J Chem Crystallogr (2011) 41:891–894
DOI 10.1007/s10870-011-0044-4

COMMUNICATION

Structure of a β-Amino Dicarbonyl Compound: 2-[(4-Chloro-Phenyl)-Pyrrolidin-1-yl-Methyl]-Malonic Acid Diethyl Ester

Ihssan Meskini · Loic Toupet · Maria Daoudi · Abdelali Kerbal · Taibi Ben Hadda

Received: 21 October 2009 / Accepted: 7 March 2011 / Published online: 29 March 2011

Abstract The titled new functionalized ligand 2-[(4-chloro-phenyl)-pyrrolidin-1-yl-methyl]-malonic acid diethyl ester **(4)** is prepared in good yield through condensation of pyrazole and 3,5-dimethyl-pyrazole, respectively, with 2-arylidene-malonic acid diethyl esters **(3)**. The structures of **(4)** is determined by spectral (IR, ^{1}H NMR), elemental analyses and X-ray diffraction data. The structure of **(4)** was solved in triclinic, space group P-1, with $a = 5.6858(2)$, $b = 10.0716(4)$, $c = 16.2885(7)$ Å, $\alpha = 94.338(3$, $\beta = 91.453(4)$, $\gamma = 97.750(3)°$, $V = 921.00(6)$ Å^3, $Z = 2$.

Keywords β-Amino dicarbonyl derivatives · Malonate · Michael reaction

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 bioorganometallic 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 malonates **(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

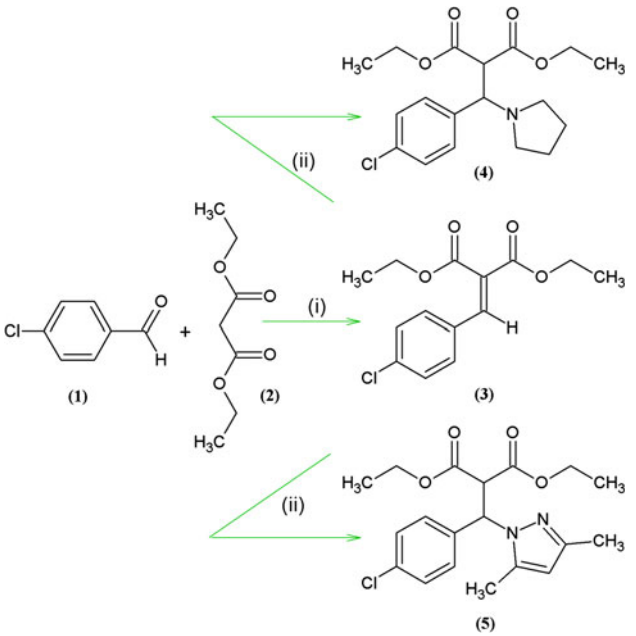
Chemistry

The treatment of 2-(4-chloro-benzylidene)-malonic acid diethyl esters **(3)** in the presence of pyrrol or 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

I. Meskini · M. Daoudi · A. Kerbal
Laboratoire de Chimie Organique, Université Sidi Mohammed Ben Abdellah, Fès, Morocco

L. Toupet
Institut de Physique-IPR-UMR CNRS 6251, Université de Rennes 1, Rennes, France

T. Ben Hadda (✉)
Laboratoire Chimie des Matériaux, FSO, Université Mohammed 1, Oujda, Morocco
e-mail: taibi.ben.hadda@gmail.com



Scheme 1 (i) Piperidine, CH_3CO_2H, EtOH/Δ; (ii) Pyrrolidine [this work] or 3,5-dimethyl-pyrazole and amines [16, 17]

dicarbonyl compounds **(4)** which is similar to previously published compound **(5)** [16, 17] (Scheme 1).

