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COMMUNICATION

Synthesis and Crystal Structure of (*S*)-2-((*S*)-2-(*N*-Ts-Amino)-3-methylbutanoyl)-3-(1H-indol-3-yl)-6-phenyl-3,4-dihydro-1,2,4-triazin-5(2H)-one

Ilya N. Egorov · Vladimir L. Rusinov · Pavel A. Slepukhin · Oleg N. Chupakhin

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Abstract The diastereoselective synthesis, NMR and X-ray structure of (*S*)-2-((*S*)-2-(*N*-Ts-amino)-3-methylbutanoyl)-3-(1H-indol-3-yl)-6-phenyl-3,4-dihydro-1,2,4-triazin-5(2H)-one—a potential antivirus agent are reported. The compound crystallizes in the triclinic space group P1 with unit cell parameters: $a = 5.9259(6)$ Å, $b = 9.6370(12)$ Å, $c = 12.9541(9)$ Å, $\alpha = 109.210(9)°$, $\beta = 90.804(7)°$, $\gamma = 105.074(10)°$ and $Z = 1$.

Keywords Antivirus agent · Crystal structure · 1,2,4-Triazinone · Asymmetric synthesis · Amino acid

Introduction

1,2,4-Triazine nuclei is associated with a high biological activity, particularly antiviral activity, [1–5] therefore synthesis of its derivatives especially of amino acid derivatives represents a notable interest in the pharmacological field. It is known, the addition of C-nucleophiles to a prochiral C=N double bond in azines in the presence of optically active acylation reagents results in formation of the addition products with a high diastereoselectivity [6, 7] Use of amino acids in the capacity of chiral auxiliarities can also leads to the high diastereoselectivity. Earlier it was shown fluoroanhydrides of amino acids [8], free amino acids activated by DCC [9], by ethylchloroformate [10] can be used as chiral auxiliaries in the reactions of this type. We report here the crystal structure of a new amino acid derivative of 1,2,4-triazin-5(4H)-one formed with use of *N*-Ts-L-valine chloroanhydride.

I. N. Egorov (✉) · V. L. Rusinov · O. N. Chupakhin
Department of Organic Chemistry, Urals State Technical University, 19, Ul. Mira, Ekaterinburg 620002, Russian Federation
e-mail: i.n.egorov@gmail.com

P. A. Slepukhin · O. N. Chupakhin
Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 20, Ul. S. Kovalevskaya, Ekaterinburg 620219, Russian Federation

Experimental

Preparation of (*S*)-2-((*S*)-2-(*N*-Ts-Amino)-3-methylbutanoyl)-3-(1H-indol-3-yl)-6-phenyl-3,4-dihydro-1,2,4-triazin-5(2H)-one (**4**).

Triazinone **1** (1.2 mmol) was added to a magnetically stirred solution of (*S*)-*N*-Ts-valine chloride (**3**) (1.2 mmol) in 3 ml of THF at the temperature −15 °C, after 5 min indole (**2**) (1.2 mmol) was added. The mixture was stirred at −15 °C for a 1 h. Then temperature was allowed to reach 20 °C during 2 h. Then unreacted residue of the triazinone **1** was filtered from the mixture, the filtrate was poured in the cooled water (15 mL) and was extracted by ethylacetate (2*20 mL). The organic layer was washed out by water, brine and was dried over Na_2SO_4. The solution was evaporated; the gummy residue was dissolved in ethylacetate and purified on silicagel column with ethylacetate as an eluent ($R_f = 0.7$). The product was dissolved in ethanol. An evaporation of the solution in open flask at the room temperature results in formation of the colorless crystals of **4**. Yield 23%, mp = 221–222 °C, $[\alpha]_D = +570.8$ ($c = 1.0$, DMF). ^{1}H NMR (400 MHz, DMSO-d6) δ: 11.03 (d, $J = 2.1$ Hz, 1H, NH), 9.70 (d, $J = 5.3$ Hz, 1H, NH), 7.97 (d, $J = 9.1$ Hz, 1H, NH), 7.89–7.81 (m, 2H, Ph), 7.75 (d, $J = 8.0$ Hz, 1H), 7.50 (d, $J = 8.2$ Hz, 2H, Ts), 7.46–7.38 (m, 3H, Ph), 7.36 (d, $J = 8.1$ Hz, 1H), 7.07–7.12 (m, 2H), 6.97–7.00 (m, 2H), 6.87 (d, $J = 8.1$ Hz, 2H, Ts), 4.80 (dd,

