J Chem Crystallogr (2010) 40:100–103
DOI 10.1007/s10870-009-9608-y

ORIGINAL PAPER

Synthesis and Crystal Structure of a Compound with Two Conformational Isomers: 2-(2,6-Difluorobenzamido)-4-methyl-*N*–*o*-tolylthiazole-5-carboxamide

Hua Cai · Ying Guo · Jian-Gang Li · Yun-Ling Zou

Received: 17 December 2008 / Accepted: 8 August 2009 / Published online: 25 August 2009
© Springer Science+Business Media, LLC 2009

Abstract The single crystal of the title compound ($C_{19}H_{15}F_2N_3O_4S$) with two conformational isomers was obtained from the solution of the title compound dissolved in the ethyl acetate by slow evaporation at room temperature. The crystal is Orthorhombic, space group Pca2(1) with $a = 21.840(2)$ Å, $b = 7.5321(8)$ Å, $c = 22.365(2)$ Å, $\alpha = 90.00°$, $\beta = 90.00°$, $\gamma = 90.00°$, empirical formula is $C_{38}H_{30}F_4N_6O_4S_2$, Mr = 774.80, $V = 3{,}679.2(6)$ Å^3, $Z = 4$, $D_c = 1.399$ g/cm^3, μ(Mo$K\alpha$) = 0.215 mm^{-1}, $F(000) = 1{,}600$, $S = 1.032$, the final $R = 0.0328$, $wR_2 = 0.0811$ for 4,708 observed reflections with $I > 2\sigma(I)$. In the unit cell, there are two independent molecules having only slightly different bond lengths, torsion angles and the corresponding dihedral angles of the two molecules are also different. In the crystal structure, molecules are linked through aromatic π–π stacking and intermolecular N–H···N hydrogen bonds interactions, forming 1D chain structure.

Keywords Thiazole · Dihedral angle · Hydrogen bond · Crystal structure

Introduction

The thiazole ring unit is a common structural feature in various bioactive molecules [1]. This heterocyclic system has been employed in the preparation of different important drugs required for treatment of inflammations [2], bacterial infections [3], and hypertension [4]. Some of the thiazole analogues are used as fungicides, inhibiting in vivo the growth of xanthomonas and as ingredients of herbicides, antischistosomicidal, and anthelmintic drugs [5]. Aminothiazoles are known to be ligands of the estrogen receptor and as a novel class of adenosine receptor antagonists [6]. As a continuous work, in this paper, the authors report the synthesis and crystal structure of a new 2-Aminothiazole compound, 2-(2,6-difluorobenzamido)-4-methyl- *N*–*o*-tolylthiazole- 5-carboxamide, in which there are two conformational isomers in the unit cell.

H. Cai (✉) · Y. Guo · J.-G. Li · Y.-L. Zou
College of Science, Civil Aviation University of China, 300300 Tianjin, People's Republic of China
e-mail: caihua-1109@163.com

Experimental

Reagents and Apparatus

All the reagents were purchased commercially and used without further purification. The melting point was determined using a WRS-1B digital melting-point apparatus and uncorrected. The C, H, and N elemental analyses were carried out with a CE-440 (Leemanlabs) analyzer. Fourier transform (FT)-IR spectra (KBr pellets) were taken on an AVATAR-330 (Nicolet) spectrometer. ^{1}H NMR spectra were recorded on a Varian-300 spectrometer using TMS as an internal reference.

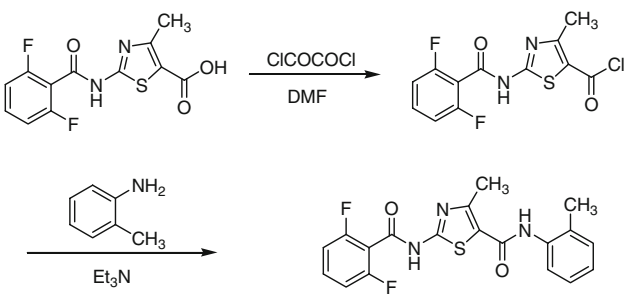
Synthesis of the Title Compound

The title compound was prepared in two stages as shown in Scheme 1 [7]. To a solution 2-(2,6-difluorobenzamido)-4-methylthiazole-5-carboxylic acid (2.98 g, 10 mmol) in dichloromethane (20 mL) was added oxalyl dichloride (0.54 g, 20 mmol). Two drops of DMF were added to the reaction mixture after 10 min. The reaction mixture was stirred at room temperature for 2 h. Then the solvent was evaporated, afforded acyl chloride, as a yellow solid. The

