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Synthesis, Characterization, Structural Elucidation and Hirshfeld Surface Analysis of a Novel *1H*-Imidazole Derivative

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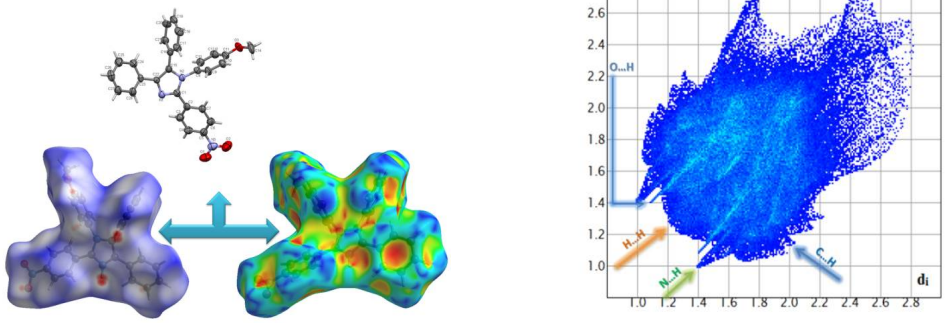
ABSTRACT

A simple synthesis of 1-(4-methoxyphenyl)-2-(4-nitrophenyl)-4, 5-diphenyl-1H-imidazole is reported. It is through one pot synthetic protocol by the reaction of mole quantities 4-methoxy aniline (1 mmol, 0.123g), benzil (1 mmol, 0.210g), ammonium acetate (1 mmol, 0.75g) and 4-nitro-benzaldehyde (1mmol, 0.150g) in glacial acetic acid medium. The IR, ^{1}H-NMR, ^{13}C NMR spectra, SEM and EDAX were used in structure elucidation. The crystal structure reveals π electron delocalization in the molecule. Inter- and intra-molecular hydrogen bonds, C-H... π interactions and H...H contribute to the stability of structure.

Graphical Abstract



Keywords: 1-(4-methoxyphenyl)-2-(4-nitrophenyl)-4,5-diphenyl-*1H*-imidazole, Synthesis, Single Crystal structure, SEM, EDAX, Hirshfeld Surface, C-H... π interactions

INTRODUCTION

Imidazoles have a broad spectrum of activities both *in vivo* and *in vitro* due to their ability to form hydrogen bond with drugs and proteins [1-2]. Imidazole moiety has a key role as template for the development of various therapeutic agents [3] in medicinal chemistry. The compounds have been in use as antifungal, antihelmintic, anti-inflammatory and anticancer agents [4-10]. In continuation of our reports dealing with the synthesis and structure elucidation of heterocyclic compounds [11-16], we report in this paper the synthesis, characterization and single crystal structure of 1-(4-methoxyphenyl)-2-(4-nitrophenyl)-4,5-diphenyl-*1H*-imidazole

MATERIALS AND METHODS

Chemicals and reagents used for the synthesis and analysis were procured from Sigma Aldrich, India. Analytical grade solvents were purchased from Loba Chemie Pvt Ltd., Mangalore. The melting point was measured on a Boetius-Mikroheiztisch the company "VEB" weighing. Rapido Radebeul / VEB NAGEMA measured and are uncorrected. TLC was done by using aluminium foil fluorescent indicator from Merck KGaA (silica gel 60 F254, layer thickness 0.2 mm). Rf -values (run level relative to the solvent front). ^{1}H-NMR spectrum was recorded on aJeol 400 MHz by using Dimethylsulfoxide (DMSO) solvent, ^{13}C NMR was recorded at 400 MHz using deuterated chloroform ($CDCl_3$) solvent and IR spectra were recorded on a Nicolet 5700 F T-IR instrument as KBr discs. Crystal structure was studied with Bruker X8 Proteum Single-crystal X-ray diffractometer. Hitachi (Table top, Model TM 3000) Scanning Electron Microscope (SEM) was employed in this investigation.