J = 8.9, 6.2 Hz, 1H, CH), 2.21 (s, 3H, CH_3), 1.99–2.08 (m, 1H, CH), 0.88 (d, J = 6.7 Hz, 3H, CH_3), 0.84 (d, J = 6.7 Hz, 3H, CH_3).

Structure Determination and Refinement

X-Ray analysis including data collection, cell refinement and data reduction was carried out with an Oxford Diffraction Xcalibur S CCD diffractometer using CrysAlisPro software package [11]. The X-ray data collection was carried out at 295(2) K with graphite monochromatized Mo–Kα radiation (α = 0.71073 Å). The structure was solved by direct methods using SHELXS-97 [12] and refined by full-marix least-squares procedure on F^2 with SHELXL-97 [12]. Non-H atoms were refined anisotropically, hydrogen atoms were placed in idealized positions and were constrained to ride on their parent atoms with $U_{iso}(H)$ = 1.5 Ueq(C) for CH_3 groups and $U_{iso}(H)$ = 1.2 Ueq(C) for all other C–H (Table 1). H-atoms of N–H groups (H3, H4, H5) were located in a difference map and then refined independently. The restraints were generated automatically.

Results and Discussion

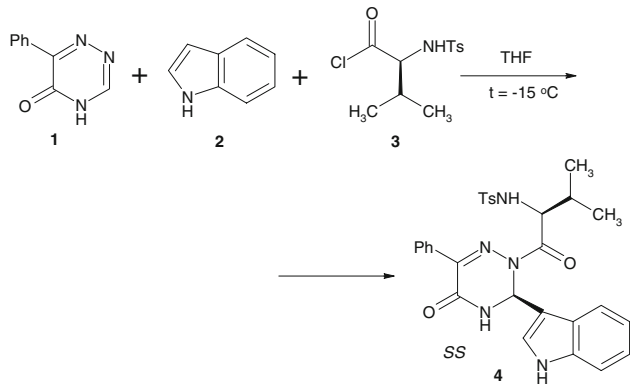
Crystal Structure of (*S*)-2-((*S*)-2-(*N*-Ts-Amino)-3-methylbutanoyl)-3-(1H-indol-3-yl)-6-phenyl-3,4-dihydro-1,2,4-triazin-5(2H)-one (**4**).

The chemical diagram of the title compound, **4**, is illustrated in Scheme 1 and experimental conditions are summarized in Table 1. Selected bond distances and bond angles are listed in Table 2. Weak interactions geometry is presented in Table 3. The data for publication were prepared with WinGX [13], ORTEP [14], and Mercury [15] program packages.

X-ray and NMR ^{1}H data shows the reaction results in formation of the diastereomerically pure compound (*S*)-2-((*S*)-2-(*N*-Ts-Amino)-3-methylbutanoyl)-3-(1H-indol-3-yl)-6-phenyl-3,4-dihydro-1,2,4-triazin-5(2H)-one (**4**) (Fig. 1). The absolute stereochemistry of the synthesized compound is

Table 1 Crystal data and structure solution methods and refinement results for **4**