acyl chloride was added dropwise to a solution of *o*-toluidine (1.07 g, 10 mmol) and Et_3N (1.06 g, 10.5 mmol) in dichloromethane (20 mL) at 0 °C. The mixture was stirred at room temperature for 3 h. The reaction mixture was evaporated at reduced pressure. The residue was extracted with CH_2Cl_2 (2 × 30 mL), washed with a solution of $NaHCO_3$, NaCl, dried over anhydrous magnesiumsulfate, the solvent evaporated again. The residue was purified by column chromatography (50% EtOAc in hexanes as eluent) to afford the target compound as a white crystalline solid (3.29 g, 85% yield). The single crystals suitable for determination were obtained by slow evaporation from the solution of the title compound dissolved in ethyl acetate at room temperature. m.p: 162.4–164.0 °C. IR(KBr, cm^{-1}): 3469(m), 3170(w), 3024(w), 2939(w), 2802(w), 1696(m), 1658(m), 1623(m), 1525(s), 1452(s), 1320(s), 1252(m), 1007(s), 806(m), 752(s). The elemental analysis found for $C_{38}H_{30}F_4N_6O_4S_2$: C, 58.85; H, 3.99; N, 10.82%. Calcd.: C, 58.91; H, 3.90; N, 10.85%. ^{1}H NMR(300 MHz, DMSO-d_6) δ(ppm): 2.26 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 7.15–7.39 (m, 6H, Ar–H), 7.61–7.71 (m, 1H, AR–H), 9.62 (s, 1H, NH), 13.6 (s, 1H, NH).

X-ray Crystallography

Single crystal X-ray diffraction data collection for the title compound (0.32 × 0.28 × 0.26 mm) was performed on a Bruker Apex II CCD diffractometer at 293(2) K with Mo Kα radiation (λ = 0.71073 Å). A total of 4,708 reflections was collected, of which 3,962 are independent. The structure was solved by direct methods and refined by full-matrix least squares techniques (SHELXTL97) [8, 9]. The empirical absorption corrections by SADABS were carried out. All non-hydrogen atoms were located by direct methods and subsequent difference Fourier syntheses. The hydrogen atoms were positioned geometrically and refined using a riding model, with U_{iso}(H) = 1.2 U_{eq}(C, N) and U_{iso}(H) = 1.5 U_{eq}(C). Crystal and structure refinement data are shown in Table 1. Selected bond lengths and bond angles are listed in Table 2, and the hydrogen bond lengths and bond angles in Table 3.



Scheme 1 Synthetic process of the title compound

Results and Discussion

The bond lengths and angles are in normal range [10] (Table 2), and in agreement with 2-[(Benzoyl)-amino]-4-methyl-*N*-(2-chloro-6-methylphenyl)-1,3-thiazole-5-carboxamide [7]. In the unit cell of the title compound, there are two independent molecules (A and B, Fig. 1) having only slightly different bond lengths, torsion angles and dihedral angles between them. The C11–C12 and N3–12 bond lengths are 1.494(4) and 1.338(5) Å, respectively, comparable with C30–C31 = 1.475(4) and N6–C31 = 1.357(4) Å, respectively. The S–C–C–O torsion angles, which are the only note worthy difference in bond geometry between *A* and *B*, namely, 4.8°[S(1)–C(11)–C(12)–O(2)] versus −16.2° [S(2)–C(30)–C(31)–O(3)] for a difference of 21°. The methylthiazole, 2-methylphenyl and 2, 6-difluorobenzene rings of each molecule are not coplanar. In molecule *A,* the dihedral angle formed by the least-squares planes of the methylthiazole and 2-methylphenyl rings being equal to 3.8°. The dihedral angles between the 2, 6-difluorobenzene and methylthiazole rings are 49.2°. However, in molecule

