

Synthesis, Crystal Structure and IR Spectrum studies of 2-(4-Methyl-2-phenyl-4,5-dihydro-oxazol-4-ylmethyl)- isoindole-1,3-dione

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Abstract: The organo-amino compound of title 2-(4-methyl-2-phenyl-4,5-dihydro-oxazol-4-ylmethyl)-isoindole-1,3-dione was synthesized by the mixture of (4-methyl-2-phenyl-4,5-dihydrooxazol-4-yl)methyl-4-methylbenzenesulfonate and isoindoline-1,3-dione in *N,N*-dimethylformamide with a yield of around 65%. The structural study of the compound, C₁₉H₁₆N₂O₃, is realized using single crystal X-Ray diffraction which shows that this compound crystallizes in the monoclinic system (P2₁/c, Z = 4) with the unit cell parameters: a = 14.3728 (13) Å, b = 9.6829 (10) Å, c = 11.8964 (12) Å and β = 107.384 (3). The refinement of the structure by the least-squares method with complete matrix leads to the following reliability factors R/R_w are 0.044/0.130.

In the crystal, the molecules are linked together by hydrogen bonds and π...π interactions.

The Infrared spectroscopic studies show the bands confirming the presence of the groups C=O, C-O, C-N, -CH₃, -CH₂ and =CH.

Keywords: Oxazolinic precursors; isoindoline-1,3-dione; *N*-alkylation.

1. Introduction

Heterocyclic compounds are known to possess useful properties, including antibacterial ¹, anti-inflammatory ², anticancer ³, analgesic ⁴, antitubercular ⁵, antifungal ⁶, antiviral ⁷ and antitumor ⁸ properties. Synthesis of heterocyclic compounds is critical in modern medicinal chemistry because of their structure and applications as antihypertensive, antiallergic, antibiotic and anticonvulsant agents ⁹⁻¹¹. The development of heterocyclic chemistry has mainly been associated with full scale of applications of these classes of compounds in medicine, biochemistry and agriculture estates ⁹⁻¹⁴. Some

heterocyclic compounds have been used both as anticancer and antimicrobial agents ¹⁵. The corrosion inhibitors of mild steel are generally heterocyclic compounds containing nitrogen. Moreover, many *N*-heterocyclic compounds have been proved to be among the best known and the most studied inhibitors ¹⁶⁻²⁶. Moreover, isoindole-1,3-dione systems represent a talented group of bioactive compounds ²⁷⁻²⁹. The synthesis of isoindole-1,3-dione fused to another heterocyclic compound has attracted particular attention due to their diverse applications. Prompted by these investigations, we reported the synthesis of 2-(4-methyl-2-phenyl-4,5-dihydro-oxazol-4-ylmethyl)-isoindole-1,3-dione and its crystal structure.

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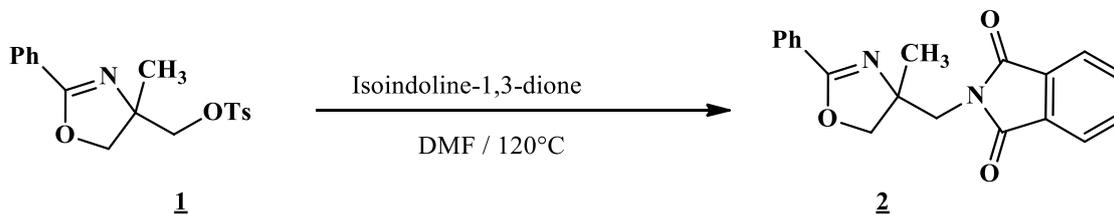
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2. Results and Discussion

The starting product **1** was prepared in two steps according to the method recommended by El Hajji ³⁰. The title compound **2** was prepared through *N*-

alkylation reaction of the *O*-tosyl oxazoline derivative **1**, by heating in *N,N*-dimethylformamide (DMF) and presence of potassium carbonate as a base (Scheme 1).



