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Single-crystal X-ray diffraction study of novel pyrazole chalcone derived from 1-phenyl-3-*p*-tolyl-1*H*-pyrazole-4-carbaldehyde

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Novel pyrazole chalcone has been synthesized by reaction of phenyl-3-*p*-tolyl-1*H*-pyrazole-4-carbaldehyde and acetophenone by Claisen-Schmidt reaction in ethanol by microwave assisted method. It has been characterized by elemental analysis and spectroscopic (FTIR, ^{1}H NMR and MS) studies. Crystal structure of the compound has been determined using single-crystal X-ray diffraction. Hydrogen-bonded chain is formed by C–H···O bonding enhanced by C–H···π interaction. Adjacent chains are connected through the π···π interactions.

Keywords: Microwave assisted pyrazole carbaldehyde, chalcone, acetophenone, single-crystal study

Chalcones represent an important class of molecules. It shows presence of an electron donor and electron acceptor group. Phenyl substituents are electron donors, whereas carbonyl groups act as electron acceptors. The aromatic ketone group and enone group in chalcones makes it more active. Chalcones are useful for the preparation of biologically and industrially important compounds[1]. They are found abundantly in edible plants of species *Leguminosae*, *Asteraceae*, *Moraceae*, *etc*.[2] Chalcones comprise of a class of compounds with important therapeutic and pharmacological potential. It's easy preparation and great potential of oral administration[3] support the feasibility of chalcone-based compounds as therapeutic agents. Chalcone and its derivatives show diverse medicinal properties including anti-inflammatory[4], immunomodulatory[5], anticancer[6], anti-HIV[7], antiproliferative[8], and α-glucosidase inhibitory activities[9]. Some pyrazole derivatives show antiviral activity against *Herpes* infections[10]. Chalcones are also used as precursors in the biosynthesis of flavonoids[11] and isoflavonoids[12].

Experimental Section

Material and Method

All the starting materials and solvents were purchased from commercial sources and were used without further purification. Microwave oven of SAMSUNG, 800W output with digital timer and clock was used for synthesis. Melting points were determined in open capillaries using Electro thermal melting point apparatus and are uncorrected. Progress of reactions was monitored by TLC. Infrared (IR) spectra (4000–600 cm^{-1}) of the samples were recorded using a Perkin–Elmer Spectrum 100, equipped with a Specac Golden Gate Diamond ATR as a solid sample support. ^{1}H NMR spectra were recorded with a BrukerAvance III 500 NMR spectrometer with TMS as internal reference. MS spectra were recorded with an Agilent 6624 Accurate Mass TOF LC/MS instrument (ESI ionization). Elemental (C, H, N) analyses were obtained using Perkin–Elmer 2400 Series II CHNS/O Elemental Analyzer.

Synthesis of 1-phenyl-3-*p*-tolyl-1*H*-pyrazole-4-carbaldehyde, 3:

A mixture of 4-methylacetophenone **1** (1.34 g, 10.0 mmol), phenylhydrazine (1.08 g, 10.0 mmol), 1 drop of conc. HCl and ethanol as a solvent was taken in a 100 mL conical flask and irradiated in microwave oven for 10-20 s at 450 watt at an interval of 5 second each. The resultant dry solid **2** was dissolved in excess of DMF, followed by addition of 15 mmol of $POCl_3$ with continuous stirring in cold condition at about 8° to 10°C. The reaction mixture was allowed to attain RT and heated at about 80°C for 1 h conventionally. On hydrolysis it gave off white colored solid. The solid obtained was washed with water to remove excess of HCl, filtered, dried and recrystallized using ethanol. The recrystallized

compound was kept for crystal growth by slow evaporation of saturated solution of compound in mixture of ethanol and chloroform (1:1 v/v) in a dark chamber at low temperature[13]. Yield 89%. m.p.100°C. IR: 3125 (Ar-CH), 2838 (C–H in CHO), 1673 (C=O), 1518 (C=N), 1450 cm^{-1} (C=C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.36 (s, 3H, Ar-CH_3), 7.23-7.25 (d, 2H, Ar-H), 7.30-7.33 (t, 1H, Ar-H), 7.42-7.45 (t, 2H, Ar-H), 7.62-7.63 (d, 2H, Ar-H), 7.71-7.73 (d, 2H, Ar-H), 8.46 (s, 1H, pyrazole-CH), 9.98 (s, 1H, –CHO).