Table 1 Crystal data and structure refinement

Empirical formula	$C_{19}H_{15}F_2N_3O_2S$
Mr	387.40
Crystal size/mm	0.32 × 0.28 × 0.26
Crystal system	Orthorhombic
Space group	Pca2(1)
a (Å)	21.840(2)
b (Å)	7.5321(8)
c (Å)	22.365(2)
α (°)	90
β (°)	90
γ (°)	90
V (Å^3)	3,679.2(6)
Z	8
D_c [g cm^{-3}]	1.399
μ [mm^{-1}]	0.215
F(000)	1,600
Flack parameter	0.06(7)
Fiedel opposites	1,374
Total/independent reflections	4,708/3,962
Parameters	491
R_{int}	0.0282
R^a, R_w^b	0.0328, 0.0803
GOF[c]	1.031
Residuals [e Å^{-3}]	0.180, −0.189

[a] $R = \sum \|F_0\| - |F_c\| / \sum |F_0|$

[b] $R_w = \left[\sum \left[w\left(F_0^2 - F_c^2\right)^2\right] / \sum w\left(F_0^2\right)^2\right]^{1/2}$

[c] $\mathrm{GOF} = \left\{\sum \left[w\left(F_0^2 - F_c^2\right)^2\right] / (n-p)\right\}^{1/2}$

Table 2 Selected bond lengths (Å), angles (°) and torsion angles (°)

S(1)–C(8)	1.720(3)	N(1)–C(7)–C(6)	114.3(3)
S(1)–C(11)	1.729(4)	O(1)–C(7)–C(6)	122.6(3)
S(2)–C(27)	1.714(3)	O(1)–C(7)–N(1)	123.1(3)
S(2)–C(30)	1.730(3)	C(7)–N(1)–C(8)	124.3(3)
F(1)–C(1)	1.362(5)	N(2)–C(9)–C(10)	117.4(3)
F(2)–C(5)	1.352(5)	N(3)–C(12)–C(11)	116.2(3)
F(3)–C(20)	1.369(5)	O(2)–C(12)–C(11)	119.3(4)
F(4)–C(24)	1.344(4)	O(2)–C(12)–N(3)	124.5(3)
O(1)–C(7)	1.217(4)	C(12)–N(3)–C(13)	129.7(3)
O(2)–C(12)	1.213(4)	C(13)–C(18)–C(19)	122.4(3)
O(3)–C(31)	1.229(4)	N(4)–C(26)–C(25)	113.9(3)
O(4)–C(26)	1.208(4)	O(4)–C(26)–C(25)	123.3(3)
N(1)–C(7)	1.351(4)	O(4)–C(26)–N(4)	122.8(3)
N(1)–C(8)	1.385(4)	C(26)–N(4)–C(27)	125.0(2)
N(2)–C(8)	1.301(4)	N(5)–C(28)–C(29)	116.4(2)
N(2)–C(9)	1.375(4)	N(6)–C(31)–C(30)	116.7(3)
N(3)–C(12)	1.338(5)	O(3)–C(31)–C(30)	119.7(3)
N(3)–C(13)	1.428(4)	O(3)–C(31)–N(6)	123.6(3)
N(4)–C(26)	1.357(4)	C(31)–N(6)–C(32)	130.1(3)
N(4)–C(27)	1.376(4)	C(32)–C(37)–C(38)	123.1(3)
N(5)–C(27)	1.309(4)	C(8)–N(1)–C(7)–C(6)	177.2(3)
N(5)–C(28)	1.373(4)	C(8)–N(1)–C(7)–O(1)	−4.3(5)
N(6)–C(31)	1.357(4)	C(5)–C(6)–C(7)–N(1)	129.8(4)
N(6)–C(32)	1.424(4)	C(13)–N(3)–C(12)–C(11)	180.0(3)
C(6)–C(7)	1.495(5)	C(13)–N(3)–C(12)–O(2)	0.3(6)
C(9)–C(10)	1.486(5)	S(1)–C(11)–C(12)–O(2)	4.8(4)
C(11)–C(12)	1.494(4)	C(27)–N(4)–C(26)–C(25)	−176.1(3)
C(18)–C(19)	1.503(6)	C(20)–C(25)–C(26)–O(4)	52.4(5)
C(25)–C(26)	1.506(5)	C(20)–C(25)–C(26)–N(4)	−128.6(4)
C(28)–C(29)	1.501(5)	C(32)–N(6)–C(31)–C(30)	172.0(3)
C(30)–C(31)	1.475(4)	C(32)–N(6)–C(31)–O(3)	−7.7(5)
C(37)–C(38)	1.515(6)	S(2)–C(30)–C(31)–O(3)	−16.3(4)