X-Ray Structure Determination of (4)

Suitable single crystal of malonate derivatives **(4)** is obtained by recrystallization from ethanol. White-transparent crystals of $C_{18}H_{24}Cl_1N_1O_4$ **(4)** are 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 MoKα radiation. The detials of the data collection and refinement are given in Table 1. Intensity controls without appreciable decay (1.2%) gives 3678 unique reflections from which 2459 with $I > 2.0\sigma(I)$. The structure was solved by direct methods using the program SIR-97 and the non-hydrogen atoms were refined anisotropically by the full-matrix least-square techniques using the program SHELXL97 [12–14]. All the hydrogen atoms bonded to C atoms were located geometrically and treated using a riding model, with C–H = 0.93–0.97 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 ligand is shown in Fig. 1. Packing and hydrogen bonding interactions are illustrated in Fig. 2.

In the molecular structure of (**4**), the nitrogen and the two carbonyl groups of two carboxylate pocess dihedral

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

X-ray data	Compound **(4)**
Empirical formula	$C_{18}H_{24}Cl_1N_1O_4$
Formula weight	353.83
Temperature	50(2) K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	$a = 5.6858(2)$ Å
	$b = 10.0716(4)$ Å
	$c = 16.2885(7)$ Å
	$\alpha = 94.338(3)°$
	$\beta = 91.453(4)°$
	$\gamma = 97.750(3)°$
Volume	921.00(6) Å^3
Z	2
Calculated density	1.276 Mg/m^3
$F(000)$	376
Absorption coefficient	0.228 mm^{-1}
Crystal size	0.18 × 0.12 × 0.12 mm
Theta range for data collection	3.11 to 26.99°
Limiting indices	$-7 \le h \le 7$, $-12 \le k \le 12$, $-20 \le l \le 20$
Reflections collected/unique	12152/3678 [R(int) = 0.0344]
Completeness to $\theta = 26.99$	91.5%
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3678/0/217
Goodness-of-fit on F^2	0.897
Final R indices [$I > 2$sigma(I)]	$R1 = 0.0386$, $wR2 = 0.0930$
R indices (all data)	$R1 = 0.0620$, $wR2 = 0.0972$
Largest diff. peak and hole	0.211 and −0.249 eÅ^{-3}
CCDC number	734196

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

N(1)–C(15)	1.457(2)	O(3)–C(6)	1.1990(18)
N(1)–C(1)	1.470(2)	O(4)–C(7)	1.4560(19)
N(1)–C(18)	1.466(2)	O(4)–C(6)	1.329(2)
O(1)–C(3)	1.197(2)	C(1)–C(9)	1.523(2)
O(2)–C(3)	1.3375(19)	C(2)–C(6)	1.523(2)
O(2)–C(4)	1.455(2)	C(4)–C(5)	1.502(3)
O(1)–C(3)–C(2)	125.05(15)	N(1)–C(1)–C(2)	107.99(12)
O(1)–C(3)–O(2)	124.46(16)	N(1)–C(1)–C(9)	115.36(14)
O(2)–C(3)–C(2)	110.47(15)	N(1)–C(15)–C(16)	104.14(13)
O(2)–C(4)–C(5)	106.42(18)	N(1)–C(18)–C(17)	102.47(13)
O(3)–C(6)–O(4)	125.16(15)	C(3)–C(2)–C(1)	108.68(13)
O(3)–C(6)–C(2)	124.69(16)	C(3)–C(2)–C(6)	108.89(13)
O(4)–C(7)–C(8)	109.46(15)	C(3)–O(2)–C(4)	116.05(14)
O(4)–C(6)–C(2)	110.15(13)	C(6)–O(4)–C(7)	117.51(12)

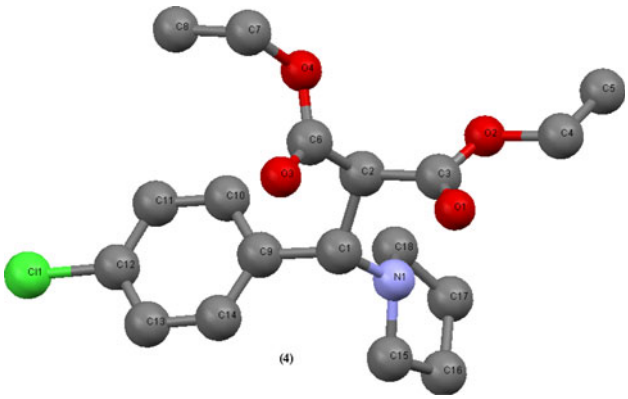


Fig. 1 ORTEP viewsof **(4)** with the atom numbering scheme. Displacement ellipsoids for non-H atoms are drawn at the 50% probability level. H atoms were omitted for clarity

