Crystals **2012**, *2*, 1201-1209; doi:10.3390/cryst2031201

OPEN ACCESS

crystals

ISSN 2073-4352

www.mdpi.com/journal/crystals

Communication

Synthesis and Crystal Structure of Benzyl [(1*S*)-1-(5-amino-1,3,4-oxadiazol-2-yl)-2-phenylethyl]carbamate

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Received: 6 June 2012; in revised form: 20 July 2012 / Accepted: 26 July 2012 / Published: 20 August 2012

Abstract: The conversion of Z-phenylalanine hydrazide with cyanogen bromide resulted in the formation of the corresponding 2-amino-1,3,4-oxadiazole by spontaneous cyclization of the intermediary cyanohydrazide. The molecular structure of the product was confirmed by single crystal X-ray diffraction. Crystals of the title compound where obtained from a saturated solution in a mixture of petroleum ether and ethyl acetate and belong to the monoclinic space group $P2_1$ with unit cell parameters a = 9.8152(2) Å, b = 9.6305(2) Å, c = 9.8465(2) Å, β = 116.785(1)°. The asymmetric unit contains one molecule.

Keywords: 1,3,4-oxadiazoles; cyanohydrazides; hydrogen bonds; edge-to-face interactions

1. Introduction

The replacement of the α-carbon in peptides by a nitrogen atom leads to azapeptides imparting distinct conformational properties to the corresponding peptide chain [1]. This concept was recently applied to the C-terminal portion of dipeptide nitriles, an important chemotype of cysteine protease inhibitors [2], affording compounds that revealed higher inhibitory potency than their carbon-based

counterparts [3]. These amino acid-derived cyanohydrazides, also referred to as azadipeptide nitriles, attracted interest in medicinal chemistry-related research [4]. Notably, peptide derivatives incorporating internal azaglycine residues, the most simple aza-amino acid, are stable in their open-chain form. In contrast to this, the nitrogen analogues of dipeptides nitriles, as represented by cyanohydrazides derived from amino acids, are only existent if both nitrogen atoms are at least methylated [3]. *N*'-Cyano-*N*,*N*'-dimethylhydrazides can be obtained by reaction of the corresponding *N*,*N*'-dimethylhydrazides with cyanogen bromide. Contrary to that, conversion of unsubstituted hydrazides leads to 2-amino-1,3,4-oxadiazoles by spontaneous cyclization of the intermediary cyanohydrazides [5,6], even though open-chain *N*,*N*'-unsubstituted cyanohydrazides have been reported erroneously in the earlier literature [7].

The heteroaromatic 1,3,4-oxadiazole ring system for itself is considerably important in the field of biologically active molecules [8,9]. In addition, these heterocycles have attracted interest for materials chemistry as well, for example as benchmark electron-transport molecules in light-emitting devices [10]. The importance of 1,3,4-oxadiazoles is mainly due to their unique geometrical and electronic properties such as high dipole moment and their susceptibility to hydrogen bond contacts. Compared to their 1,2,4-isomers, 1,3,4-oxadiazoles are characterized by a considerably higher dipole moment (1.8 D *versus* 3.1 D, respectively, for the unsubstituted heterocycles) and thus exhibit improved water solubility [9].

Due to its rather facile synthetic accessibility, the 1,3,4-oxadiazole system is employed in the design of constrained peptidomimetics [11,12].

