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Research Article

Synthesis and X-Ray Crystal Structure of (1*E*)-1-(4-Chlorophenyl)-*N*-hydroxy-3-(1*H*-imidazol-1-yl)propan-1-imine

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Synthesis and characterization of (1*E*)-1-(4-chlorophenyl)-*N*-hydroxy-3-(1*H*-imidazol-1-yl)propan-1-imine (**4**) are reported. X-ray crystal structure of the title oxime **4** confirmed its assigned (*E*)-configuration. The compound crystallizes in the monoclinic space group *P2₁/c* with $a = 13.4292\,(3)$ Å, $b = 8.8343\,(2)$ Å, $c = 11.1797\,(3)$ Å, $\alpha = 90°$, $\beta = 108.873\,(2)°$, $\gamma = 90°$, $V = 1255.03\,(5)$ Å^3, and $Z = 4$. The molecules are packed in crystal structure by weak intermolecular O–H$\cdots$N hydrogen bonding interactions. Compound **4** is a useful intermediate for the synthesis of new imidazole-containing antifungal agents.

1. Introduction

During the past few decades, the incidence of both community-acquired and nosocomial invasive fungal infections has increased substantially. Nosocomial invasive and systemic fungal infections associated with considerable morbidity and mortality have significantly grown, particularly in immunocompromised individuals including HIV-1 infected, organ transplanted, and those undergoing cancer chemotherapy [1–3]. *Candida* species appear to become the main agent responsible for nosocomial fungal infections in mankind with *Candida albicans*, which is commensal in healthy individuals [4], accounting for the majority of invasive candidiases with about 30–40% of mortality [5]. Nevertheless, the clinical use of most antifungal agents has been limited due to the development of drug resistance, undesirable side effects, high risk of toxicity, and insufficiencies in their antifungal activity. Therefore, it is necessary to develop new and more potent antifungals to address these therapeutic issues.

Antifungal drugs are mainly classified into five major classes: azoles, polyenes, allylamines, thiocarbamates and fluoropyrimidines and they are used alone or associated in combination therapy [6–8]. Azole antifungals, featuring either an imidazole (e.g., miconazole, econazole, ketoconazole, and clotrimazole) or a 1,2,4-triazole moiety (e.g., fluconazole) as the pharmacophore, are the most widely used antifungal agents due to their high therapeutic index. They inhibit ergosterol synthesis, the main sterol constituent of fungal membranes, by blocking the cytochrome P450-dependent enzyme lanosterol 14-α-demethylase [9].

Examination of the literature exposed that some potent clinically used azole antifungals were prepared from oxime-containing starting materials [10]. Additionally, many imidazole-containing antifungals have a spacer of two carbon atoms between the imidazole pharmacophore and an aromatic moiety, but only limited information about imidazole-containing antifungals having a three-carbon atom bridge between the pharmacophore and the aromatic moiety is available [11, 12]. Accordingly, we report herein the synthesis and single crystal X-ray structure of a pivotal oxime, namely, (1*E*)-1-(4-chlorophenyl)-*N*-hydroxy-3-(1*H*-imidazol-1-yl)propan-1-imine (**4**). The target oxime **4** has a three-carbon atom linker between the imidazole pharmacophore and the aromatic moiety to be utilized as an intermediate for new imidazole-containing antifungal agents.

2. Experimental

2.1. General. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. NMR

Spectra were measured in $CDCl_3$ on a Bruker NMR spectrometer operating at 500 MHz for ^1H and 125.76 MHz for ^{13}C at the Research Center, College of Pharmacy, King Saud University, Saudi Arabia. Chemical shifts are expressed in δ-values (ppm) relative to TMS as an internal standard. Mass spectra were measured on Agilent Triple Quadrupole 6410 QQQ LC/MS with electrospray ionization (ESI) source. The X-ray diffraction measurements of compound **4** were performed using Bruker SMART APEXII CCD diffractometer.

