The Synthesis of 4-Acylamino-1,2,4-triazole Derivatives in the Reaction of α-Hydroxyacid Hydrazides and Orthoesters

W. Zieliński*, A. Kudelko and W. Czardybon

Department of Organic Technology and Petrochemistry Silesian University of Technology, Ul. Krzywoustego 4, PL-44101 Gliwice, Poland

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The reaction of α-hydroxyacid hydrazides and orthoesters in ethanol-acetic acid solution has been studied and a series of 4-acylamino-1,2,4-triazoles has been obtained as the final products. Some acyclic intermediates: 1-acyl-2-ethoxymethylenehydrazines and *N,N'*-bis(methanecarbonylamino)formamidine derivative have been also separated during the process. The structures of products was confirmed by typical spectroscopic methods and X-ray analysis.

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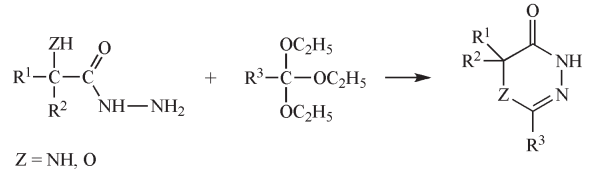
α-Hydroxyacid hydrazides constitute potential precursors for the synthesis of nitrogen- and nitrogen-oxygen-containing heterocyclic systems. We know the reactions of α-hydroxyacids with hydrazine hydrate yielding 4-amino-1,2,4-triazoles substituted symmetrically in positions 3,5- with hydroxymethyl groups, used principally as building blocks for macrocyclic systems [1-4]. Similarly, the unsubstituted alkanecarboxylic acid hydrazides due to heating with hydrazine hydrate give 1,2,4-triazoles [5]. The amino derivatives are also obtained with satisfactory yields from ester formylhydrazones in the reaction with hydrazine hydrate, ethyl carbazate or *tert*-butyl carbazate [6]. Some reactions of alkanecarboxylic and arylcarboxylic acid hydrazides with orthoesters yielding the derivatives of 1,3,4-oxadiazoles are also described in the literature [7,8]. Authors reported that the first stage of the reaction between hydrazides of alkanecarboxylic acids and triethyl orthoformate yields 1-acyl-2-ethoxymethylenehydrazines, which subjected to heating undergo condensation to 1,3,4-oxadiazoles. On the other hand, there are also mentions about the formation of six-membered ring such as 1,4,5,6-tetrahydro-1,2,4-triazine-6-one in the reaction of aminoacid hydrazides with orthoesters [9] or 4,5-dihydro-1,2,4-triazine-6-one from amino acid imidates and hydrazines [10]. Considering this fact we came to the conclusion that replacing the amino group with a hydroxy group in hydrazide followed by the reaction with orthoesters would lead to the corresponding 1,3,4-oxadiazine-5-ones (Scheme 1).

Scheme 1



This paper describes the investigation studies on the reactions of hydrazides of α-hydroxyacids with orthoesters, taking into consideration the possibility to synthesize in this way 1,3,4-oxadiazine derivatives.

Heating the hydrazides of α-hydroxyacids with an excess of orthoesters in the presence of boiling ethanol and acetic acid we obtained the products whose structure did not correspond to the expected 1,3,4-oxadiazine but to 1,2,4-triazole. In fact, the compound obtained from the reaction of benzilic acid hydrazide with triethyl orthopropionate showed the structure corresponding to 4-(1,1-diphenyl-1-hydroxymethanecarbonylamino)-3-(1-hydroxy-1,1-diphenylmethyl)-5-ethyl-1,2,4-triazole (**4i**) as demonstrated by X-ray crystallographic analysis (Figure 1).