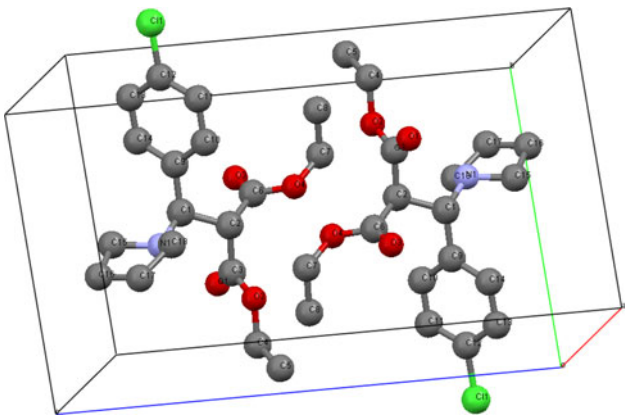


Fig. 2 View of the packing of the title ligand **(4)** in the unitcell

angles of −17.8(5), 101.1(1)° and −145.8(6)° for O1–C3–C6–O2, O1–C3–C1–N1 and O3–C6–C1–N1, respectively. By the same way we note a *trans* addition around initial C1=C2 double band; the angles are different of 180° [H1–C1–C2–H2 = 177.1(3)°, C3–C2–C1–C9 = 174.4(4)° and N1–C1–C2–C6 = 176.6(4)°]. The trans chacater of this trans addition is confirmed again by the angle of atoms in *trans* positions which is always different of 180° [N1–C1–C2–H2 = 62.5(6)°]. The crystal structure of the title ligand is stabilized by intra-molecular C–H···O = C type-hydrogen bonding interactions forming a 3D network (Table 3 and Fig. 2).

Experimental Section

All materials and solvents used were of reagent grade as received from commercial sources. The starting material 2-(4-chloro-benzylidene)-malonic acid diethyl ester **(3)** was synthesized and transformed to the malonate derivative as described in our previous work [15]. ^{1}H NMR spectra were recorded on AC 250 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). Elemental analyses were performed by CNRST Service central d'analyse CURI (Fès, Morocco) Table 4.

Synthesis of Diethyl (4-Chlorobenzyl)Propanedioate (3)

To a solution of ethyl malonate **(2)** (15 g, 93 mmol) in 40 mL of ethanol, were added the respective aldehyde (4-chloro-benzaldehyde **(1)** (15 g, 107 mmol)] and 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 bisulfite (20 ml). The product was extracted by diethyl ether (2 × 20 mL), dried with sodium sulphate and evaporated to give the pure oil.

Yellow oil. 77% yield, R*f* 0.73 (ether/hexane, 1/1). IR (KBr, ν cm^{-1}): 2906-2982 (CH), 1724 (CO) 1591/1631 (C=C), 1254/1308 (C–O). ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 7.7 (s, 1H, C=C<u>H</u>-ph), 7.45–7.30 (m, 4H, Ph), 4.31–4.4 (2 q, 4H, 2C<u>H</u>$_2$–CH_3, ^3J = 7.12 Hz), 1.31–1.25 (2 t, 6H, $2H_2$C–C<u>H</u>$_3$, ^3J = 7.11 Hz). ^{13}C-NMR (300 MHz, $CDCl_3$) δ ppm: 166.36–163.86 (2C=O); 140.01 (ClPh–<u>C</u>H=), 132.90 (C_{quat}, <u>C</u>–Cl–Ph), 130.30 ($2C_{meta}$), 130.49 (C_{quat}, para/Cl), 129.07 ($2C_{ortho}$), 125.40 (C=<u>C</u>-$(CO_2Et)_2$), 61.44–61.79 (2<u>C</u>H_2–CH_3), 13.74–13.88 (2<u>C</u>H_3–CH_2). MS (IE): Calcd for $[M]^+ \cdot C_{14}H_{15}ClO_4$: 282.07; $[M + H]^+$ = 283 (100%).