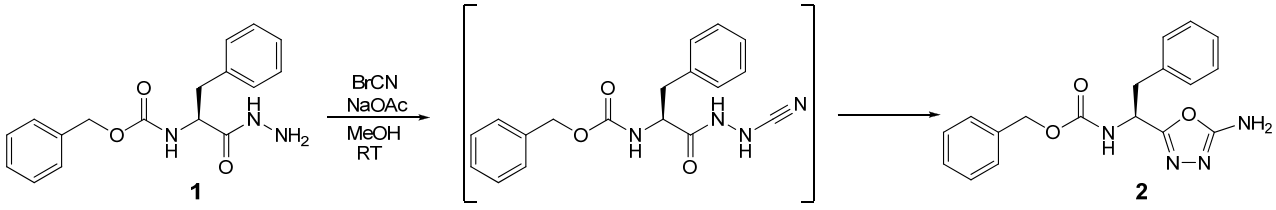
Amino acid-derived 2-amino-1,3,4-oxadiazoles have been reported occasionally in the patent literature in the context of IκB kinase inhibitors [13] and ligands of the cannabinoid receptor CB_1 [14]. Furthermore, the synthesis of derivatives containing an additional amino acid-derived substituent attached to the exocyclic amino group has been reported [15].

In the course of our systematic investigations to synthetically access azadipeptide nitriles [3] we also converted an *N*,*N*'-unsubstituted hydrazide derived from phenylalanine with cyanogen bromide. Herein, the obtained product and its crystal structure will be described.

2. Results and Discussion

The synthesis followed the scheme outlined in Figure 1. Z-protected phenylalanine hydrazide (**1**), which was prepared as published [3], was reacted with cyanogen bromide using sodium acetate and methanol as solvent. The obtained crude product was purified by recrystallization from a mixture of petroleum ether and ethyl acetate to obtain crystals proved to be suitable for structure analysis.

Figure 1. Synthesis of 2-amino-1,3,4-oxadiazole **2**.

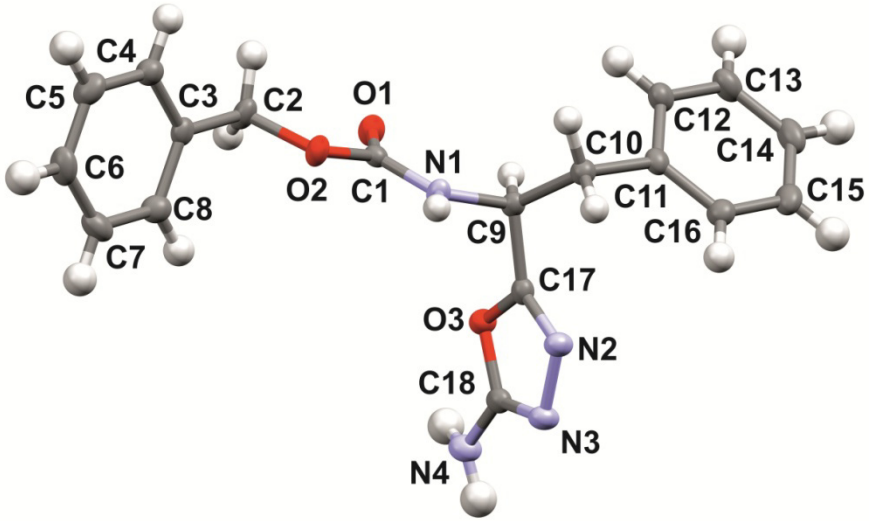


Data characterizing the crystals as well as parameters for data collection and structure refinement can be found in Table 1. The asymmetric unit consists of one molecule whose structure is shown in Figure 2.

Table 1. Crystal data and parameters for structure refinement of **2**.

Parameter	**Value**
Empirical formula	$C_{18}H_{18}N_4O_3$
Formula weight	338.36
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, $P2_1$ (No. 4)
Unit cell dimensions	a = 9.8152(2) Å b = 9.6305(2) Å β = 116.785(1) c = 9.8465(2) Å
Volume	830.88(3) Å^3
Z	2
Density (calcd.)	1.352 g/cm^3
Absorption coefficient	0.095 mm^{-1}
F(000)	356
Crystal size	0.30 × 0.20 × 0.10 mm^3
$\theta_{max.}$ for data collection	27.5°
Limiting indices	$-12 \le h \le 12$, $-12 \le k \le 12$, $-12 \le l \le 12$
Reflections collected/unique	15066/3795 [R(int) = 0.034]
Completeness to θ = 25.00	99.6%
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3795/4/235
Goodness-of-fit on F^2	0.985
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.029, wR_2 = 0.061
R indices (all data)	R_1 = 0.034, wR_2 = 0.062
Absolute structure parameter	x = −0.1(6) (Flack's x-parameter [16]); y = 0.0(5) (Hooft's y-parameter [17])
Largest diff. peak and hole	0.116 and −0.193 e A^{-3}