2.2. Preparation of 1-(4-Chlorophenyl)-3-(dimethylamino) propan-1-one Hydrochloride (2). Compound **2** was synthesized according to the literature procedure [13], m.p. 172–174°C (lit. [12] 172.5-173.5°C).

2.3. Preparation of 1-(4-Chlorophenyl)-3-(1H-imidazol-1-yl) propan-1-one (3). A solution of **2** (16.8 g, 100 mmol) and imidazole (13.6 g, 200 mmol) in water (100 mL) was heated at 100°C for 5 h. The cooled reaction mixture was filtered and the collected solid was dried to furnish **3** (10.3 g, 68%) as a white solid, m.p. 99–101°C (lit. [14] 104°C) which was pure enough to be used in the next step without any purification.

2.4. Preparation of (1E)-1-(4-Chlorophenyl)-N-hydroxy-3-(1H-imidazol-1-yl)propan-1-imine (4). A mixture of **3** (2.36 g, 10 mmol), hydroxylamine hydrochloride (1.39 g, 20 mmol), and KOH (1.12 g, 20 mmol) in ethanol (10 mL) was refluxed under stirring for 18 h. The reaction mixture was allowed to cool to room temperature and the insolubles were removed by filtration. The filtrate was concentrated under vacuum and the residue was poured onto ice-cold water (15 mL). The precipitated solid was filtered, dried, and recrystallized from ethanol to give 1.3 g (52%) of the title oxime **4** m.p. 164–166°C.

IR (KBr): ν (cm^{-1}) 3510 (OH), 3135, 3026, 2632, 1644 (C=N), 1608, 1566, 1228, 752; ^1H NMR (CDCl$_3$): δ 3.27 (*t*, *J* = 6.9 Hz, 2H, –CH$_2$–CH$_2$–N), 4.29 (*t*, *J* = 6.9 Hz, 2H, –CH$_2$–CH$_2$–N), 6.94 (s, 1H, –N–CH=CH–N=), 7.06 (s, 1H, –N–CH=CH–N=), 7.33 (*d*, *J* = 8.6 Hz, 2H, Ar–H), 7.40 (*d*, *J* = 8.6 Hz, 2H, Ar–H), 7.74 (s, 1H, –N–CH=N–); ^{13}C NMR (CDCl$_3$): δ 28.6 (–CH$_2$–CH$_2$–N), 43.3 (–CH$_2$–CH$_2$–N), 119.2 (–N–CH=CH–N=), 127.3, 128.9, 133.7 (–N–CH=CH–N=, Ar–CH), 136.9 (–N–CH=N–), 137.2, 137.5 (Ar–C), 154.3 (C=N–OH); MS *m/z* (ESI): 250.3 [M + 1]$^+$. See Supplementary Materials available online at http://dx.doi.org/10.1155/2013/418601.

2.5. Crystal Structure Determination. Slow evaporation of ethanolic solution of pure oxime **4** gave its colorless single crystals. A single crystal of dimensions, 0.21 mm × 0.22 mm × 0.89 mm, was selected for X-ray diffraction analysis. Data were collected on a Bruker APEX-II CCD area diffractometer equipped with graphite monochromatic CuK\a radiation (λ = 1.54178 Å) at 293 (2) K. Cell refinement and data reduction were done by Bruker SAINT [15]. SHELXS-97 [16] was used to solve structure and refine structure. The final refinement was performed by full-matrix least-squares techniques with anisotropic thermal data for nonhydrogen atoms on F^2. All the hydrogen atoms were placed in calculated positions and

TABLE 1: The crystallographic data and refinement information.