Scheme 1. Synthesis strategy of compound **2**

The title compound **2** was recrystallized from ether and was obtained in the form of a single crystal and its structure was established based on (¹H, ¹³C) NMR, IR spectroscopy, MS data and X-ray diffraction ³¹. The structure is solved by direct method and refined by the full-matrix least-squares fitting on F² using SHELXT-2014 and SHELXL-2018 programs ³²⁻³³.

All atomic positions were refined anisotropically except these of hydrogen atoms. The experimental details, crystallographic data and refinement details for the title compound are given in Table 1. All atomic coordinates, in the crystal structure, are reported in Table 2, while Table 3 summarized the hydrogen bonds.

Table 1. Crystallographic data and details of X-ray diffraction analysis for the title compound.

Crystal data	
Chemical formula	C ₁₉ H ₁₆ N ₂ O ₃
<i>M_r</i>	320.34
Crystal system, space group	Monoclinic, <i>P</i> 2 ₁ / <i>c</i>
Temperature (K)	296
<i>a</i> , <i>b</i> , <i>c</i> (Å)	14.3728 (13), 9.6829 (10), 11.8964 (12)
β (°)	107.384 (3)
<i>V</i> (Å ³)	1580.0 (3)
<i>Z</i>	4
Radiation type: INCOATEC IμS micro-focus source	Mo <i>K</i> α radiation, λ = 0.71073 Å
μ (mm ⁻¹)	0.09
Crystal size (mm)	0.32 × 0.21 × 0.16
Data collection	
Diffractometer	Bruker D8 VENTURE Super DUO
Absorption correction	Multi-scan : <i>SADABS</i> ³⁴
<i>T_{min}</i> , <i>T_{max}</i>	0.688, 0.747
No. of measured, independent and observed [<i>I</i> > 2σ(<i>I</i>)] reflections	43569, 4009, 3142
<i>R_{int}</i>	0.037
(sin θ/λ) _{max} (Å ⁻¹)	0.672
Refinement	
<i>R</i> [<i>F</i> ² > 2σ(<i>F</i> ²)], <i>wR</i> (<i>F</i> ²), <i>S</i>	0.044, 0.130, 1.07
No. of reflections	4009
No. of parameters	219
H-atom treatment	H-atom parameters constrained
Δ _{max} , Δ _{min} (e Å ⁻³)	0.21, -0.17

Moreover, the most significant interatomic bond distances and angles are included in Table 4. The single-crystal structure analysis of 2-(4-methyl-2-

phenyl-4,5-dihydro-oxazol-4-yl methyl)-isoindole-1,3-dione leads to the asymmetric unit plotted in Figure 1.

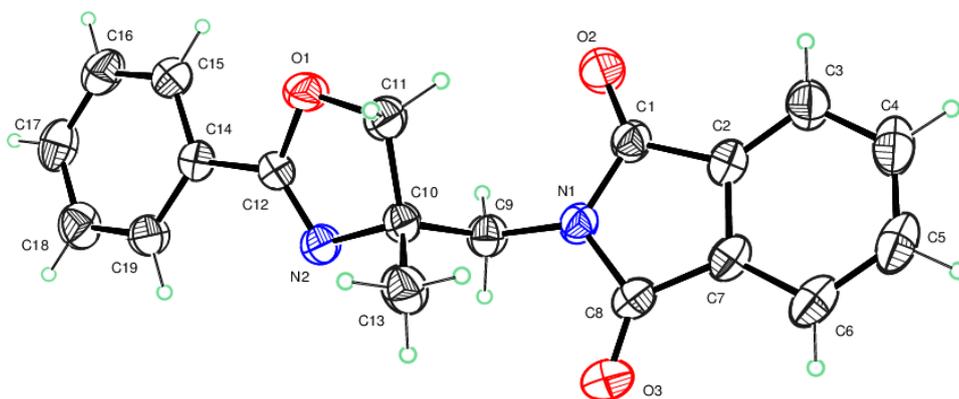


Figure 1. Molecular structure of the title compound with the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level ³⁵

In the crystal structure of $C_{19}H_{16}N_2O_3$, the two fused rings building the isoindole-1,3-dione moieties are almost coplanar with the maximum deviation from the mean plan being 0.032(1) Å at N1 atom. Furthermore, the dihydrooxazole cycle is slightly inclined to the bonded phenyl ring, and the dihedral angle between

them is of 20.19 (8)°. The crystal cohesion is ensured by bifurcated hydrogen bonds $C-H \dots O3$ and $\pi \dots \pi$ interaction between the phenyl rings, as shown in Figure 2 and Table 3. The intramolecular hydrogen bond $C11-H11B \dots O2$ contributes to the stabilization of the molecular configuration.