Table 3 Hydrogen bond lengths (Å) and bond angles (°)

D–H···A (Å)	D···A (Å)	H···A (Å)	D–H···A (°)
N1–H1···N5^{i}	2.9284	2.07	175
N4–H4···N2^{ii}	2.9371	2.08	174

Symmetry transformations used to generate the equivalent atoms: (i) $-1/2 + x, 1 - y, z$; (ii) $1/2 + x, 1 - y, z$

B, the dihedral angles are 19.0 and 54.1° respectively. The dihedral differences between molecules A and B are 15.2, 4.9° respectively. The difference in the bond lengths, torsion angles and dihedral angles above can be attributed to the different conformations of the two molecules.

The π–π stacking interactions were observed with the centroid–centroid separation of 3.658(2) Å, which link the two independent molecule *A* and *B* into a dimer (Fig. 1).

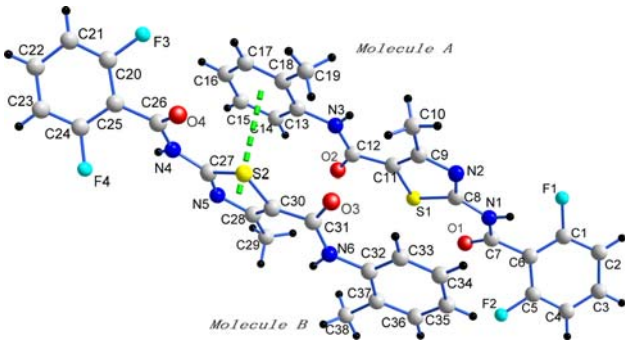


Fig. 1 Molecular structure of the title compound. (*Dotted lines* indicate π–π stacking interactions)

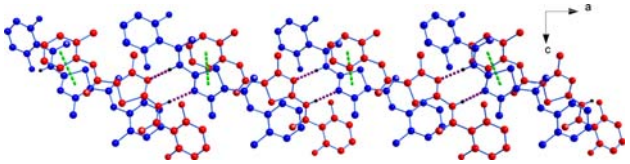


Fig. 2 1-D chain structure along [100] direction via multiple N–H···N and π–π stacking interactions

The dimers are further linked by the intermolecular N–H···N hydrogen bonds (Table 3), which form the R_2^2 (8) rings. This creates 1D chain in the [100] direction (Fig. 2).

Supplementary Material

CIF file has been deposited with the Cambridge Crystallography Data Center. Supplementary data are available from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, on request, quoting the deposition numbers 712255.

Acknowledgments We acknowledge financial support by the Scientific Research Foundation of Civil Aviation University of China (No. 08CAUC-S01, No. 07KYS05) and Natural Science Foundation of Tianjin (09JCYBJC04200).

References

1. Lewis JR (1999) Nat Prod Rep 16:389–416
2. Clemence F, Marter OL, Delevalle F, Benzoni J, Jouanen A, Jouquey S, Deraedt MR (1988) J Med Chem 31:1453–1462
3. Tsuji K, Ishikawa H (1994) Biorg Med Chem Lett 4:1601–1606
4. Patt WC, Hamilton HW, Taylor MD, Ryan MJ, Taylor DG Jr, Connolly CJC, Doharty AM, Rapundalo ST, Michniewicz BM, Olzon SCJ (1992) J Med Chem 35:2562–2572
5. Metzger JV (1984) Comprehensive heterocyclic chemistry, vol 6. Pergamon Press, Oxford, p 328
6. Fink BE, Mortensen DS, Stauffer SR, Aron ZD, Katzenellenbogen JA (1999) Chem Bio 6:205–219
7. Das J, Chen P, Norris D, Padmanabha R, Lin J, Moquin RV, Shen ZQ, Cook LS, Doweyko AM, Pitt S, Pang SH, Shen DR, Fang Q,

Fex HF, McIntyre KW, Shuster DJ, Gillooly KM, Behnia K, Schieven GL, Wityak J, Barrish JC (2006) J Med Chem 49:6819–6832
8. Sheldrick GM (1997) SHELXS97. Structure determination programs. University of GÖttingen, Germany
9. Sheldrick GM (1997) SHELXL97. Program for crystal structure refinement. University of GÖttingen, Germany
10. Allen FH, Kennard O, Watson DG, Brammer L, Orpen AG, Taylor R (1987) J Chem Soc Perkins Trans II S1–19