Synthesis of 2-[(4-Chloro-phenyl)-Pyrrolidin-1-yl-Methyl]-Malonic Acid Diethyl Ester (4)

To a solution of the 2-(4-chloro-benzylidene)-malonic acid diethyl ester **(3)** (8.1 mmol) in water (25 mL) was added the respective secondary amine (6 mmol) and the mixture and the stirring was continued at room temperature until the complete consume of the starting material. After removing solvent, the crude products were dissolved in diethyl ether (2 × 40 mL) and washed with water until the pH became neutral. The organic solvent was dried with sodium sulphate and then evaporated to give the pure compounds **(4)**.

White powder, Mp 77–79 °C. R*f* = 0.68 (ether/hexane: 1/1). IR (KBr, ν cm^{-1}): 2969 (C–H, Ph), 2674/2806 (C–H), 1747/1720 (C=O), 1592/1464 (C=C), 1329/1256 (C–O). ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 7.29–7.29 (m, 2H, aromat), 7.14–7.18 (m, 2H, Ph), 4.5 (d, 1H, PhC^3<u>H</u>,

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

N(1)–C(1)–C(2)–C(3)	−57.06(16)	C(1)–C(9)–C(14)–C(13)	−178.12(15)
N(1)–C(1)–C(9)–C(10)	−90.71(18)	C(1)–N(1)–C(18)–C(17)	−172.38(14)
N(1)–C(1)–C(9)–C(14)	88.33(18)	C(1)–C(2)–C(6)–O(3)	35.8(2)
N(1)–C(15)–C(16)–C(17)	−22.51(18)	Cl(1)–C(12)–C(13)–C(14)	178.64(13)
N(1)–C(1)–C(2)–C(6)	−176.64(13)	C(2)–C(1)–C(9)–C(10)	33.8(2)
C(1)–N(1)–C(15)–C(16)	171.86(14)	C(2)–C(1)–C(9)–C(14)	−147.13(15)
C(1)–C(9)–C(10)–C(11)	178.75(15)	C(3)–O(2)–C(4)–C(5)	176.28(18)
C(1)–C(2)–C(3)–O(1)	−62.0(2)	C(3)–C(2)–C(6)–O(3)	−83.6(2)
C(1)–C(2)–C(3)–O(2)	119.46(14)	C(3)–C(2)–C(6)–O(4)	95.75(16)
C(1)–C(2)–C(6)–O(4)	−144.80(14)	C(4)–O(2)–C(3)–O(1)	3.2(2)

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

D–H···A	d(D–H)	d(H···A)	d(D···A)	<(D–H···A)
C7 H7A O1	0.99	2.54(6)	3.23(2)	126.3(1)

^3J = 11.40 Hz), 4.09 (d, 1H, C^{2}H(CO$_2$Et)$_2$, ^3J = 11.40 Hz), 4.25 (q, 2H, CH$_2$OCH$_3$, ^3J = 7.1 Hz), 3.95 (m, 2H, CH$_2$OCH$_3$), 2.49 (m, 2H, N-C$^{1'}$H$_2$, pyrol), 2.35 (m, 2H, NC$^{1'}$H$_2$, pyrol), 1.59 (m, 4H, 2C$^{1'}$H$_2$C$^{2'}$H$_2$, pyrol), 1.30 (t, 3H, CH$_2$OCH$_3$, ^3J = 7.1 Hz), 1.03 (t, 3H, CH$_2$OCH$_3$, ^3J = 7.1 Hz). ^{13}C-NMR (300 MHz, CDCl$_3$) δ ppm: 166.97/167.88 (2C=O), 133.35 (C$_{quat}$, CCl, Ph), 133.22 (C$_{quat}$, Ph, para/Cl), 130.35 (C$_{tert}$, 2C ortho, Ph), 128.05 (C$_{tert}$, 2Cmeta, Ph), 64.05 (C$_{tert}$, C^{3}HPh), 61.40 (C, OCH$_2$CH$_3$, ester), 61.30 (C, OCH$_2$CH$_3$, ester), 56.50 (C$_{tert}$, C^{2}H(CO$_2$Et)$_2$), 48.41/46.88 (2C, 2C$^{1'}$H$_2$N, pyrol), 22.84 (2C, 2C$^{1'}$H2C$^{2'}$H2), pyrol), 13.91/14.12 (2C, 2OCH$_2$CH$_3$). 2D-NMR confirms the observed signals. MS (IE): Calcd for [M]$^+$ C$_{18}$H$_{24}$ClNO$_4$: 353.14, [M + H]$^+$ (*m/z*) = 354 (18%), [M-CH(CO$_2$Et)$_2$]$^+$ (*m/z*) = 194 (100%), [M- pyrol]$^+$ (*m/z*) = 283. Elemental analysis for C$_{18}$H$_{24}$ClNO$_4$ Calcd (Found): C 62.12 (62.10), H 7.08 (7.28), N 3.18 (4.04).