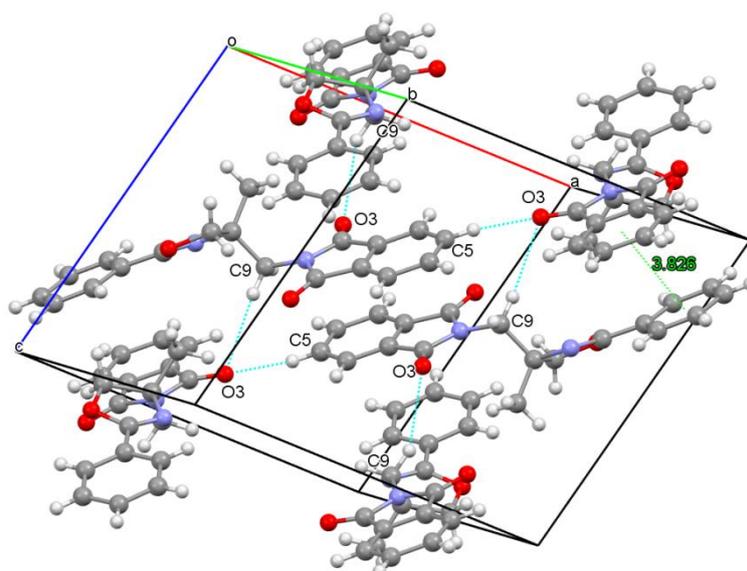


Figure 2. Three-dimensional view of the structure showing hydrogen bonds (dashed blue lines) and $\pi \dots \pi$ interaction (dashed green line).

Table 2. Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2) for the title compound.

	x	y	z	U_{iso}^*/U_{eq}
C1	0.68102 (10)	0.49710 (15)	0.47327 (12)	0.0442 (3)
C2	0.64374 (9)	0.39570 (15)	0.54343 (12)	0.0438 (3)
C3	0.64130 (11)	0.25342 (17)	0.53964 (15)	0.0555 (4)
H3	0.665390	0.204310	0.487172	0.067*
C4	0.60124 (12)	0.18661 (19)	0.61771 (17)	0.0638 (5)
H4	0.598197	0.090663	0.617346	0.077*
C5	0.56596 (12)	0.2597 (2)	0.69563 (16)	0.0635 (5)
H5	0.539694	0.212056	0.746885	0.076*
C6	0.56877 (11)	0.40268 (19)	0.69927 (14)	0.0575 (4)
H6	0.545094	0.451856	0.752082	0.069*
C7	0.60812 (9)	0.46937 (16)	0.62135 (12)	0.0443 (3)
C8	0.62040 (10)	0.61874 (16)	0.60288 (12)	0.0436 (3)