Synthesis of 1-(4-methoxyphenyl)-2-(4-nitrophenyl)-4,5-diphenyl-*1H*-imidazole (5): A mixture of mole quantities 4-methoxy aniline (1 mmol, 0.123g), benzil (1 mmol, 0.210g), ammonium acetate (1 mmol, 0.75g) and 4-nitro-benzaldehyde (1mmol, 0.150g) was taken in glacial acetic acid. The reaction mixture was then subjected to ultrasonication for 30 min and kept for refluxing for 4-5 h on heating mantle. The progress of the reaction was monitored by TLC [2:8 (v/v) ethyl acetate-pet ether mixture]. After the completion of the reaction, the mixture was cooled to room temperature and poured into ice cold water. The reaction mixture was quenched in water and neutralized by aqueous sodium bicarbonate solution and the product was extracted with ethyl acetate. The crude product was then recrystallized by hot THF and ethyl acetate (2:6) to get fine crystals of analytically pure 1-(4-methoxyphenyl)-2-(4-nitrophenyl)-4,5-diphenyl-*1H*-imidazole **(5)** with a good yield of 70-80%.M.P.210° - 212° C. The reaction scheme is shown in figure 1.

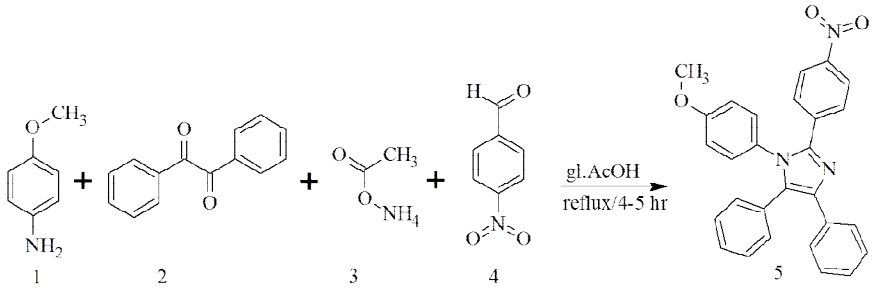


Figure 1. Reaction scheme

Spectra and Physico-chemical data: IR (KBr) (ν_{max}/cm^{-1})): 1483 (C=C), 1577.43 (N-O), 1577.43 (C=N), 2966.80 (alkyl C-H), 3040.39(Ar C-H),

^{1}H NMR(400 MHz, DMSO): =3.724 (s 3H, O-CH_3), 6.875-6.914 (m, 2H, Ar-H), 7.166-7.208(m, 1H, Ar-H), 7.236(d, J=1.6, 1H, Ar-H), 7.254-7.284(m, 5H, Ar-H), 7.310-7.335(m, 3H, Ar-H), 7.472-

7.502(m, 2H, Ar-H), 7.621-7.656(m, 2H, Ar-H), 8.144-8.179(m, 2H, Ar-H) ppm. ^{13}C NMR (400MHz, $CDCl_3$): 60, 113, 117.5, 118, 125.2, 126, 127, 127.3, 127.5, 127.7, 128.6, 128.8, 130, 130.8, 131, 133, 135.6, 143.8, 144.6, 158.6.

SEM and EDAX Analysis: The exterior morphology, an important characteristic of chemical compound, of the 1-(4-methoxyphenyl)-2-(4-nitrophenyl)-4,5-diphenyl-1H-imidazole was studied with Scanning Electron Microscope (Fig. 2).

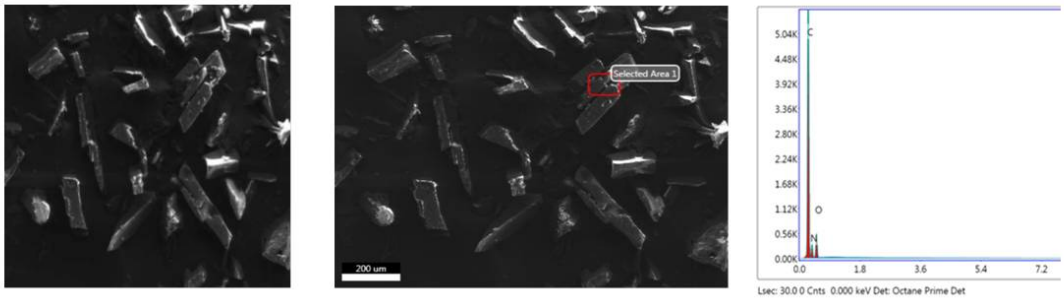


Figure 2.SEM image and EDAX spectra of 1-(4-methoxyphenyl)-2-(4-nitrophenyl)-4,5-diphenyl-*1H*-imidazole

