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ORIGINAL PAPER

Structure of 2-[(Phenyl)-(3,5-Dimethyl-Pyrazol-1-yl)-Methyl]-Malonic Acid Diethyl Ester

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Abstract The titled new functionalized ligand of type 2-[(phenyl)-(3,5-dimethyl-pyrazol-1-yl)-methyl]-malonic acid diethyl ester (**4**) is prepared in good yield through condensation of 3,5-dimethyl-pyrazole, with 2-arylidene-malonic acid diethyl esters **3**. The structure of **4** was determined by spectral (IR, ^{1}H and ^{13}C NMR), elemental analyses and X-ray diffraction data. The title compound (**4**) crystallizes in the monoclinic space group $P2_1/a$, with $a = 7.9253$ (2), $b = 17.1299$ (5), $c = 13.4522$ (4) Å, $\beta = 90.220$ (2)°, $V = 1{,}826.25$ (9) Å^3, $Z = 4$ and with $R_{int} = 0.021$. The molecular conformation shows two possible pockets ready to coordinate two metal atoms. The crystal structure of (**4**) is stabilized by inter-molecular C–H···O and C–H···N hydrogen bonding.

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Keywords Polydentate N,O,O-ligand · β-Amino dicarbonyl compound · Malonate · Michael reaction · Aqueous medium

Introduction

The rational design of new HIV-1 Integrase (H–I) inhibitors, one validated target for chemotherapeutic intervention [1], is fundamentally based on intermolecular coordination between H–I/chemical inhibitor/metals (Mg^{+2} and Mn^{+2}, co-factors of the enzyme), leading in the formation of bimetallic complexes [2, 3]. Thereby, several bimetallic metal complexes, in many cases exploring the known-well polydentate ligands, appear in this scenario as the most promising concept to employ in either enzyme/drug interaction or electron transfer process, in the last case involving the biological oxygen transfer [4–6]. Another exciting example of application for such polydentate ligand involves the synergic water activation, that occurs via the so-called "remote metallic atoms". Such organometallic compounds are structurally deemed to promote or block the H–I activity [7]. These explanations above detailed clearly demonstrate that polydentate ligands are of special interest in the bio-organometallic chemistry field [8]. Looking for the design of new bimetallic coordinating ligands to further explore in the building of intermolecular system involving H–I/inhibitor/metal complexation, we have targeted to study the crystallographic structure of polydendate malonate O,N,O-ligand (**4**).

To prepare such polydentate ligands, aza-Michael reactions appear to be key-step to lead the β-amino esters. In fact, this kind of reaction has been largely employed to generate structurally diverse β-amino dicarbonyl compounds, where the undoubtedly importance of this aza-Michael step it is

viewed by the large number of unconventional methodologies as well as the broadened of applications [9–11].

Results and Discussion

Chemistry

The treatment of 2-(benzylidene)-malonic acid diethyl esters (**3**) in the presence of 3,5-dimethyl-pyrazole, in an aqueous medium at room temperature brings about highly and efficient regioselective aza-Michael addition to produce the corresponding β-amino dicarbonyl compound **4** (Scheme 1) as it was previously published for analogue compound [12].

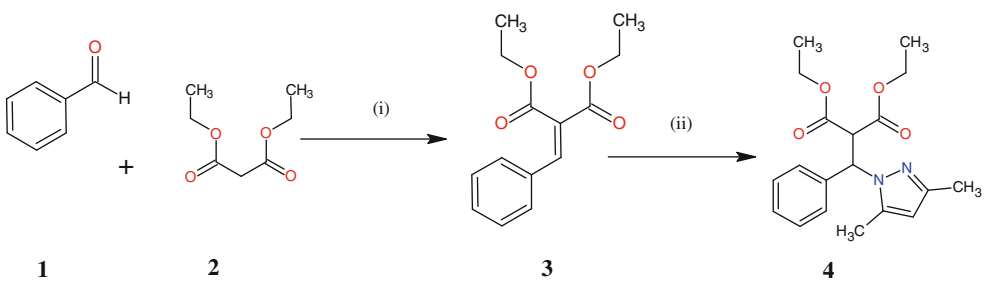
X-ray Structure Determination of O,N,O-ligand (4)

Suitable single crystal of malonate derivative **4** was obtained by recrystallization from ethanol. A white-transparent crystal of $C_{19}H_{24}N_2O_4$ having approximate dimensions of 0.25 × 0.25 × 0.15 mm was mounted on a glass fibre. All measurements were made in the ω-scan technique on a CCD Saphire 3 Xcalibur diffractometer (Oxford Diffraction) with graphite monochromatized Mo K_α radiation. The structure was solved by direct methods using the program SIR-97 [13]. The non-hydrogen atoms were refined anisotropically by the full-matrix least-square techniques using the program SHELXL97 [14]. All the hydrogen atoms bonded to C atoms were located geometrically and treated using a riding model, with C–H = 0.95–1.00 Å and $U_{iso}(H) = 1.2$ or $1.5U_{eq}(C)$. The details of the crystal and experimental data were listed in Table 1. Selected bond distances and bond angles are given in Table 2. The molecular structure of the title O,N,O-ligand is shown in Fig. 1. Packing and hydrogen bonding interactions are illustrated in Figs. 2 and 3.

