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Synthesis, characterization and crystal structure of ethyl 4-(3-chloro benzamido)benzoate

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ABSTRACT

The title compound was efficiently synthesized in two steps starting from esterification of 4-aminobenzoic acid followed by amidation with 3-chlorobenzoyl chloride in dry tetrahydrofuran. The structure was confirmed by spectroscopic data and elemental analysis. The molecular structure was determined from single crystal X-ray diffraction data. It crystallizes in the triclinic space group *P*-1 with $Z = 2$ and unit cell dimensions $a = 5.2941(15)$ Å, $b = 8.157(2)$ Å, $c = 16.238(4)$ Å, $\alpha = 82.682(6)°$, $\beta = 84.481(6)°$, $\gamma = 80.100(6)°$ and $V = 683.2(3)$ Å^3.

1. Introduction

Ethyl 4-(3-chlorobenzamido)benzoate is an exceptionally important intermediate towards the synthesis of a variety of heterocyclic compounds including 1,3,4-oxadiazoles, 1,2,4-triazoles, 1,3,4-thiadiazoles and 1,2,4-triazines, all of which exhibit a wide spectrum of bioactivities [1-4]. The benzanilide core is present in compounds with such a wide range of biological activities that it has been called a privileged structure. Benzanilides have established their efficacy as centroid elements of ligands that bind to a wide variety of receptor types [5]. Imatinib is a drug used to treat certain types of cancer that belongs to a new class of agents that act by inhibiting particular tyrosine kinase enzymes, instead of non-specifically inhibiting rapidly dividing cells [6]. Pyridylmethyl-containing benzanilides are vascular endothelial growth factor receptors and tyrosine kinase inhibitors [7]. The title compound (I), (Figure 1) was synthesized in order to investigate the combined effects on biological activities of the benzanilide and other heterocycles combined in a single structural unit.

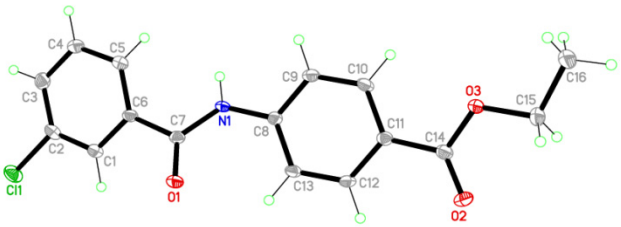

Figure 1. Molecular structure of the title compound with the atom-numbering scheme. Displacement ellipsoids are plotted at 50% probability level.

2. Experimental

2.1. Instrumentations

Melting points were recorded using a digital Gallenkamp (SANYO) model MPD.BM 3.5 apparatus and are uncorrected. ^{1}H NMR spectra were determined in $CDCl_3$ at 300 MHz using a Bruker machine. FTIR spectra were recorded on an FTS 3000 MX spectrophotometer. Mass spectrometry (EI, 70 eV) were conducted on a MAT 312 instrument, and elemental analyses were conducted using a LECO-183 CHNS analyzer. Crystallographic data were collected on a Bruker-AXS SMART APEX CCD diffractometer using MoK_α-radiation. The crystal structure was solved by direct methods. H-atoms were located from difference Fourier maps and then refined at idealized positions with the riding model. Details on data collection and refinement are given in Table 1.

2.2. Synthesis

Ethyl 4-aminobenzoate was prepared from commercial 4-aminobenzoic acid by refluxing with dry ethanol for 20 h. A solution of 4-chlorobenzoyl chloride (10 mmol) in dry tetrahydrofuran (THF) (25 mL) was added dropwise to a solution of ethyl 4-aminobenzoate (10 mmol) in dry THF (15 mL) under a nitrogen atmosphere at reflux for 4 h. The reaction mixture was poured into five times its volume of cold water when the amide was precipitated as a solid. Recrystallization from ethanol afforded the title compound as colorless crystals. Yield: 81%. M.p.: 156-158 °C. IR (KBr, cm^{-1}): 3300 ν(NH), 1721 ν(ester C=O), 1665 ν(C=O, amide), 1290 ν(C-O), 1154 ν(C–N), 1593 ν(Arom.). ^{1}H NMR (δ, ppm): 1.94 (*t*, 3H, CH_3), 3.44 (*q*, 2H, CH_2), 6.62-7.16 (m, 10H, Ar), 9.04 (s, 1H, broad, NH). EI MS (m/z): 305, 303 (M^+), 138.9 (100%). Anal. calcd. for

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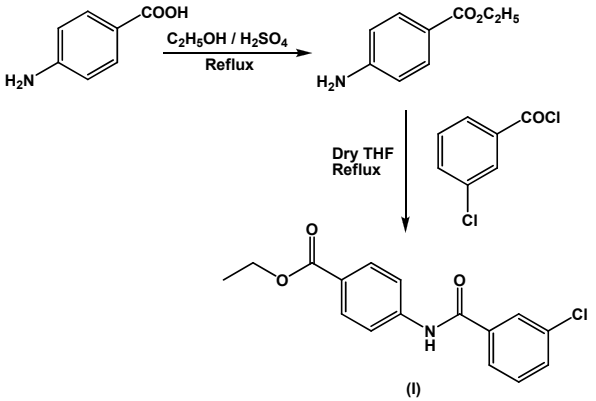
$C_{16}H_{14}ClNO_3$, C, 63.27; H, 4.65; N, 4.61. Found C, 63.34; H, 4.56; N, 4.68.