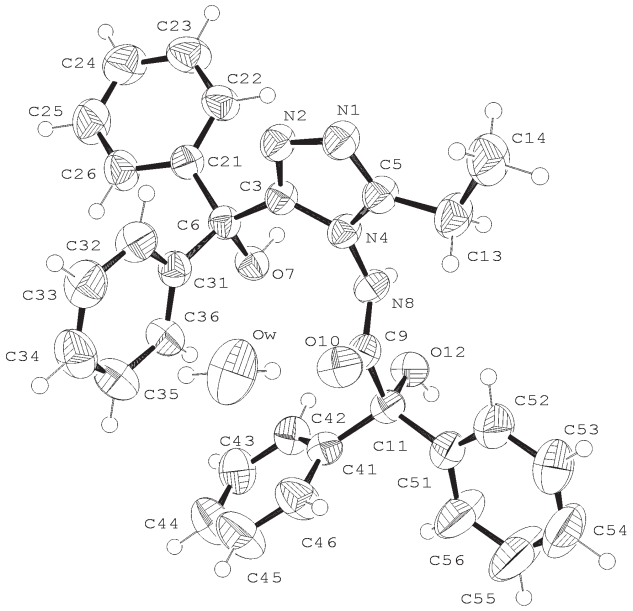
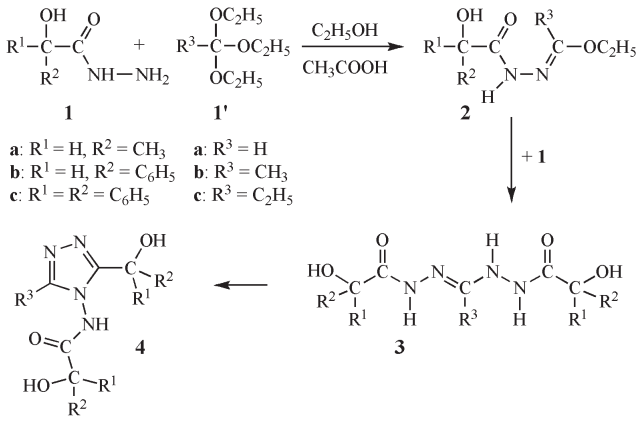


Figure 1. View of the molecule of 4-(-(1,1-diphenyl-1-hydroxymethanecarbonylamino)-3-(1,1-diphenyl-1-hydroxymethyl)-5-ethyl-1,2,4-triazole (**4i**) by X-ray analysis with numbering of the atoms.

Analogous compounds are formed in the reaction of other hydrazides of α-hydroxyacids with orthoesters. Based on the structure of the products, the following reaction scheme can be proposed:

Scheme 2



	R^1	R^2	R^3		R^1	R^2	R^3
4a	H	CH_3	H	**4f**	H	C_6H_5	C_2H_5
4b	H	CH_3	CH_3	**4g**	C_6H_5	C_6H_5	H
4c	H	CH_3	C_2H_5	**4h**	C_6H_5	C_6H_5	CH_3
4d	H	C_6H_5	H	**4i**	C_6H_5	C_6H_5	C_2H_5
4e	H	C_6H_5	CH_3				

Following literature [7] we assumed that the first stage of the reaction between the hydrazides of α-hydroxyacids (**1**) and orthoesters yields acyclic intermediates, 1-acyl-2-ethoxymethylenehydrazines (**2**). Initial research on the reactions of α-hydroxyacid hydrazides with the excess of orthoester has proved that the main products are indeed acyclic derivatives of 1-(alkanecarbonyl)-2-ethoxymethylenehydrazine (**2**). ^{1}H- and ^{13}C-nmr spectra of two intermediates (**2h**, **2i**) produced in the reaction of benzilic acid hydrazide with triethyl orthoacetate and orthopropionate showed a double number of peaks certainly due to the presence of *E* and *Z* form. In the case of the unsubstituted arrangement (**2g**, R^3=H) only one isomer was recorded. Imine carbon atom in the compound **2** is susceptible to the attack of nucleophiles, so we assumed that using an excess of orthoester, the reaction would yield the derivatives of 1,3,4-oxadiazine, which might have been formed as a result of intramolecular reaction, similarly as it takes place in the case of the reaction with the hydrazides of α-aminoacids [9]. However, the formation of 4-amino-1,2,4-triazole (**4**) derivatives in the reaction indicates that the first step of reaction leading to **2** is much slower than the following steps, and as the result, the more nucleophilic molecule of α-hydroxyacid hydrazide reacts with the compound **2** yielding acyclic *N,N′*-bis(1-hydroxy-1-phenylmethanecarbonylamino)formamidine (**3d**).

The cyclization of *N,N′*-bisformamidine derivative **3** takes place in acidic medium at elevated temperature. Important roles in this process are played by acetic acid, which is the catalyst and ethanol which is used as a solvent. According to our examination, in the absence of both of them the reaction stops at the intermediate product - 1-alkanecarbonyl-2-ethoxymethylenehydrazine (**2**). The structures both of acyclic intermediates and final 4-acylamino-1,2,4-triazoles were confirmed by means of elemental analyses, typical spectroscopic methods and X-ray analysis.