The values of the geometric parameters of the title molecule are in normal. The molecule has not a planar conformation (Fig. 2). Except the H-atoms, the pyrozole ring and the C-atoms of the methyl groups connected to it are essentially in the same plane, with maximum deviations of −0.037(2) Å for C18 and 0.003(2) Å for C19. The pyrazole ring is not coplanar with the phenyl ring. There is an interplanar angle of 62.01(9)° between them. The torsion angles N1–C1–C2–C6, C9–C1–C2–C3, N1–C1–C2–C3 and C9–C1–C2–C6 are −49.84(16), 65.30(17), −168.37(12) and −176.17(13)°, respectively. In addition, the torsion angles C15–N1–C1–C2 of 125.04(16)° and C2–C1–C9–C10 of −117.66(16)° also confirm that the molecule has a non planar conformation. In the crystal structure, there is no classic hydrogen bond found (Tables 3, 4).

Table 1 Crystal data and structure refinement for **4**

Empirical formula	$C_{19}H_{24}N_2O_4$
Formula weight	344.40
Temperature	110(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, $P2_1/a$
Unit cell dimensions	
$a = 7.9253$ (2) Å	$\alpha = 90°$
$b = 17.1299$ (5) Å	$\beta = 90.220$ (2)°
$c = 13.4522$ (4) Å	$\gamma = 90°$
Volume	1826.25 (9) Å^3
Z	4
Calculated density	1.253 Mg/m^3
$F(000)$	736
Absorption coefficient	0.09 mm^{-1}
θ range for data collection	2.82–27.00°
Limiting indices	$-10 \le h \le 10$, $-21 \le k \le 21$, $-17 \le l \le 16$
Reflections collected/unique	24138/3827 [$R_{int} = 0.021$]
Completeness to $\theta = 27.00$	96.3%
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3827/0/226
Goodness-of-fit on F^2	1.10
Final R indices [3,056 reflections with $I > 2\sigma(I)$]	$R_1 = 0.048$, $wR_2 = 0.150$
R indices (all data)	$R_1 = 0.058$, $wR_2 = 0.155$
Largest diff. peak and hole	−0.52 and 0.58 e Å^{-3}



1 2 3 4

Scheme 1 Conditions for reaction: (i) piperidine, CH_3CO_2H, EtOH/Δ; (ii) 3,5-dimethyl-pyrazole, H_2O/R.T

Table 2 Bond lengths (Å) and angles (°) for **4**

O1–C3	1.192(2)	O4–C6	1.320(2)
O2–C3	1.326(2)	O4–C7	1.460(2)
O2–C4	1.464(3)	N1–C15	1.354(2)
O3–C6	1.203(2)	N1–N2	1.364(2)
O1–C3–C2	125.1(2)	N2–N1–C1	119.7(1)
O1–C3–O2	124.1(2)	C1–C2–C3	111.0(1)
O3–C6–C2	122.5(1)	C1–C2–C6	108.7(1)
O3–C6–O4	125.3(2)	C2–C1–C9	113.7(1)
N1–C1–C2	108.6(1)	C3–C2–C6	107.9(1)
N1–C1–C9	112.7(1)	C2–C3–O2	110.8(1)

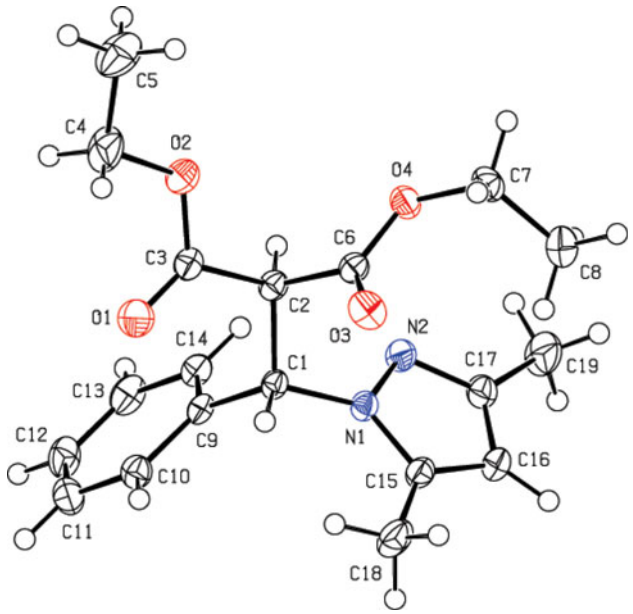


Fig. 1 ORTEP view of the title compound with the atom numbering scheme. Displacement ellipsoids for non-H atoms are drawn at the 50% probability level. Critical spatial distances [O1···O3 = 3.52, O3···N2 = 3.94 and O1···N2 = 5.06 Å]