The SEM micrograph exhibits the soft surface morphology and cutting edges having rod like shape for 1-(4-methoxyphenyl)-2-(4-nitrophenyl)-4, 5-diphenyl-*1H*-imidazolecompound. The width and length of the rods were observed to be200 µm. Further, it was confirmed that the rod like structures are not distributed uniformly. Elemental composition of the title compound was studied using EDAX (Fig. 2).The CNO composition of compound from EDAX spectrum of 1-(4-methoxyphenyl)-2-(4-nitrophenyl)-4,5-diphenyl-*1H*-imidazoleis carbon (66.24), nitrogen (19.76), and oxygen(14.01) atoms.

Table 1. Elemental composition from EDAX Analysis

Element	Weight %	Atomic %
C	66.24	70.69
N	19.76	18.08
O	14.01	11.22

X-ray diffraction studies: A white colored rectangle shaped single crystal of dimensions 0.29×0.26×0.25 mm of the title compound was chosen for an X-ray diffraction study. X-ray intensity data for the title compound was collected at temperature 293 K on Rigaku XtaLAB Mini Mercury3 diffractometer with X-ray generator operating at 50 kV and 12 mA, using MoK_α radiation of wavelength 0.71073 Å. Data were collected with χ fixed at 54° and for different settings of φ(0° and 360°), keeping the scan width of 0.5°, exposure time of 4 s, the sample to detector distance of 50 mm. The complete intensity data sets were processed using *CRYSTAL CLEAR* [17]. The crystal structure was solved by direct method and refined by full-matrix least squares method on F^2 using *SHELXS* and *SHELXL* [18]. All the non-hydrogen atoms were refined an isotropically and the hydrogen atoms were positioned geometrically, with C-H = 0.93 – 0.98 Å and refined using a riding model with U_{iso}(H) = 1.2 U_{eq}(C, N), U_{iso}(H) = 1.5 U_{eq}(C_{methyl}). A total of 309 parameters are refined with 5026 unique reflections of 9522 observed reflections. After several cycles of refinement, the final difference Fourier map showed peaks of no chemical significance and the residuals saturated to 0.0789. The geometrical calculations were carried out using the program *PLATON* [19].The molecular and packing diagrams were generated using the software *MERCURY* [20]. Figure 3 represents the ORTEP of the molecule with thermal ellipsoids drawn at 50% probability.

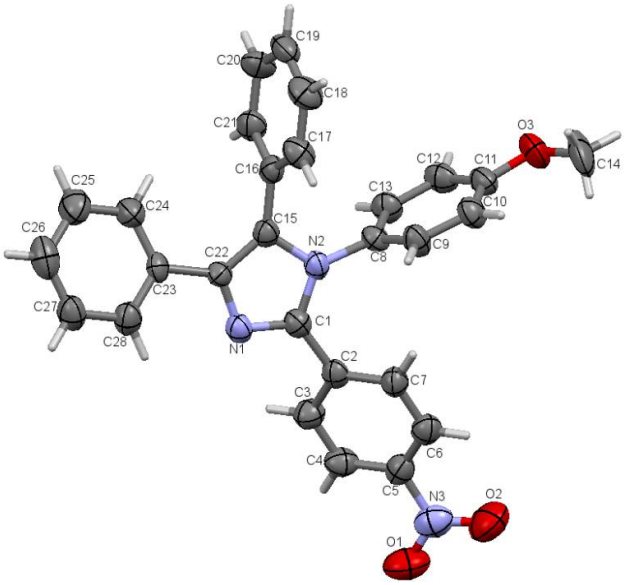


Figure 3. ORTEP diagram of the molecule with thermal ellipsoids drawn at 50% probability.

The typical data of crystal structure and data refinement are given in table 2. The list of selected bond lengths and bond angles are given in tables 3 and 4 respectively.

Table 2. Crystal data and structure refinement details.