C9	0.68462 (10)	0.75791 (14)	0.46360 (12)	0.0432 (3)
H9A	0.634547	0.822990	0.468075	0.052*
H9B	0.677515	0.742234	0.380921	0.052*
C10	0.78483 (10)	0.82327 (13)	0.52146 (12)	0.0412 (3)
C11	0.86914 (11)	0.74431 (15)	0.49558 (15)	0.0512 (4)
H11A	0.922996	0.732013	0.566911	0.061*
H11B	0.847642	0.654363	0.461859	0.061*
C12	0.84514 (9)	0.94923 (13)	0.40441 (11)	0.0379 (3)
C13	0.80281 (12)	0.84667 (17)	0.65255 (13)	0.0534 (4)
H13A	0.865003	0.890369	0.685208	0.080*
H13B	0.802303	0.759547	0.690878	0.080*
H13C	0.752470	0.904873	0.664369	0.080*
C14	0.86566 (9)	1.05674 (14)	0.32768 (11)	0.0393 (3)
C15	0.91147 (11)	1.02425 (17)	0.24349 (13)	0.0498 (3)
H15	0.932134	0.934329	0.237266	0.060*
C16	0.92631 (12)	1.12591 (19)	0.16890 (14)	0.0580 (4)
H16	0.955846	1.103681	0.111561	0.070*
C17	0.89762 (12)	1.25965 (18)	0.17911 (14)	0.0582 (4)
H17	0.907771	1.327611	0.128785	0.070*
C18	0.85394 (12)	1.29274 (17)	0.26377 (15)	0.0582 (4)
H18	0.835460	1.383482	0.271308	0.070*
C19	0.83729 (11)	1.19180 (15)	0.33786 (13)	0.0482 (3)
H19	0.807088	1.214596	0.394448	0.058*
N1	0.66820 (8)	0.62768 (12)	0.51639 (9)	0.0409 (3)
N2	0.78379 (9)	0.95743 (12)	0.46125 (11)	0.0481 (3)
O1	0.89743 (8)	0.83033 (10)	0.41255 (9)	0.0491 (3)
O2	0.71541 (10)	0.47648 (13)	0.39399 (10)	0.0660 (4)
O3	0.59505 (9)	0.71655 (13)	0.64949 (11)	0.0627 (3)

Table 3. Hydrogen bonding parameters (Å, °) for the title compound.

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
C9—H9B \cdots O3 ⁱ	0.97	2.68	3.5787 (18)	154
C5—H5 \cdots O3 ⁱⁱ	0.93	2.59	3.387 (2)	144
C11—H11B \cdots O2	0.97	2.51	3.387 (2)	150

Symmetry codes: (i) $x, -y+3/2, z-1/2$; (ii) $x, -y+3/2, z+1/2$.

Table 4. Bond lengths (Å) and angles (°) for the title compound.

C1—O2	1.2050 (16)	C10—C11	1.5398 (19)
C1—N1	1.3973 (18)	C11—O1	1.4403 (17)
C1—C2	1.4884 (18)	C11—H11A	0.9700
C2—C3	1.378 (2)	C11—H11B	0.9700
C2—C7	1.383 (2)	C12—N2	1.2638 (17)
C3—C4	1.390 (2)	C12—O1	1.3624 (16)
C3—H3	0.9300	C12—C14	1.4712 (17)
C4—C5	1.378 (3)	C13—H13A	0.9600
C4—H4	0.9300	C13—H13B	0.9600
C5—C6	1.385 (3)	C13—H13C	0.9600
C5—H5	0.9300	C14—C19	1.386 (2)
C6—C7	1.3818 (19)	C14—C15	1.3892 (19)
C6—H6	0.9300	C15—C16	1.384 (2)
C7—C8	1.481 (2)	C15—H15	0.9300
C8—O3	1.2074 (18)	C16—C17	1.375 (3)
C8—N1	1.4001 (16)	C16—H16	0.9300
C9—N1	1.4590 (17)	C17—C18	1.374 (2)
C9—C10	1.5350 (19)	C17—H17	0.9300
C9—H9A	0.9700	C18—C19	1.384 (2)
C9—H9B	0.9700	C18—H18	0.9300
C10—N2	1.4814 (16)	C19—H19	0.9300