Experimental Section

All materials and solvents used were of reagent grade as received from commercial sources. The starting material 2-(benzylidene)-malonic acid diethyl ester (**3**) was synthesized and transformed to the malonate derivative as described in our previous work [12]. ^{1}H NMR spectra were recorded on AC 300 MHz NMR Bruker Spectrometer at ambient temperature and chemical shifts were reference to the internal tetramethylsilane. Infrared spectra were recorded in KBr pellets using a Perkin-Elmer 1310 spectrophotometer. Mass spectra were determined by platform II Micromass (ESI+, CH_3CN/H_2O: 50/50) and elemental analyses were performed by CNRST Service Central d'Analyse (Rabat, Morocco).

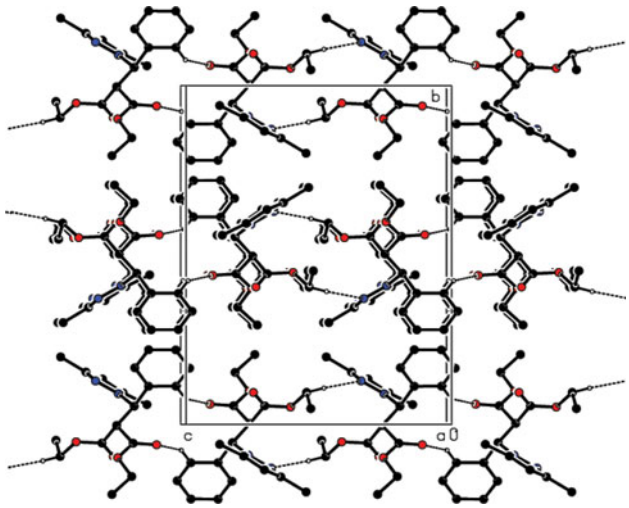


Fig. 2 The packing and the C–H···O and C–H···O hydrogen bonding interactions of the title ligand (4) viewed down a axis. Hydrogen atoms not involved in hydrogen bonding have been omitted for clarity

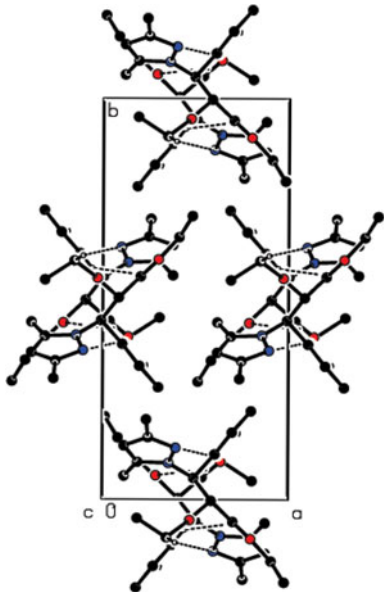


Fig. 3 View of the packing and the hydrogen bonding interactions of the title ligand (**4**) viewed down c axis. Hydrogen atoms not involved in hydrogen bonding have been omitted for clarity

Table 3 Torsion angles (°) for (**4**)

N1–C1–C2–H2	70.2(2)	O1–C3–C2–C6	−109.4(2)
N2–N1–C1–H1	−170.2(1)	O1–C3–C2–H1	−12.1(2)
N2–N1–C1–C2	−54.8(2)	O3–C6–C2–H2	−176.6(2)
N2–N1–C1–C9	72.2(2)	O3–C6–C2–H1	−31.5(2)
O1–C3–C2–H2	131.0(2)	H1–C1–C2–H2	−174.3(1)

Table 4 Electrostatic-bond parameters for **4** (Å, °)

	D–H	H···*A*	D···A	*D*–H···*A*
C7–H7B···N2^{i}	0.9900	2.53	3.486 (2)	164
C10–H10···O1^{ii}	0.9500	2.49	3.294 (2)	143
C13–H13···Cg1^{iii}	0.95	2.74	3.435 (2)	131

Symmetry codes: (i) 1 − x, −y, 1 − z; (ii) 1 − x, −y, 2 − z; (iii) −1/2 + x, −1/2 − y, z. Cg1 is a centroid of the five-membered ring (N1/N2/C15–C17)

2-Benzylidene-malonic acid diethyl ester (3)

To a solution of ethyl malonate **3** (15 g, 93 mmol) in 40 mL of ethanol, were added the respective aldehyde [(benzaldehyde **1** (11.8 g, 110 mmol), 1.5 mL of piperidine and 1 mL of glacial acetic acid. Then the mixture was stirred at refluxing temperature of ethanol for 12 h, until thin-layer chromatography indicated the complete consume of the starting material. After removing solvent, the crude product was washed with a saturated solution of sodium bisulphite (20 mL). The product was extracted by diethyl ether (2 × 20 mL), dried with sodium sulphate and evaporated to give the respective pure oil.