Empirical formula	$C_{28}H_{21}N_3O_3$
Formula weight	447.48
Temperature	293(2) K
Wavelength	1.54178 Å
Reflections for cell determination	5026
θ range for above	4.82° to 64.22°
Crystal System	Monoclinic
Space Group	*P21/n*
Cell dimensions	a = 9.455(8) Å
	b = 15.631(13) Å
	c = 15.304(13) Å
	β = 95.052(11)°
Volume	2253(3) Å^3
Z	4
Density (calculated)	1.319 mgm^{-3}
Absorption coefficient	0.087 mm^{-1}
F_{000}	936
Crystal size	0.29 x 0.26 x 0.25 mm
Index ranges	$-12 \le h \le 12$
	$-18 \le k \le 20$
	$-15 \le l \le 19$
Reflections collected	9522
Independent reflections	5026 [R_{int} = 0.071]
Absorption correction	Multi-scan
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	5026 / 0 / 309
Goodness of fit on	0.95
R indices [I > 2s(I)]	$R1$ = 0.0789, $\omega R2$ = 0.3242
Largest diff. Peak and hole	0.34 and -0.39 e Å^{-3}

Table 3. Bond lengths (Å).

Atoms	Angle	Atoms	Angle
O1-N3	1.244(5)	C19-C18	1.373(6)
O3-C11	1.346(5)	C3-C2	1.377(6)
O3-C14	1.444(6)	C21-C16	1.393(5)
O2-N3	1.240(6)	C2-C7	1.396(5)
N1-C1	1.337(5)	C2-C1	1.504(6)
N1-C22	1.351(5)	C22-C15	1.383(5)
N2-C1	1.391(5)	C22-C23	1.480(5)
N2-C15	1.394(5)	C16-C17	1.381(5)
N2-C8	1.451(5)	C16-C15	1.460(5)
C25-C26	1.393(7)	C18-C17	1.396(6)
C25-C24	1.398(6)	C23-C24	1.374(6)
C26-C27	1.382(7)	C7-C6	1.363(6)
C28-C23	1.389(6)	C10-C11	1.385(6)
C28-C27	1.410(6)	C10-C9	1.387(6)
N3-C5	1.450(6)	C5-C6	1.373(6)
C4-C3	1.372(6)	C9-C8	1.371(5)
C4-C5	1.382(6)	C8-C13	1.390(5)
C20-C19	1.399(6)	C12-C11	1.381(6)
C20-C21	1.409(6)	C12-C13	1.384(6)

RESULTS AND DISCUSSION

The synthesis of 1-(4-methoxyphenyl)-2-(4-nitrophenyl)-4,5-diphenyl-*1H*-imidazole (5) was carried out by the reaction of 4-methoxyaniline (1), benzil (2), ammonium acetate (3), and 4-nitro-benzaldehyde (4) in glacial acetic acid medium by one pot reaction approach. The yield is 85%.The structure of the compound was arrived at by such as IR, and 1H-NMR 13C NMR spectral analysis, SEM and EDAX techniques. The crystals structure of 1-(4-methoxyphenyl)-2-(4-nitrophenyl)-4,5-diphenyl-1H-imidazole was determined by X-ray diffraction studies.

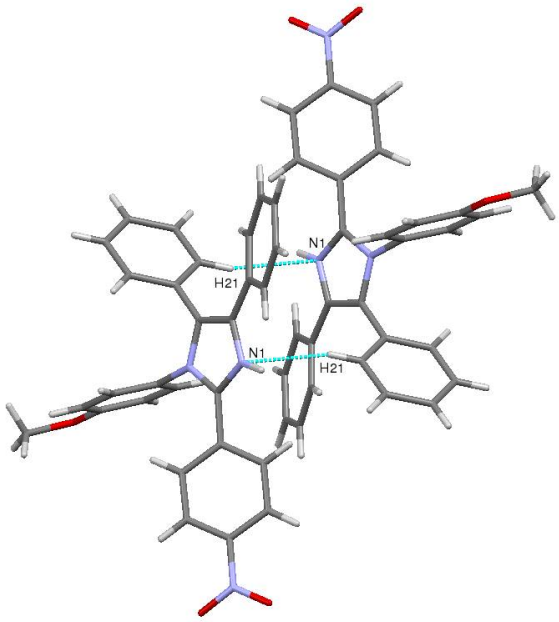


Figure 4: C21…H21…N1 hydrogen bond forming an inverted dimer.