Empirical formula	$C_{29}H_{29}N_5O_4S$
Formula weight	543.63
Crystal system	Triclinic
Space group	P1
a(Å)	5.9259(6)
b(Å)	9.6370(12)
c(Å)	12.9541(9)
α(°)	109.210(9)
β(°)	90.804(7)
γ(°)	105.074(10)
Volume (Å^3)	670.51(12)
Z	1
Calculated density (g/cm^3)	1.346
Absorption coefficient (mm^{-1})	0.166
F (000)	286
Crystal size (mm)	0.45 × 0.41 × 0.34
Crystal color/shape	Colorless/prismatic
θ Range for data collection (°)	3.35–28.28
Reflections collected/independent (R_{int})	7142/3703 (0.0241)
Observed reflections [I > 2σ(I)]	2571
Completeness (%)	97.1 (to θ = 28.28°)
Refinement method	Full matrix least-squares procedure on F^2
Weight, w	$1/[\sigma^2(F_o^2)] + (0.0262P)^2 + 0.00P]$ where $P = (F_o^2 + 2F_c^2)/3$
Data/restraints/parameters	3703/3/364
Goodness of fit on F^2	1.000
Final R indices [I > [2σ(I)]	R_1 = 0.0325, wR_2 = 0.0573
Absolute structure parameter	−0.02(5)
Largest peak and hole (eÅ^{-3})	0.159 and −0.190



Scheme 1 Synthesis of (*S*)-2-((*S*)-2-(*N*-Ts-amino)-3-methylbutanoyl)-3-(1H-indol-3-yl)-6-phenyl-3,4-dihydro-1,2,4-triazin-5(2H)-one (**4**)

Table 2 Selected geometrical parameters for **4** (Å and °)

N1–N2	1.372(3)	N1–N2–C1	120.7(2)
N2–C1	1.463(4)	N3–C1–N2	107.4(2)
C1–N3	1.439(3)	C1–N3–C2	122.8(2)
N3–C2	1.332(3)	N3–C2–C3	114.4(2)
C2–C3	1.489(4)	N1–C3–C2	122.8(2)
C3–N1	1.294(3)	C18–N2–C1–C11	80.3(2)
N1–N2–C18	117.8(2)	N1–N2–C18–O4	176.2(2)
N2–C1–C11	110.7(2)	O4–C18–C19–C20	105.6(3)
N2–C18–C19	117.6(2)	O4–C18–C19–N4	−17.4(3)
C18–C19–N4	110.9(2)	N1–C3–C4–C9	37.6(3)

Table 3 Hydrogen bonds and weak interactions for **4** (Å and °)

D–H···A	d(D–H)	d(H···A)	d(D···A)	<(DHA)	Symmetry operation
N3–H3···O2	0.86(3)	2.30(3)	3.148(4)	170.0(17)	$x, -1 + y, z$
N3–H3···O1	0.86(3)	2.60(3)	3.213(4)	129.4(17)	$x, -1 + y, z$
N3–H3···S1	0.86(3)	2.84(3)	3.651(4)	159.6(17)	$x, -1 + y, z$
N4–H4···O3	0.85(3)	2.33(3)	3.032(4)	140.4(18)	$1 + x, 1 + y, z$
C22–H22···O3	0.960	2.480(4)	3.356(4)	7.7(2)	$1 + x, 1 + y, z$
C21–H21···O3	0.961	2.651(4)	3.458(4)	142.0(2)	$1 + x, 1 + y, z$
C10–H10···O4	0.930	2.425(4)	3.069(4)	126.4(2)	$-1 + x, y, z$