Synthesis of 1-phenyl-3-(1-phenyl-3-*p*-tolyl-1*H*-pyrazole-4-yl)prop-2-en-1-one, 4:

A mixture of phenyl-3-*p*-tolyl-1*H*-pyrazole-4-carbaldehyde (2.62 g, 10 mmol), acetophenone (1.20 g, 10 mmol) and 2–3 drops of saturated NaOH solution was subjected to microwave irradiation in presence of ethanol as a solvent for 1–2 min at 450 watt at an interval of 5 second each. The dark yellow solid so obtained was added to crushed ice followed by acidification using 0.1 M HCl to give pale yellow solid. The product obtained was filtered, dried and recrystallized using ethanol. The recrystallized compound was allowed for crystal growth by slow evaporation of its saturated solution with mixture of ethanol and chloroform (1:1 v/v) in a dark chamber at low temperature. Yield 79%. m.p.140°C. IR: 3117 (CH=CH), 3066 (Ar-CH), 1643 (C=O), 1539(C=N), 1448 (C=C), 831 cm^{-1} (Ar-CH_3); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.36 (s, 3H, Ar-CH_3), 7.18 (s, 2H, Ar-H), 7.23 (d, 2H, Ar-H), 7.30 (s, Ar-H), 7.40-7.44 (m, 4H, Ar-H), 7.48 (d, 1H, CH=CH), 7.72 (d, 2H, Ar-H), 7.81 (d, 1H, CH=CH), 7.89 (d, 2H, Ar-H), 8.27 (s, 1H, pyrazolic CH); MS (ESI+): *m*/*z* 365 (MH^+); HRMS: Calcd for $C_{25}H_{21}N_2O$: 365.1648. Found: 365.1648. Anal. Calcd for $C_{25}H_{20}N_2O$ (364.43 g/mol): C, 82.39; H, 5.53; N, 7.69. Found: C, 81.69; H, 5.31; N, 7.35%.

X-ray crystallographic study

Single-crystal X-ray diffraction data was collected on an Agilent Technologies SuperNova Dual diffractometer with an Atlas detector using monochromated Cu-Kα radiation (λ = 1.54184 Å) at RT. The data was processed using CrysAlis Pro[14]. Structure was solved by charge-flipping methods implemented in Superflip[15] and refined on F^2 using full-matrix least-squares procedures using SHELX2014[16]. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were readily located in a difference Fourier maps and were subsequently treated as riding atoms in geometrically idealized positions, with C–H = 0.93 (aromatic and alkenyl) or 0.96 Å (methyl) with U_{iso}(H) = kU_{eq}(C), where k = 1.5 for methyl groups, which were permitted to rotate but not to tilt, and 1.2 for all other H atoms. CCDC 1848478 contains the supplementary crystallographic data for this paper. This data is provided free of charge by The Cambridge Crystallographic Data Centre. Crystallographic data is listed in Table I.