Figure 2. Molecular structure of **2** as represented by the asymmetric unit. Atoms are represented by thermal ellipsoids at the 50% probability level.



The compound crystallized in the space group $P2_1$, which is one of the 65 Sohncke space groups characterized by containing only rotation or screw axes as symmetry elements. This fact combined with the observed optical rotation of the compound in solution indicates that only one enantiomer is present in the crystal structure [18,19]. The absolute configuration could not be determined by anomalous dispersion effects in the diffraction measurement on the crystal due to the absence of atoms heavier than oxygen. However, as the complete inversion of the configuration at the phenylalanine-derived C_α atom is highly unlikely, it can be concluded that the configuration at atom C9 is *S*. This indicates that all synthetic transformations leading to compound **2** starting from enantiopure Z-protected L-phenylalanine proceed without racemization at the C_α atom. The 1,3,4-oxadiazole ring is completely planar, which is in accordance with the aromatic character of this heterocycle. The bond angles for the five-membered ring and the corresponding bond lengths are shown in Table 2. The length of the C18-N4 bond is with 1.345 Å similar to the nitrogen-carbon distance observed in other arylamines [20] and indicates the overlap of the nitrogens lone electron pair with the electron-deficient hetarene.

Table 2. Bond angles and lengths for the 2-amino-1,3,4-oxadiazole moiety of **2**.

Internal angle	Value (°)	Bond	Interatomic distance (Å)
C17-N2-N3	106.4(1)	C17-N2	1.282(1)
N2-N3-C18	105.5(1)	N2-N3	1.424(1)
N3-C18-O3	113.2(1)	N3-C18	1.294(2)
C18-O3-C17	102.3(1)	C18-O3	1.360(1)
O3-C17-N2	112.6(1)	O3-C17	1.376(1)
–	–	C18-N4	1.345(2)

Three types of intermolecular hydrogen bond contacts could be identified in the crystal structure (Figure 3). Two of them involve the exocyclic amino group (N4) as two-fold hydrogen bond donor forming contacts to the carbonyl oxygen (O1) of one neighboring molecule and one of the ring nitrogen atoms (N2). A further hydrogen bond contact is formed between the other ring nitrogen atom (N3) that is acting as acceptor towards the NH bond (N1) of the carbamate moiety. The atomic distances and geometries of the three hydrogen bonds are listed in Table 3. The observation that both ring nitrogens are acting as hydrogen bond acceptors whereas the ring oxygen does not is in agreement with quantum chemical calculations that assign a strong acceptor capacity to the nitrogen atoms of 1,3,4-oxadiazoles [9].

A hydrogen bond pattern similar to the one observed in the crystal structure of compound **2** has been suggested for the complex of 5-(4-nitrophenyl)-*N*-(4-methoxyphenyl)-1,3,4-oxadiazol-2-amine and glycogen synthase kinase 3β (GSK-3β) on the basis of molecular docking studies [21]. The results of this *in silico* study provided evidence for the formation of hydrogen bond contacts between the 1,3,4-oxadiazol-2-amine moiety and the backbone of two consecutive amino acids in the hinge region of the ATP binding pocket of GSK-3β, Tyr134 and Val135. Both ring nitrogens presumably act as hydrogen bond acceptors towards the NH bonds of both amino acids while the exocyclic NH is accepted by the carbonyl oxygen of Val 135. The fact that the hydrogen bond pattern observed in here matches the one predicted for the enzyme-inhibitor complex emphasizes the 2-amino-1,3,4-oxadiazole

system as a structural element privileged for interaction with the ATP binding pockets of kinases and other proteins [22].