Empirical formula	$C_{12}H_{12}ClN_3O$
Formula weight	249.70
Temperature (K)	293 (2)
Crystal system	Monoclinic
Space group	$P2_1/c$
Cu Kα radiation, λ	1.54178 Å
a (Å)	13.4292 (3)
b (Å)	8.8343 (2)
c (Å)	11.1797 (3)
α (°)	90
β (°)	108.873 (2)
γ (°)	90
V (Å^3)	1255.03 (5)
Z	4
$F(000)$	520
Theta range for data collection (°)	3.5–68.6
μ (mm^{-1})	2.60
Density (calc.) (g/cm^3)	1.557
Crystal shape and color	Needle, colorless
Crystal size (mm^3)	0.89 × 0.22 × 0.21
$h/k/l$	−15,15/−10,10/−9,12
Measured reflections	7918
Independent reflections	2069 [R_{int} = 0.029]
Reflections with $I > 2\sigma(I)$	1708
Goodness-of-fit on F^2	1.04
$R[F^2 > 2\sigma(F^2)]$	0.041
$wR(F^2)$	0.118
$\Delta\rho_{max}$ (e Å^{-3})	0.21
$\Delta\rho_{min}$ (e Å^{-3})	−0.21

constrained to ride on their parent atoms. Multiscan absorption correction was applied by use of SADABS software [15]. The crystallographic data and refinement information are summarized in Table 1.

3. Results and Discussion

3.1. Chemistry. The title compound **4** was synthesized as portrayed in Scheme 1. Synthesis was commenced by reacting 4-chloroacetophenone with paraformaldehyde and dimethylamine hydrochloride in the presence of a catalytical amount of concentrated hydrochloric acid to give Mannich base **2**. *N*-Alkylation of imidazole was accomplished via its reflux with the Mannich base **2** in water for 5 hours. Imidazole-ketone **3** was allowed to react with hydroxylamine hydrochloride and potassium hydroxide in ethanol at reflux temperature to give the title oxime **4** in 52% yield. The structure of compound **4** was confirmed via IR, ^1H NMR, ^{13}C NMR, and mass spectral data.

X-ray crystallography is a crucial analytical tool which can confirm the configuration of the title oxime **4**. Accordingly, the assigned (*E*)-configuration of compound **4** was established via its single crystal X-ray structure.
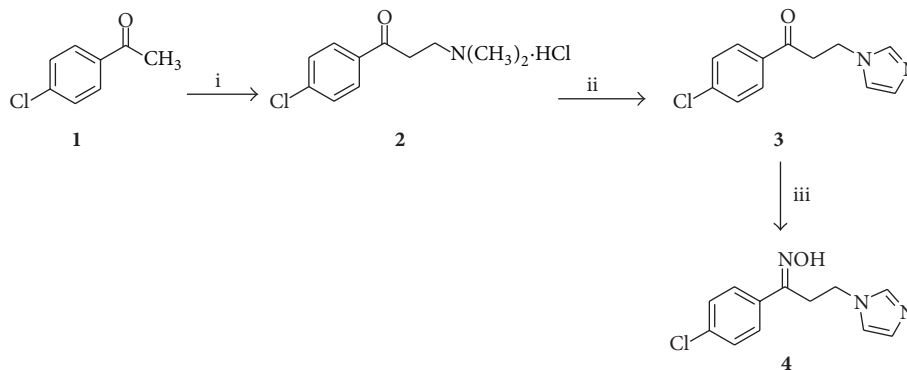
SCHEME 1: Synthetic pathway for preparation of the title compound **4**. Reagents and conditions: (i) $HN(CH_3)_2 \cdot HCl$, $(CH_2O)_n$, conc. HCl, ethanol, reflux, 2 h; (ii) imidazole, water, reflux, 5 h; (iii) $H_2NOH \cdot HCl$, KOH, ethanol, reflux, 18 h.
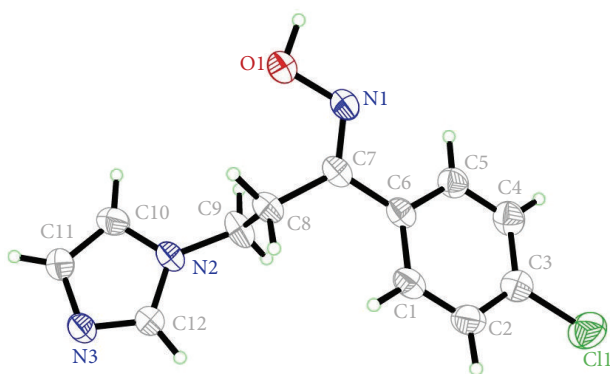

FIGURE 1: ORTEP diagram of the title compound **4** drawn at 50% ellipsoids for nonhydrogen atoms.