Table 1. Crystal and experimental data of the title compound.

Empirical formula	$C_{16}H_{14}ClNO_3$
Formula weight	303.73
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	*P*-1
Unit cell dimensions	a = 5.2941(15) Å
	b = 8.157(2) Å
	c = 16.238(4) Å
	α= 82.682(6)°
	β= 84.481(6)°
	γ= 80.100(6)°
Volume	683.2(3) Å^3
Z	2
Density (calculated)	1.477 Mg/m^3
F(000)	316
Crystal size	0.38 x 0.22 x 0.17 mm^3
Theta range for data collection	1.27 to 27.88°
	$-6 \le h \le 6$
Index ranges	$-10 \le k \le 10$
	$-21 \le l \le 20$
Reflections collected	5988
Independent reflections	3221 [R*int* = 0.0585]
Completeness to theta = 27.88°	99.1 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9525 and 0.8981
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3221 / 0 / 190
Goodness-of-fit on F^2	0.990
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0538, wR_2 = 0.111
R indices (all data)	R_1 = 0.0846, wR_2 = 0.1208
Largest diff. peak and hole	0.498 and 0.362 e.Å^{-3}
CCDC	679109

3. Results and discussion

Commercial 4-aminobenzoic acid was converted into its ethyl ester by refluxing with dry ethanol according to the standard procedure. Treatment of an equimolar quantity of ethyl 4-aminobenzoate with 3-chlorobenzoyl chloride in dry THF afforded the title amide (**I**) in 81% yield (Scheme 1). The ester amide was characterized by typical IR stretching vibrations for ν_{NH} (3300), $\nu_{C=O}$ (1665), ν_{C-O} (1290), ν_{C-N} (1154) and ester $\nu_{C=O}$ (1721) and 1593 (aromatic ring) cm^{-1}, respectively. In ^{1}H NMR the characteristic broad singlet for the amide proton appeared at δ 9.09 ppm besides the signals for aromatic protons at δ 6.62-7.16 ppm and the triplet and quartet for the ethyl moiety at δ 1.94 and 3.44 ppm, respectively. The mass spectrum of the compound showed the molecular ion peaks at *m/z* 304 and 305 and the base peak at *m/z* 138.9, which originated from the 3-chlorobenzoyl cation.



Scheme 1

The molecular structure of the title compound is depicted in Figure 1. Table 1 gives the crystal data and structure refinement. The selected bond lengths and angles as well as hydrogen bond parameters are presented in Table 2. The two aromatic rings are almost coplanar; the accompanying dihedral angle is 8.4(1) °. The carboxylate group is also coplanar to the attached phenyl ring with a torsion angle C10-C11-C14-O2 of –176.7(2) °. The crystal packing exhibits a strong N-H…O (*x*-1, *y*, *z*) interaction that connects molecules to endless sheets extended along the [100] plane. The planes of these sheets are then stacked in the [010] direction (Figure 2).

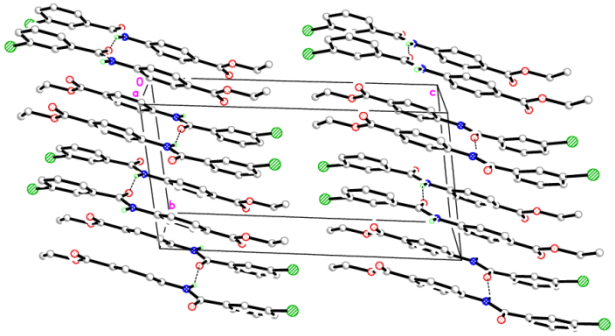


Figure 2. Crystal packing viewed along [100] with hydrogen bonds as dotted lines. Hydrogen atoms not involved in bonding pattern are omitted.

Table 2. Selected geometric parameters (Å, °) for the title compound.

Bond distances	
Cl1-C2	1.742(2)
O1-C7	1.232(3)
N1-C7	1.356(3)
N1-C8	1.410(3)
C6-C7	1.486(3)
N1-H1B	0.88
H1B…O1^i	2.29
N1…O1^i	3.110(2)
Bond angles	
C7-N1-C8	127.03(18)
O1-C7-N1	123.0(2)
O1-C7-C6	121.23(19)
N1-C7-C6	115.80(18)
N1-H1B…O1	155.2

Symmetry code: (*i*) *x*-1, *y*, *z*.

Supplementary materials

CCDC-679109 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

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