Figure 3. Crystal packing of **2**. Dashed lines are indicating hydrogen bond contacts. Lattice constants are shown in different colors: (**a**) red; (**b**) green; (**c**) blue.

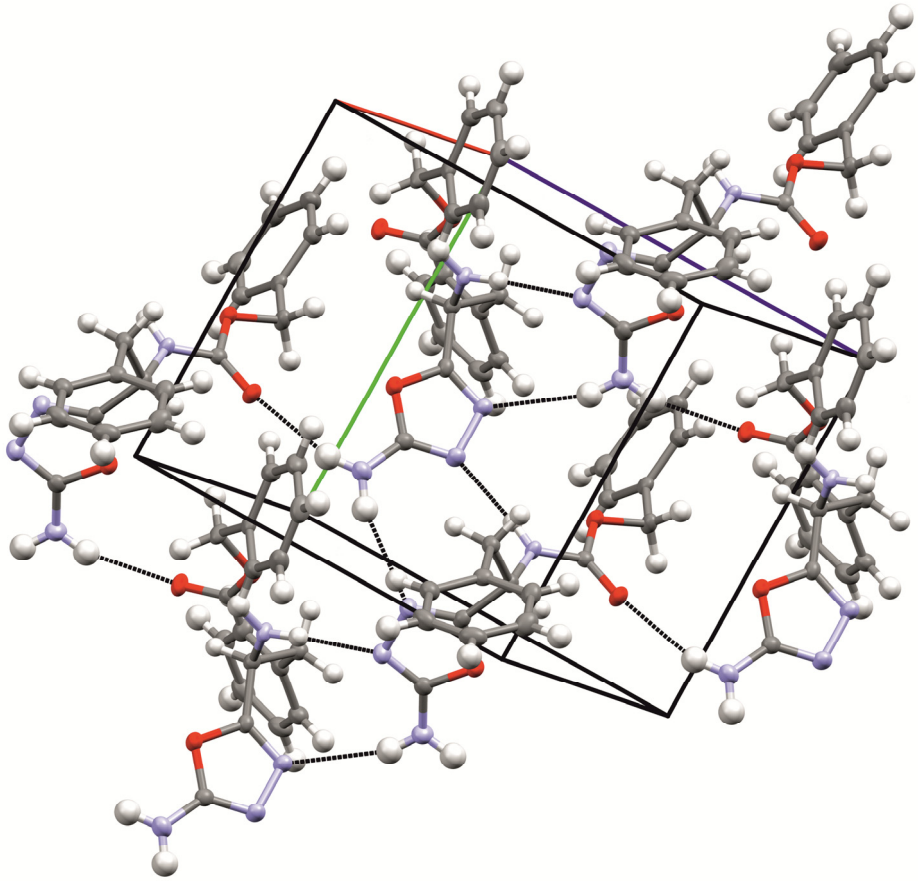


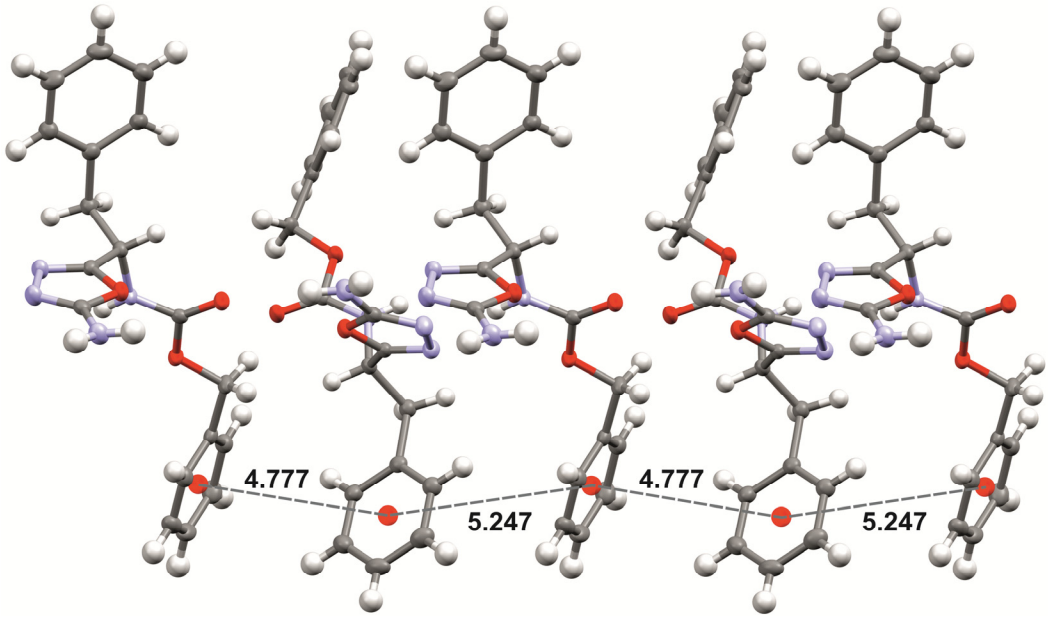
Table 3. Interatomic distances and geometries for hydrogen bonds in the crystal structure of **2**.

D*-H...*A	**d(*D*-H) (Å)**	**d(H...*A*) (Å)**	**d(*D*...*A*) (Å)**	**∢ (*D*-H*A*) (°)**
N(1)-H(1)...N(3) [i]	0.87(1)	2.04(1)	2.90(1)	168(1)
N(4)-H(4A)...O(1) [ii]	0.88(1)	2.32(1)	3.17(1)	164(1)
N(4)-H(4B)...N(2) [iii]	0.89(1)	2.55(1)	3.40(2)	161(1)

Symmetry codes for generation of equivalent atoms: [i]: −x + 1, y − 1/2, −z + 1; [ii]: − x+ 1, y + 1/2, −z; [iii]: −x + 1, y + 1/2, −z + 1.

Considering the packing of the molecules in the crystal, interactions between the phenyl rings of the carbobenzoxy and phenylalanine-derived moieties of adjacent molecules become obvious. These interactions can be interpreted as aromatic T-shaped or edge-to-face contacts as indicated by alternating centroid-centroid distances of 5.247 Å and 4.777 Å (Figure 4). The angle of inclination between the planes of the adjacent phenyl rings is 74.83°, corresponding to a deviation of 25.17° from the ideal perpendicular orientation [23,24]. This suggests that the intermolecular forces in the crystal are strongly determined by aromatic interactions originating from the two phenyl rings of the compound in addition to hydrogen bond contacts.

Figure 4. Aromatic interactions in the crystal packing of **2** illustrated by centroid-centroid distances in Å.



3. Experimental Section

Melting points were determined on a Büchi 510 oil bath apparatus and are not corrected. Thin layer chromatography was performed on Merck aluminum sheets. Optical rotations were determined on a Perkin-Elmer 241 polarimeter. ^{1}H NMR spectra (500 MHz) and ^{13}C NMR spectra (125 MHz) were recorded on a Bruker Avance 500 spectrometer. Mass spectra were obtained on an A.E.I. MS-50 spectrometer (EI, 70 eV).