C10—C13	1.520 (2)		
O2—C1—N1	124.56 (13)	O1—C11—H11A	110.9
O2—C1—C2	129.06 (14)	C10—C11—H11A	110.9
N1—C1—C2	106.38 (11)	O1—C11—H11B	110.9
C3—C2—C7	121.76 (13)	C10—C11—H11B	110.9
C3—C2—C1	130.61 (14)	H11A—C11—H11B	108.9
C7—C2—C1	107.64 (13)	N2—C12—O1	118.25 (11)
C2—C3—C4	117.06 (16)	N2—C12—C14	126.06 (12)
C2—C3—H3	121.5	O1—C12—C14	115.69 (11)
C4—C3—H3	121.5	C10—C13—H13A	109.5
C5—C4—C3	121.30 (17)	C10—C13—H13B	109.5
C5—C4—H4	119.4	H13A—C13—H13B	109.5
C3—C4—H4	119.4	C10—C13—H13C	109.5
C4—C5—C6	121.43 (15)	H13A—C13—H13C	109.5
C4—C5—H5	119.3	H13B—C13—H13C	109.5
C6—C5—H5	119.3	C19—C14—C15	119.46 (13)
C7—C6—C5	117.38 (16)	C19—C14—C12	119.65 (12)
C7—C6—H6	121.3	C15—C14—C12	120.87 (13)
C5—C6—H6	121.3	C16—C15—C14	119.89 (15)
C6—C7—C2	121.08 (15)	C16—C15—H15	120.1
C6—C7—C8	130.28 (14)	C14—C15—H15	120.1
C2—C7—C8	108.64 (12)	C17—C16—C15	120.36 (15)
O3—C8—N1	124.79 (14)	C17—C16—H16	119.8
O3—C8—C7	129.20 (13)	C15—C16—H16	119.8
N1—C8—C7	106.01 (12)	C18—C17—C16	119.92 (14)
N1—C9—C10	114.47 (11)	C18—C17—H17	120.0
N1—C9—H9A	108.6	C16—C17—H17	120.0
C10—C9—H9A	108.6	C17—C18—C19	120.39 (16)
N1—C9—H9B	108.6	C17—C18—H18	119.8
C10—C9—H9B	108.6	C19—C18—H18	119.8
H9A—C9—H9B	107.6	C18—C19—C14	119.96 (14)
N2—C10—C13	109.85 (11)	C18—C19—H19	120.0
N2—C10—C9	105.80 (11)	C14—C19—H19	120.0
C13—C10—C9	111.76 (11)	C1—N1—C8	111.18 (11)
N2—C10—C11	103.51 (10)	C1—N1—C9	124.60 (11)
C13—C10—C11	112.12 (13)	C8—N1—C9	123.22 (12)
C9—C10—C11	113.24 (12)	C12—N2—C10	107.20 (11)
O1—C11—C10	104.49 (11)	C12—O1—C11	105.95 (10)

The presence of the hydrogen bonds C—H...O in the crystal structure of this compound contributes to building up layers perpendicular to the crystallographic axis, as can be evidenced from [Figure 3](#) and [Figure 4](#). The distances C—C in the compound are of the order of 1.53 Å, and they are longer than the distance C=C which has a distance close to the 1.38 Å. The presence of C-N bonds is confirmed by the band in the IR spectrum at the

frequency 1425 cm⁻¹, where the distance C-N value is between 1.48 and 1.39 Å. The C=N bond lengths are in the region of 1.264 at 1.481 Å. The average distance of the links C—O and C=O is respectively of the order of 1.40 and 1.20 Å, while the distance C-H is in the order of 0.93 Å. The intra-molecular angles of the compound: C—O—C, C—N—C, C—C—C, C—C—H and O—C—N are close to values 105.94 (10), 123.21 (11), 121.5 and 124.56 (12) respectively.

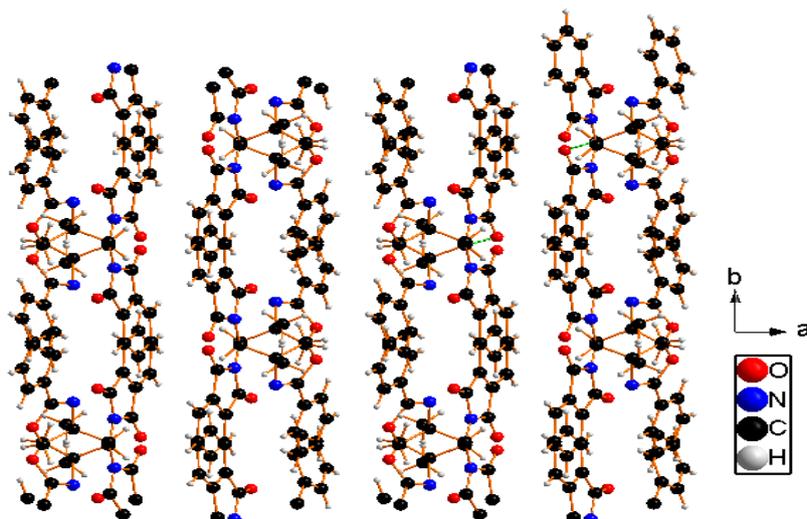


Figure 3. Crystal structure of compound, projection down c-axis (H-bonds as dashed lines)