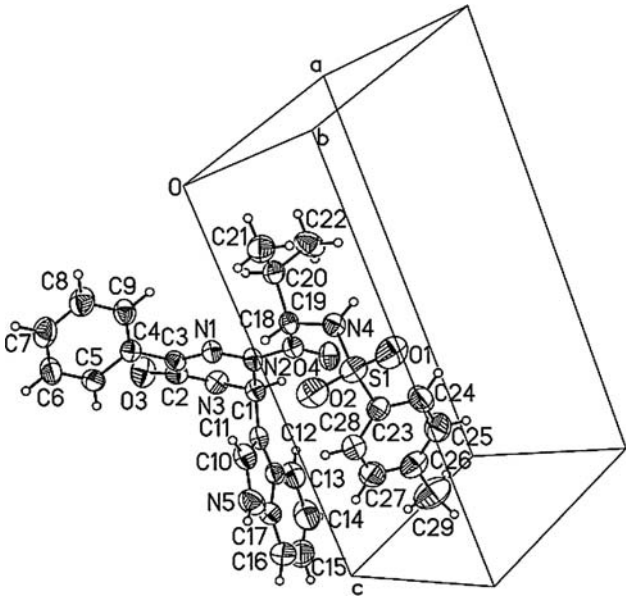


Fig. 1 View of the structure of **4**, drawn with 50% probability displacement ellipsoids and showing the atom labeling scheme. H-atoms are shown as small spheres of arbitrary radii

assigned on the base of known stereochemistry of starting material (*S*)-*N*-Ts-valine chloride (**3**). In CCDC [16] the structures of hundreds compounds with C–SO_2–N-group are presented and only six of them have C–SO_2–NH–CH(i-Pr)–CO-fragment (as in the structure **4**). The measured bond lengths and angles are typical for this class of compounds. For example, the measured S–O bond lengths (1.439(2) and 1.428(2) Å) and S–N bond lengths (1.597(2)) are near to the medium bond lengths for C–SO_2N-group from CCDC [16]. The measured torsion angles S1N4C19C20 156.2(3)° and

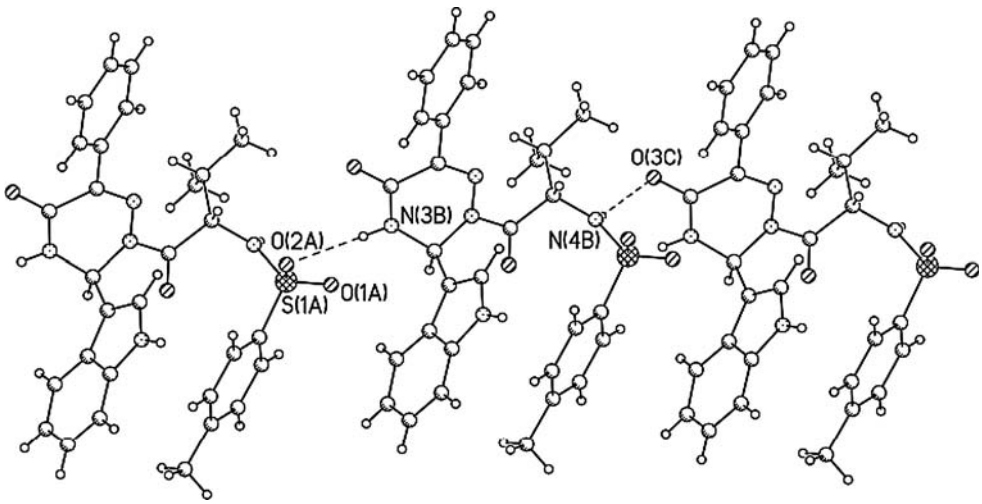


Fig. 2 Packing diagram with H-bonds of **4**. *Dotted lines* indicate intermolecular hydrogen-bonding interactions

N4C18C18O4-17.2(3)° also are typical for Ts-amines with polar substituents [16]. The triazine ring has a "pseudo-cover" conformation, the sp^3-atom C1 was pulled out from the triazine plane on 0.503(3) Å. The most prominent hydrogen bonding contacts in the crystal of **4** occurs between the N4–H amino group atoms and O3 of ketone group, between atoms of amino group N3–H and atoms S1–O1, S1–O2 of SO_2 group (Fig. 2). Were founded C–H···O contacts C22–H22···O3, C21–H21···O3 (Table 3) also responsible for a packing of molecules in the crystal structure **4**.

Supplementary Materials

CCDC 724265 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, 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: +44-0-1223336033.

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