*3.1. Synthesis of Benzyl [(1*S*)-1-(5-amino-1,3,4-oxadiazol-2-yl)-2-phenylethyl]carbamate* (**2**)

To a solution of *N*-(benzyloxycarbonyl)-phenylalanine hydrazide (**1**; prepared as published in [3]; 0.30 g, 0.96 mmol) in methanol (10 mL) and THF (5 mL), sodium acetate (0.22 g, 2.69 mmol) and cyanogen bromide (0.11 g, 1.10 mmol) were added as solids. Caution: cyanogen bromide is highly toxic and may cause death by inhalation. It should be handled in a well ventilated hood only with the utmost care. After stirring for 8 h at room temperature the solvent was removed *in vacuo* and the obtained residue was washed with water, dried in a desiccator over P_4O_{10} and recrystallized from petroleum ether/ethyl acetate to afford **2** (0.19 g, 58%) as colorless crystals. m.p. 142–144 °C; $[\alpha]_D^{20}$ = −41.5° (c = 1.88, dioxane); ^{1}H NMR (500 MHz, $CDCl_3$): δ in ppm = 3.14 (dd, ^{2}J = 12.6 Hz, ^{3}J = 6.9 Hz, 1H, C10HH); 3.25 (dd, ^{2}J = 13.9 Hz, ^{3}J = 6.3 Hz, 1H, C10HH); 5.03 (d, ^{2}J = 12.3 Hz, 1H, C2HH); 5.07 (d, ^{2}J = 12.3 Hz, 1H, C2HH); 5.13–5.20 (m, 1H, C9H); 5.31 (br s, 2H, N4H_2); 5.40 (d, ^{3}J = 8.9 Hz, 1H, N1H); 7.09–7.13 (m, 2H, C16H/C12H); 7.18–7.34 (m, 8H, H_{arom}); ^{13}C NMR (125 MHz, $CDCl_3$): δ in ppm = 39.15 (C10); 48.56 (C9); 67.17 (C2); 127.21 (C14); 128.05 (C4/C8); 128.22 (C6); 128.52, 128.68, 129.32 (C12/C16, C13/C15, C5/C7); 135.37, 136.02 (C11, C3); 155.54 (C1); 159.98 (C18); 163.10 (C17); MS (EI) *m/z* (%): 338 (10, M^+); 247 (18, $[M\text{-}C_7H_7]^+$); 230 (15, $[M\text{-}C_7H_7\text{-}NH_3]^+$); 203 (10, $[M\text{-BnOCO}]^+$); 91 (100, $C_7H_7^+$).

3.2. Crystal Structure Determination

The X-ray crystal structure of compound **2** was determined with a Nonius KappaCCD diffractometer at a temperature of 123 K and a wavelength of 0.71073 Å (Mo-K_α radiation). The structure was solved by direct methods using the program SHELXS-97, refinement was done with SHELXL-97 (both programs are part of SHELX-97 [25]). Non-hydrogen atoms were refined anisotropically and hydrogens with a riding model. Exceptionally, hydrogen atoms bound to nitrogen were refined freely. The absolute configuration has not been established by anomalous dispersion effects in diffraction measurement on the crystal. The enantiomer has been assigned by reference to an unchanging chiral centre in the synthetic procedure. Structures were visualized and evaluated using Mercury 3.0, The Cambridge Crystallographic Data Centre [26]. Errors of presented bond lengths and angles are given in brackets and refer to the last decimal place.

Crystallographic data (excluding structure factors) for the structure reported in this work have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 884101 (**2**). Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge DB2 1EZ, UK.

4. Conclusions

The title compound **2** was prepared and its molecular structure was deduced from its X-ray diffraction pattern. This unequivocally confirms the non-existence of *N*'-cyanohydrazides bearing hydrogen atoms at both nitrogens due to spontaneous cyclization to 2-amino-1,3,4-oxadiazoles. To the best of our knowledge, a crystal structure of an amino acid-derived 2-amino-1,3,4-oxadiazole has not been reported before.

An extensive network of hydrogen bonds as well as edge-to-face interactions could be identified in the crystal packing. The observed hydrogen bond pattern involving the heterocycle as well the exocyclic amino group supports the importance of such moieties for the design of biologically active molecules able to interact with the ATP-binding pockets of some proteins.

Acknowledgments

We are grateful to Gloria Ruiz Gómez for support regarding the graphical presentation of the structures.

Conflict of Interest

The authors declare no conflict of interest.

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