FIGURE 2: Crystal packing showing intermolecular N–H⋯O and C–H⋯O hydrogen bonds as dashed lines.

TABLE 2: Hydrogen-bond geometry (Å, °).

D–H⋯A	D–H	H⋯A	D⋯A	D–H⋯A
O1–H1O1⋯N3^{i}	1.00 (3)	1.69 (3)	2.686 (2)	177 (3)
C11–H11⋯O1^{ii}	0.92 (3)	2.53 (3)	3.424 (3)	167 (2)

Symmetry codes: (i) x, $y - 1$, z; (ii) $-x$, $-y + 1$, $-z - 1$.

3.2. Crystal Structure of Compound 4. The crystal structure of the title compound **4** contains one molecule in the asymmetric unit. The labeled displacement ellipsoid plot of this molecule is shown in Figure 1. The hydrogen-bonding interactions are listed in Table 2. Figure 2 depicts the packing of the molecules in the crystal structure. The crystal structure is stabilized by O–H⋯N and C–H⋯O hydrogen bonds into a three-dimensional framework structure.

4. Conclusion

The synthesis and characterization of a novel imidazole-containing oxime, namely, (1*E*)-1-(4-chlorophenyl)-*N*-hydroxy-3-(1*H*-imidazol-1-yl)propan-1-imine (**4**), have been successfully achieved. The assigned (*E*)-configuration of the title oxime **4** was confirmed via its single crystal X-ray structure. Results and analysis of the X-ray crystal structure of
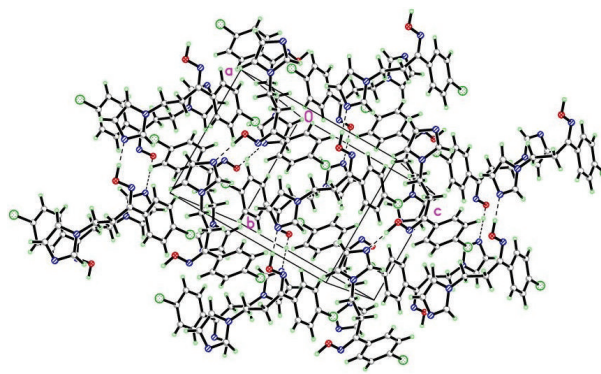
compound **4** are also reported. The pivotal imidazole-oxime **4** can be used as a starting synthon for novel antifungal agents.

Conflict of Interests

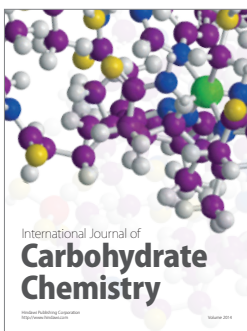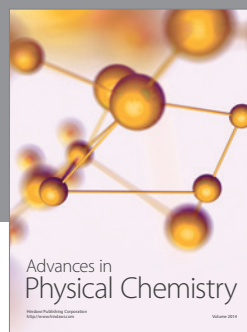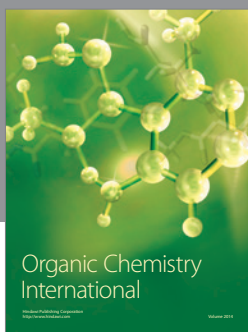The authors have declared that there is no conflict of interests.

Acknowledgment

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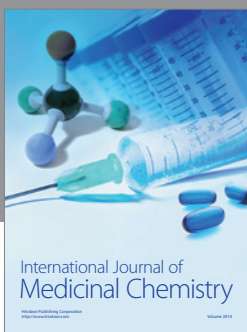
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