Yellow oil. 71% of yield, R*f* 0.7 (ether/hexane, 1/1). IR (KBr, ν cm^{-1}): 2875–2982 (CH), 1722 (C=O), 1629 and 1497 (C=C), 1294–1254 (C–O). ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 7.72 (s, 1H, C=C<u>H</u>–Ph), 7.45–7.32 (m, 5H, Ph), 4.32 (q, 2H, C<u>H</u>$_2$–CH$_3$, ^{3}J = 7.2 Hz), 4.28 (q, H, C<u>H</u>$_2$–CH$_3$, ^{3}J = 7.2 Hz), 1.31 (t, 3H, CH$_2$–C<u>H</u>$_3$, ^{3}J = 7.1 Hz), 1.25 (t, 3H, H$_2$C–C<u>H</u>$_3$, ^{3}J = 7.1 Hz). ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ ppm: 166.6 and 166.2 (2CO), 142.0 (ph–<u>C</u>H), 132.8 (C$_{quat}$, Ph), 130.5 (2C$_{tert}$, meta), 129.4 (C$_{tert}$, para), 128.7 (2C$_{tert}$, ortho), 126.1 (C$_{quat}$, =C–), 61.6/61.6 (2C, 2<u>C</u>H$_2$–CH$_3$), 14.1/13.8 (2C, 2CH$_2$–<u>C</u>H$_3$). MS (IE): Calcd for $[M]^+$ $C_{14}H_{16}O_4$: 248, $[M + H]^+$ (*m/z*) = 249 (100%).

2-[(phenyl)-(3,5-dimethyl-pyrazol)-1-yl-methyl]-malonic acid diethyl ester (4)

White powder, Mp 86–88 °C. Rf = 0.69 (ether/hexane: 1/1). IR (KBr, ν cm^{-1}): 2868–2974 (C–H), 1747/1719 (C=O), 1586/1554 (C=C), 1460/1419 (C=N), 1269/1264 (C–O). ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 7.45–7.25 (m, 5H, Ph), 7.78 (d, 1H, ph–C^{3}H, ^{3}J = 11.2 Hz), 5.74 (s, 1H, H$^{2'}$, pyrazol), 4.9 (d, 1H, PhC^{3}H<u>C</u>^{2}H, ^{3}J = 11.4 Hz), 4.16–3.99 (2q, 2H, C<u>H</u>$_2$CH$_3$, ^{3}J = 7.3 Hz), 3.97(q, 2H, C<u>H</u>$_2$CH$_3$, ^{3}J = 7.1 Hz), 2.25 (s, 1H, C$^{1'}$<u>H</u>, pyrazol), 2.21 (s, 1H, C$^{3'}$<u>H</u>, pyrazol), 1.17 (t, 3H, CH$_2$C<u>H</u>$_3$, ^{3}J = 7.1 Hz), 0.98 (t, 3H, CH$_2$C<u>H</u>$_3$, ^{3}J = 7.1 Hz). ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ ppm: 166.90/166.85 (2C=O), 147.3 (C$_{quat}$, C$^{1'}$, pyrazol), 139.30 (C$_{quat}$, ph), 137.30 (C$_{quat}$, C$^{3'}$, pyrazol), 128.50/128.3/127.93 (5C, Ph), 105 (C$_{tert}$, <u>C</u>$^{2'}$H, pyrazol), 61.57 (2C, 2<u>C</u>H$_2$CH$_3$), 60.35 (C$_{tert}$, PhC^{3}HC^{2}H), 57.52 (C$_{tert}$, Ph–C^{3}HC^{2}H), 13.87 (C, <u>C</u>$^{1'}$H3, pyrazol), 13.67 (C, <u>C</u>$^{3'}$H$_3$, pyrazol), 13.64/10.06 (2C, 2CH$_2$<u>C</u>H$_3$). MS (IE): Calcd for $[M]^+$ $C_{19}H_{24}N_2O_4$: 344.17, $[M + H]^+$ (*m/z*) = 345 (11%), 83 (100%). Elemental analysis for $C_{19}H_{24}N_2O_4$ Calcd (Found): C 66.27 (65.71), H 6.97 (5.80), N 8.13 (8.78).

Supplementary Information

Crystallographic data for the structural analysis has been deposited with the Cambridge crystallographic Data Centre, CCDC No. 734199 for compound (**4**). Copies of this information can be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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