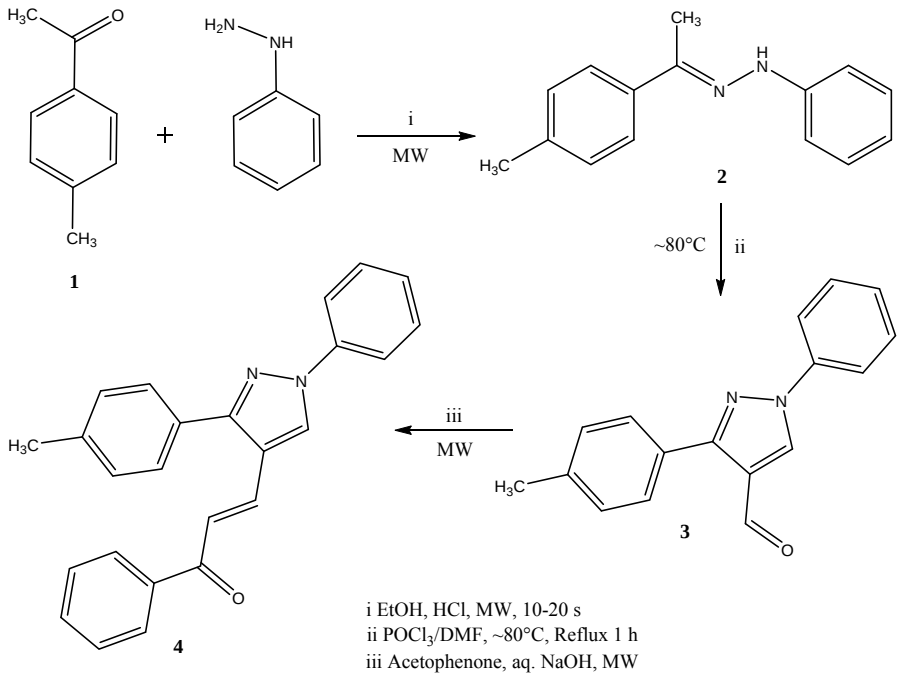
Results and Discussion

The compound 1-phenyl-3-(1-phenyl-3-*p*-tolyl-1*H*-pyrazole-4-yl)prop-2-en-1-one **4** was obtained by microwave assisted Claisen-Schmidt reaction between acetophenone and 1-phenyl-3-*p*-tolyl-1*H*-pyrazole-4-carbaldehyde **3** (Scheme I). The IR spectrum of compounds **3** showed characteristic υ(-CH=O) absorption band in the region 1660–1677 cm^{-1}, and υ(-C=N) band in the region 1513–1522 cm^{-1}. The ^{1}H NMR spectra of compounds **3** in $CDCl_3$ exhibit characteristic singlet at 9.95–9.99 ppm attributed to –CH=O protons, singlet at 8.46–9.28 ppm is

Table I — Crystallographic data for **4**

Compd code	**4**
CCDC number	1848478
Molecular formula	$C_{25}H_{20}N_2O$
Molecular weight	364.43
Crystal System	Monoclinic
Space group	$P2_1/c$
a (Å)	12.7305(4)
b (Å)	15.5517(5)
c (Å)	10.9948(4)
α (°)	90
β (°)	110.267(4)
γ (°)	90
Z	4
V (Å^3)	2041.99(13)
D_{calc} (g cm^{-3})	1.185
μ (mm^{-1})	0.570
F(000)	768
Reflections collected	7919
Independent reflections	3874
R_{int}	0.0216
Parameters	255
R_1, wR_2 [$I > 2\sigma(I)$][a]	0.0463, 0.1300
R_1, wR_2 (all data)[a]	0.0575, 0.1442
GOF[b]	1.036
$\Delta\rho_{min}$, $\Delta\rho_{max}$ (e Å^{-3})	0.174, –0.136

[a] $R = \sum||F_o| - |F_c||/\sum|F_o|$; $wR_2 = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}^{1/2}$. [b] $S = \{\sum[(F_o^2 - F_c^2)^2]/(n/p)\}^{1/2}$ where n is the number of reflections and p is the total number of parameters refined.



Scheme I — Synthesis of 1-phenyl-3-(1-phenyl-3-*p*-tolyl-1*H*-pyrazole-4-yl)prop-2-en-1-one

attributed to pyrazolic –CH protons. The IR spectrum of compounds **4** shows characteristic absorption band at 3117 cm^{-1} representing olefinic stretching and at 1643 cm^{-1}attributed to ketonic C=O group. Absorption band in the region 1539 cm^{-1} represents pyrazolic N–N bond. The ^{1}H NMR of compound **4** exhibit characteristic singlet at 2.36 ppm attributed to three protons of CH_3 in tolyl ring, singlet at 8.27 ppm attributed to pyrazolic CH, doublet at 7.48 ppm and 7.81 ppm, respectively, representing CH=CH of chalcone moiety. Furthermore, the mass spectra and elemental analysis support the structure of compound **4**.

Single crystal structure of compound **4** shows that all the bond lengths are within normal ranges (Figure 1)[17]. In the compound the pyrazole ring N1/N2/C10–C12 is essentially planar with the maximum deviation from planarity of –0.003 (2) for atom C 11. Also, the pyrazolylphenylpropenone backbone is almost planar with the dihedral angle between pyrazole ring and the phenyl ring C4-C9 of 7.63 (10)°. Similar small dihedral angle of 7.54 (11)° is present also between the pyrazole ring and the phenyl ring C13–C18. On the other hand, the dihedral angle between pyrazole and tolyl ring C19–C24 is much larger being 32.95 (9)°.

Supramolecular structure of the studied compound is achieved through a hydrogen-bonded chain formed by C12–H12···O1 bonding between the pyrazole CH moiety as a hydrogen-bond donor and the carbonyl O atom as a hydrogen-bond acceptor forming a C(7) graph set motif[18]. (Table II, Figure 2). This chain is further enhanced by a C23–H23···π interaction between the tolyl CH moiety and pyrazole ring. Adjacent chains are connected through the π···π interactions between pyrazole ring and phenyl ring C13–C18 with centroid-to-centroid distance of 3.9714 (12) Å, and dihedral angle between the rings of 7.54 (11)° and this 2D motif is further enhanced by C21–H21·π interactions between the tolyl CH moiety and the phenyl C4–C9 ring.