Acknowledgements This work was supported by the Centre National de Recherche Scientifique, University of Rennes 1 (France) and University of Mohammed 1 of Oujda (Morocco).

References

1. Dayam R, Al-Mawsawi LQ, Neamati N (2007) Bioorg Med Chem Lett 17:6155–6159
2. Dayam R, Neamati N (2004) Bioorg Med Chem Lett 12: 6371–6381
3. Zeng L-F, Zhang H-S, Wang Y-H, Sanchez T, Zheng Y-T, Neamati N, Long Y-Q (2008) Bioorg Med Chem Lett 18:4521–4524
4. Sechi M, Carta F, Sannia L, Dallocchio R, Dessì A, Al-Safi RI, Neamati N (2009) Antiviral Res 81(3):267–276
5. Sechi M, Rizzi G, Bacchi A, Carcelli M, Rogolino D, Pala N, Sanchez TW, Taheri L, Dayam R, Neamati N (2009) Bioorg Med Chem 17(7):2925–2935
6. Ramkumar K, Tambov KV, Gundla R, Manaev AV, Yarovenko V, Traven VF, Neamati N (2008) Bioorg Med Chem 16:8988–8998
7. Zeng LF, Jiang XH, Sanchez T, Zhang HS, Dayam R, Neamati N, Long YQ (2008) Bioorg Med Chem 16:7777–7787
8. Patil S, Kamath S, Sanchez T, Neamati N, Schinazi RF, Buolamwini JK (2007) Bioorg Med Chem Lett 15(3):1212–1228
9. Pommier Y, Neamati N (2006) Bioorg Med Chem 14:3785–3792
10. Metobo S, Mish M, Jin H, Jabri S, Lansdown R, Chen X, Tsiang M, Wright M, Kim CU (2009) Bioorg Med Chem Lett 19(4): 1187–1190
11. Pommier Y, Johnson AA, Marchand C (2005) Nature Rev Drug Discov 4:236–248
12. Sheldrick GM (1997) SHELXL97. Program for the refinement of crystal & structures. University of Göttingen, Germany
13. Spek AL (1997) HELENA program for the handling of CAD4-diffractometer output SHELX(S/L). Utrecht University, Utrecht, The Netherlands
14. Altomare A, Burla MC, Camalli M, Cascarano GL, Giacovazzo C, Guagliardi A, Moliterni AGG, Polidori G, Spagna R (1999) J Appl Cryst 32:115
15. Akkurt M, Yıldırım SO, Benjelloun OT, Larbi NB, Hadda TB, Büyükgüngör O (2007) Acta Cryst E63:o1656–o1657
16. Meskini I, Toupet L, Daoudi M, Kerbal A, Bennani B, Dixneuf PH, Chohan ZH, Leite ACL, Ben Hadda T (2010) J Braz Chem Soc 21(6):1129–1135
17. Meskini I, Daoudi M, Kerbal A, Bennani B, Sheikh J, Parvez P, Toupet L, Ben Hadda T (2011) J Saudi Chem Soc. doi:10.1016/j.jscs.2010.12.005