Crystal structure studies: In the crystal structure of the title compound, the nitrogen atom of the nitrophenyl ring is in distorted trigonal conformation. This is due to delocalization of π electron and is confirmed by the bond angle values of 122.2(5)°, 118.9(4)° and 118.9(4)° about N3 atom. The imidazole ring is planar within the experimental limits with the maximum deviation of 0.013(4) Å for C1 atom. The partial double bond character with the bond length values of 1.398(5) Å and 1.396(5) Å for N2-C1 and N2-C15 can be attributed to sp^2 hybridization. These values are on par with the reported values of 1.372(4) Å and 1.394(5) Å reported earlier for an imidazole derivative [5]. Bisectional and equatorial conformation of the nitrophenyl and methoxyphenyl rings with respect to the imidazole ring is confirmed by the dihedral angle values of 35.0(2)° and 84.0(2)°. The molecules are linked via intermolecular hydrogen bonds of the type C-H...N which has a length of 3.438(6) Å and an angle of 159° to form an inverted dimer Figure 4. Further the molecular structure is stabilized by the C-H...N intramolecular hydrogen bond and C-H... π interactions.

Table 4. Bond angles (°).

Atoms	Angle	Atoms	Angle
C11-O3-C14	117.0(4)	N2-C1-C2	126.9(3)
C1-N1-C22	106.8(3)	C22-C15-N2	105.0(3)
C1-N2-C15	107.0(3)	C22-C15-C16	135.5(3)
C1-N2-C8	129.2(3)	N2-C15-C16	119.6(3)
C15-N2-C8	123.5(3)	C19-C18-C17	119.6(4)
C26-C25-C24	120.5(5)	C24-C23-C28	118.8(4)
C27-C26-C25	117.9(4)	C24-C23-C22	122.5(4)
C23-C28-C27	119.6(4)	C28-C23-C22	118.6(3)
O2-N3-O1	122.1(4)	C23-C24-C25	121.4(4)
O2-N3-C5	119.0(4)	C16-C17-C18	121.4(4)
O1-N3-C5	118.9(5)	C6-C7-C2	119.7(4)
C3-C4-C5	119.0(4)	C26-C27-C28	121.7(4)
C19-C20-C21	120.6(4)	C11-C10-C9	118.9(4)
C18-C19-C20	119.8(4)	C6-C5-C4	121.1(4)
C4-C3-C2	120.4(4)	C6-C5-N3	119.0(4)
C16-C21-C20	118.9(4)	C4-C5-N3	119.9(4)
C3-C2-C7	119.8(4)	C8-C9-C10	120.4(4)
C3-C2-C1	118.3(3)	C9-C8-C13	120.9(4)
C7-C2-C1	121.8(4)	C9-C8-N2	120.7(3)
N1-C22-C15	111.2(3)	C13-C8-N2	118.3(3)
N1-C22-C23	119.4(3)	C7-C6-C5	119.9(4)
C15-C22-C23	128.6(3)	C11-C12-C13	120.4(4)
C17-C16-C21	119.7(4)	O3-C11-C12	114.2(4)
C17-C16-C15	119.9(3)	O3-C11-C10	125.2(4)
C21-C16-C15	120.4(4)	C12-C11-C10	120.6(4)
N1-C1-N2	109.9(3)	C12-C13-C8	118.8(4)
N1-C1-C2	123.2(3)		

Hirshfeld surface analysis: Hirshfeld surface analysis is used for visually analyzing intermolecular interactions in crystal structures employing molecular surface contours and 2D fingerprint plots were used to examine the molecular shapes. It was carried out and fingerprint plots were plotted using Crystal Explorer version 3.0 [21]. The d_{norm} plots were mapped with color scale in between -1.105 au (blue, shorter intermolecular contacts) and 0.901 au (red, longer intermolecular contacts) respectively. The expanded 2D fingerprint plots were displayed in the range of 0.6-2.8 Å with the d_e and d_i distance scales displayed on the graph axes. Shaped-index surfaces are specified on the basis of local curvature of the Hirshfeld surface [22] as shown in figure 5.

