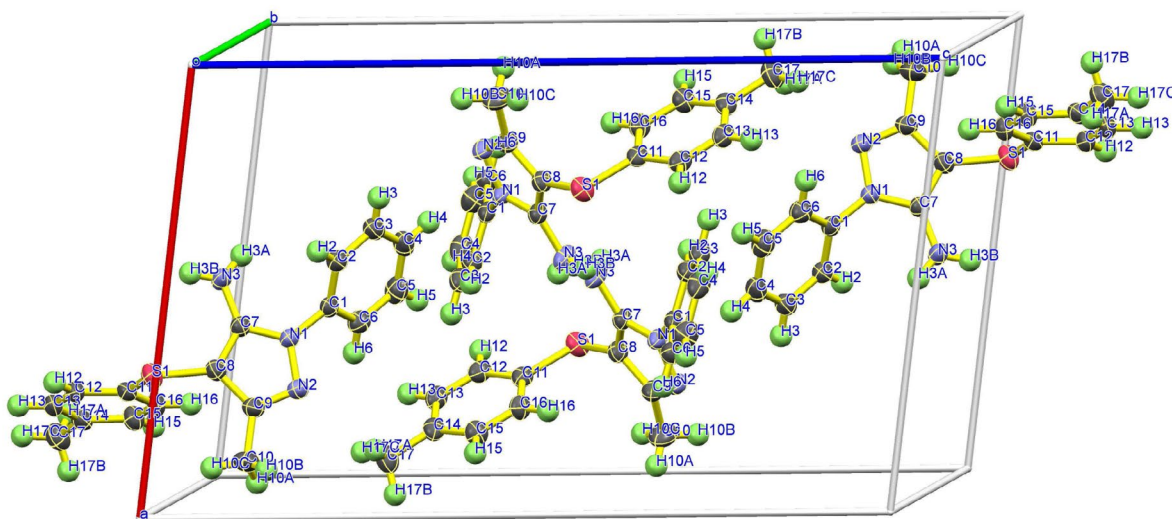


Table 4 Hydrogen-bonding geometry ($\text{\AA}$ $^\circ$)

Donor	H	Acceptor	D...A	D-H	H...A	D-H...A	Symmetry Codes
N3	H3A	N3 ¹	3.098(3)	0.86	2.42	135.92	-X+1,-Y,-Z+2

*The D–H and H–A distances are essentially standard values and are not derived from the experiment.

However, intermolecular hydrogen bonds N3–H3A–N3¹ this order is likely the cause of the apparent short H...H contacts involving the 5-amino pyrazole ring.

Supplementary Material

Crystallographic data for the structure analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. for crystal of 3-Methyl-1-phenyl-4-(*p*-tolylthio)-1*H*-pyrazol-5-amine (**4**) is **1054817**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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