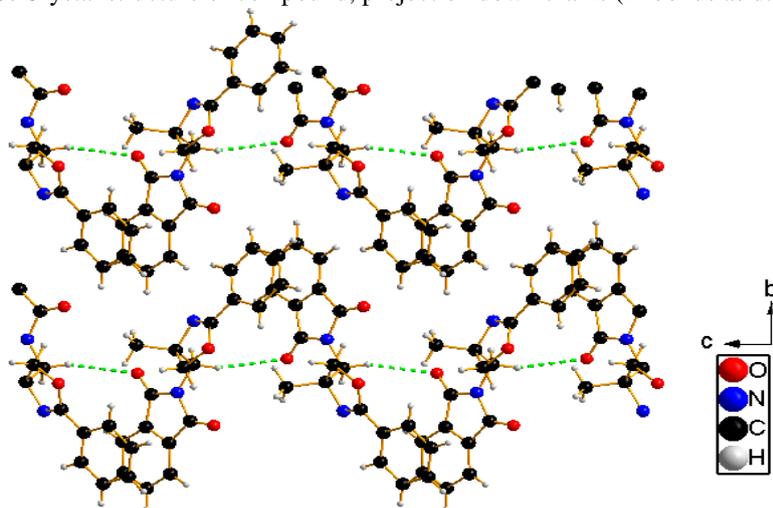


Figure 4. The crystal structure of compound 2, viewed perpendicular to the c axis.

3. Infrared spectroscopy

The IR spectrum of the title compound is represented in [Figure 5](#) and the assignments of the bands observed

and the wavenumbers relative intensities are listed in [Table 5](#).

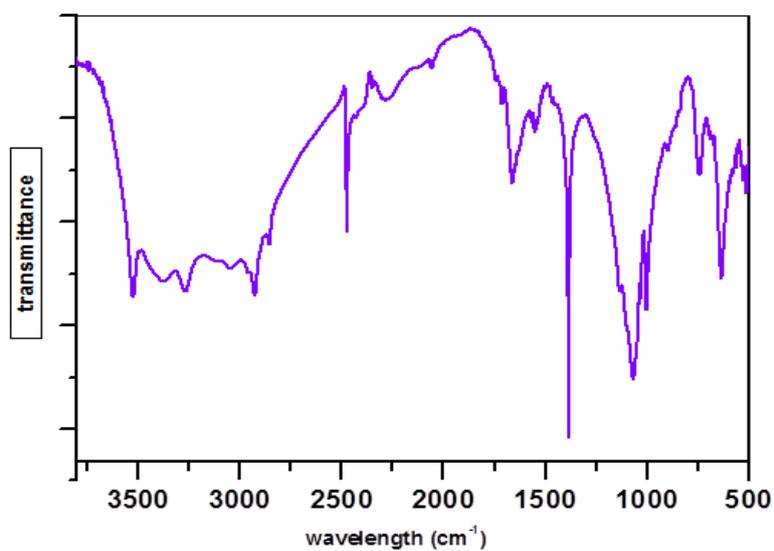


Figure 5. IR spectrum of compound 2

Table 4. Bands assignments (cm^{-1}) in the IR spectrum of compound **2**.