The red concave region on shape index is the acceptor and the blue region is the donor atoms. The dark-red spots on the d_{norm} surface arise as results of the short inter atomic contacts. The adjacent red-blue indicates the C—H…π staking interactions over the surface. The fingerprint plots reveal the percentage of contribution of intermolecular contacts to the surface which is represented in terms of

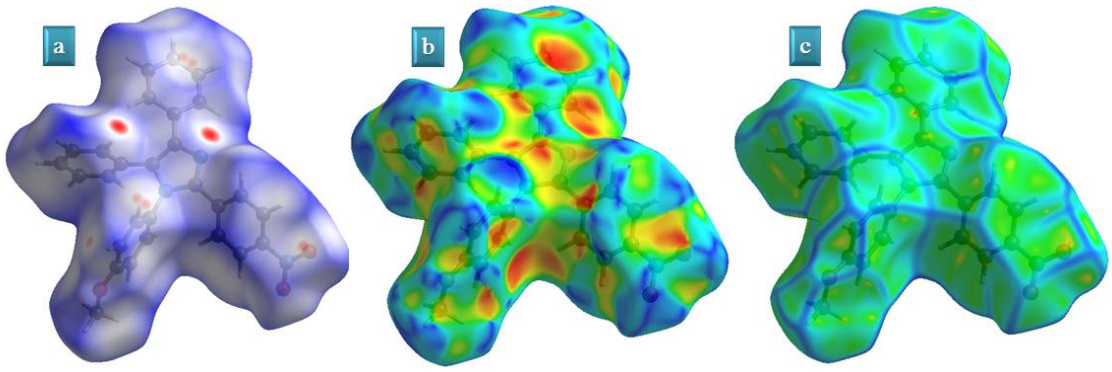


Figure 5. a) d_{norm} mapped with b) shape index, c) curvedness of the title compound.

color codes. H···H contacts has maximum (41.6%) contribution whereas O···O and O···C have minimum (0.6%) contributions respectively. Similarly, C···H (28.8%) O···H (19%), N···H (5%), C···C (3.4%) and N···C (0.8%) contacts contribute to the total area of the surface as shown in figure 6.

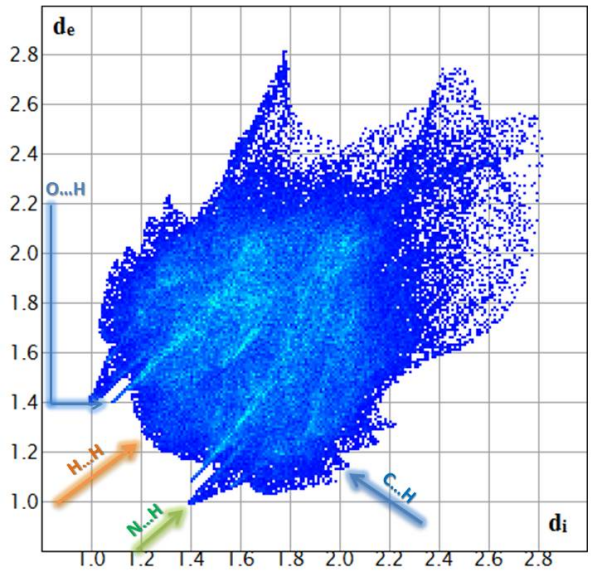


Figure 6. Fingerprint plot of the title compound (Atom $_{inside}$…Atom $_{outside}$).

APPLICATION

The results of Hirshfeld surface analysis is useful for visually analyzing intermolecular interactions in crystal structures employing molecular surface contours and 2D fingerprint plots were used to examine the molecular shapes.

CONCLUSIONS

The title compound (*1-(4-methoxyphenyl)-2-(4-nitrophenyl)-4,5-diphenyl-1H-imidazole*)has been synthesized and structure elucidation was carried out by spectroscopic and X-ray diffraction techniques. The SEM images confirmed the width and length of the rods were of the order of 200 µm and EDAX spectrum outputted elemental composition. The nitrogen atom of the nitrophenyl ring is in

distorted trigonal conformation with a consequence of delocalization of π electron. Hirshfeld surface analysis for visually analyzing intermolecular interactions in crystal structures employing molecular surface contours and 2D fingerprint plots throw light on molecular shapes.

ACKNOWLEDGEMENTS

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