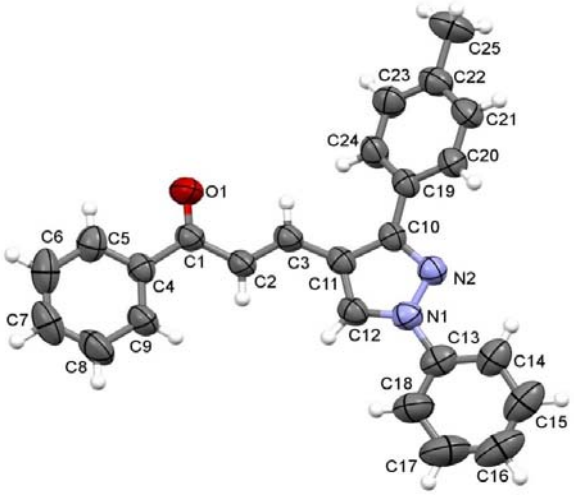


Figure 1 — Molecular structures and atom numbering scheme for **4**. Probability ellipsoids are drawn at the 50% level

Table II — Hydrogen bond geometry of **4**

D–H·A	D–H (Å)	H·A (Å)	D·A (Å)	D–H·A (°)	Symmetry code
C12–H12·O1	0.93	2.38	3.308(2)	174	x, 3/2 – y, ½ + z
C21–H21·*Cg*2	0.93	3.00	3.775(2)	142	–x, ½ + y, ½ – z
C23–H23·*Cg*1	0.93	2.83	3.593(2)	140	x, 3/2 – y, –½ + z

*Cg*1 and *Cg*2 are N1/N2/C10–C12 and C4–C9 ring centroids, respectively.

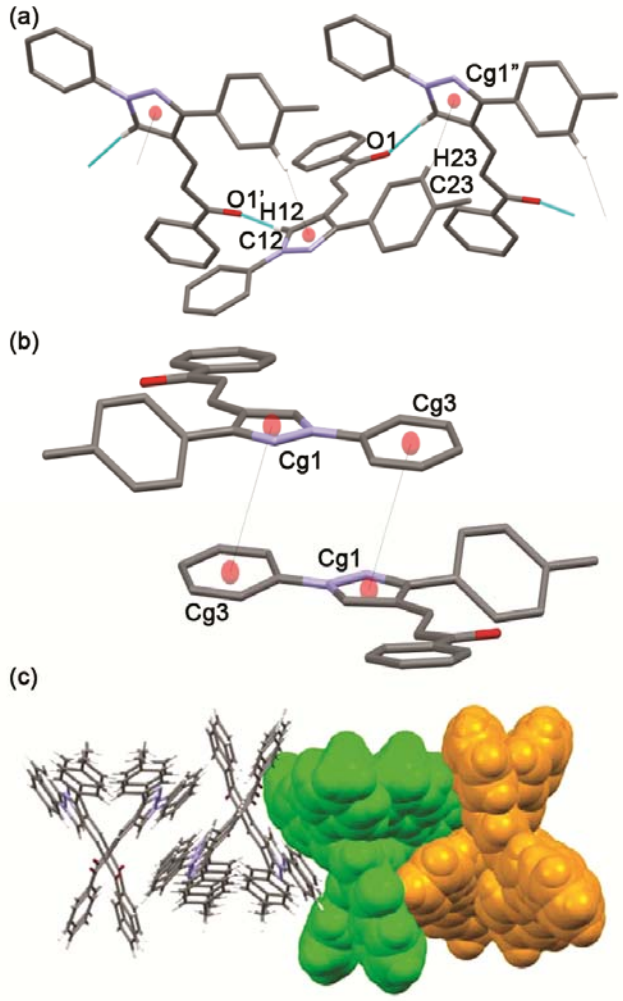


Figure 2 — (a) Chain formation generated by C12–H12···O1 hydrogen bonding (blue dashed lines) and C23–H23···π interactions (black dashed lines). Hydrogen atoms not involved in the motif shown have been omitted for clarity. (b) π···π interactions between pyrazole and phenyl rings (black dashed lines). (c) Packing of hydrogen-bonded chains along *c*-axis.

Conclusion

Novel pyrazole chalcone was synthesized by microwave assisted Claisen-Schimdt condensation reaction with good yield. Spectroscopic analysis and single crystal study proves the formation of desired compound. In the crystal structure hydrogen-bonded chain is formed by C12–H12···O1 bonding enhanced by a C23–H23···π interaction. Adjacent chains are connected through the π···π interactions.

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