Assignment	Frequencies (cm^{-1})
$\nu(\text{O-H}), \nu(\text{N-H})$	3600-3200
$\nu(\text{C-H})$ aromatic	3100-3000
$\nu(\text{CH}_3, \text{CH}_2)$	3000-2750
$\delta(\text{CH}_2)$	1450
$\delta(\text{CH}_3)$	1378
$\nu(\text{C=O})$	1700-1690
$\nu(\text{C-N})$	1280
$\delta(\text{C-N})$	740
$\nu(\text{C-O})$	1150-1125

- The bands observed in the region 3500–3125 cm^{-1} in IR spectrum are corresponding to the stretching vibrations $\nu(\text{C-H})$,
- the bands observed in the region 3000-2750 cm^{-1} are attributed to stretching vibrations asymmetric and asymmetric of the CH_3 and CH_2 groups,
- the bands located in the region 1450-1378 cm^{-1} corresponding to the bending vibration of CH_3 and CH_2 groups,
- the bands at 1280 cm^{-1} and 740 cm^{-1} are associated with the stretching and bending vibrations of C–N respectively,
- the vibration of the C=O groups are observed in 1700-1690 cm^{-1} region,
- the vibration modes at 1425 cm^{-1} are assigned to the symmetric vibrations of the C–N groups and finally, the stretching vibration of C–O appears at 1150 to 1125 cm^{-1} .

4. Experimental

The melting point was determined with an electrothermal melting point apparatus and was uncorrected. NMR spectra (^1H and ^{13}C) were recorded on a Bruker AM 300 (operating at 300.13 MHz for ^1H , at 75.47 MHz for ^{13}C) spectrometer (City of Innovation, USMBA-Fez, Morocco). NMR data are listed in ppm and are reported relative to tetramethylsilane (^1H , ^{13}C) and the residual solvent peaks being used as an internal standard. All reactions were followed by thin-layer chromatography(TLC). TLC analyses were carried out on 0.25 mm thick precoated silica gel plates (Merck Fertigplatten Kieselgel 60F₂₅₄), and spots were visualized under UV light or by exposure to vaporized iodine. Mass spectra were recorded on a Polaris Q Ion Trap GC/MSn Mass Spectrometer (CNRST-Rabat, Morocco).

To a stirred solution of isoindoline-1,3-dione (2.14 g, 14.55 mmol) in 150 mL of *N,N*-dimethylformamide (DMF) and (1.5 g, 10.85 mmol) of potassium carbonate (K_2CO_3) by small portions and a catalytic amount of tetra-*n*-butylammonium bromide were added. The mixture was stirred and heated at 120°C for 45 minutes, then (1.0 g, 2.9 mmol) of (4-methyl-2-phenyl-4,5-dihydrooxazol-4-yl)methyl 4-methyl-benzenesulfonate was added. After 24 hours, the

solvent is evaporated under vacuum and the obtained residue is taken up in ethyl acetate and then washed with water several times. The organic layer is dried with sodium sulfate and is concentrated by evaporation of the solvent. The product was purified by column chromatography on silica gel using ethyl acetate/hexane as eluant. Single crystals of the title compound were obtained by recrystallization from the ether.

2-(4-Methyl-2-phenyl-4,5-dihydro-oxazol-4-ylmethyl)-isoindole-1,3-dione 2: Yield = 65% (white solid); m.p. = 148-150°C; R_f = 0.51 (Ethyl acetate/Hexane 1:4);

$^1\text{H-NMR}$ (CDCl_3 , δ ppm): 1.46 (s, 3H, CH_3); 3.85-4.01 (AB, 2H, J = 14.1 Hz, CH_2 -phtalimide), 4.03-4.71 (AB, 2H, J = 9.0 Hz, CH_2 -O (4,5-dihydro-oxazole)), 7.34-7.91 (m, 9H_{arom}).

$^{13}\text{C-NMR}$ (CDCl_3 , δ ppm): 25.00 (CH_3), 46.08 (1C, CH_2 - phtalimide), 71.87 (1C, 4,5-dihydro-oxazole), 76.63 (1C, CH_2 (4,5-dihydro-oxazole)), 123.39, 127.53, 128.28, 128.42, 131.42, 131.86 and 134.07 (6C, phenyl ring + 6C, phtalimide), 163.70 (1C, C=N), 168.65(2CO).

MS–EI: $[\text{M}+1]^+ = 321$.

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