The X-ray investigation revealed that 4-(1,1-diphenyl-1-hydroxy-methanecarbonylamino)-3-(1,1-diphenyl-1-hydroxymethyl)-5-ethyl-1,2,4-triazole (**4i**, Figure 1) crystallizes in amino-carbonyl tautomeric form with one molecule of the water per one molecule of the free base. Selected geometrical parameters for the investigated crystal structure **4i** taken from X-ray analysis are given in Table 1 and Table 2.

Table 1

Selected bond lengths [Å] for 4-(1,1-diphenyl-1-hydroxymethanecarbonylamino)-3-(1,1-diphenyl-1-hydroxymethyl)-5-ethyl-1,2,4-triazole (**4i**) taken from X-ray analysis.

Selected bond	Lenght [Å]	Selected bond	Lenght [Å]
O7-C6	1.4174(15)	N8-C9	1.3452(18)
O10-C9	1.2192(16)	C3-C6	1.5247(18)
O12-C11	1.4259(16)	C5-C13	1.4930(2)
N1-C5	1.3014(18)	C6-C31	1.5403(18)
N1-N2	1.4003(16)	C6-C21	1.5398(18)
N2-C3	1.3065(17)	C9-C11	1.5414(18)
N4-C5	1.3644(18)	C11-C41	1.5301(2)
N4-C3	1.3763(16)	C11-C51	1.5306(19)
N4-N8	1.3845(15)	C13-C14	1.5150(3)

Table 2

Selected angles [°] for 4-(1,1-diphenyl-1-hydroxymethanecarbonylamino)-3-(1,1-diphenyl-1-hydroxymethyl)-5-ethyl-1,2,4-triazole (**4i**) taken from X-ray analysis.

Selected bonds	Angle [°]	Selected bonds	Angle [°]
C5-N1-N2	107.94(11)	O7-C6-C21	109.19(10)
C3-N2-N1	107.92(11)	C3-C6-C31	107.21(10)
C5-N4-C3	107.00(11)	C3-C6-C21	111.04(11)
C5-N4-N8	123.83(11)	C31-C6-C21	111.65(10)
C3-N4-N8	129.08(11)	O10-C9-N8	123.45(13)
C9-N8-N4	119.28(11)	O10-C9-C11	122.50(12)
N2-C3-N4	108.26(11)	N8-C9-C11	114.05(11)
N2-C3-C6	125.61(11)	O12-C11-C41	111.06(11)
N4-C3-C6	125.94(11)	O12-C11-C51	109.85(11)
N1-C5-N4	108.87(12)	C41-C11-C51	113.22(11)
N1-C5-C13	127.43(13)	O12-C11-C9	105.61(10)
N4-C5-C13	123.69(13)	C41-C11-C9	106.12(11)
O7-C6-C3	110.81(10)	C51-C11-C9	110.65(11)
O7-C6-C31	106.85(10)	C5-C13-C14	112.96(15)

Bond lengths and angles in this ring do not differ significantly from those reported for other related structures [11-13]. The N1–C5 of 1.3014(18) Å and N2–C3 of 1.3065(17) Å bonds have rather double-bond character, while the other N1-N2 and N–C ring bonds have intermediate values between single- and double-bond lengths characteristic for delocalizated π-electron systems (Table 1). The ethyl substituent in the position 5 lies almost in the plane of the tria-

zole ring: torsion angle N1–C5–C13–C14 is -6.9(3)° and displacements of C13 and C14 are 0.024(2) and -0.120(3) Å, respectively. The conformation of the molecule observed in the crystal of **4i** is forced mainly by steric repulsion between the three large substituents in the adjacent 3, 4 and 5 positions of the triazole ring and the intramolecular hydrogen bonds N8–H8⊃O12, C36–H361⊃O7, C42–H421⊃O12 and OW–H1W⊃O10 (Table 3).

Table 3

The geometry of intra- and intermolecular hydrogen bonds in **4i**.

Type	Position code	D-H [Å]	H…A [Å]	D…A [Å]	D-H…A [°]
N8-H8…O12	intra	0.911(18)	2.11(2)	2.4777(16)	102.8(15)
C36-H361…O7	intra	0.977(18)	2.30(2)	2.664(2)	101.1(16)
C42-H241…O12	intra	0.97(2)	2.34(2)	2.748(2)	104.5(14)
OW-H1W…O10	intra	0.95(3)	1.93(4)	2.8295(19)	157.0(3)
O7-H7…N1	2645 [a]	0.94(2)	1.79(2)	2.7217(17)	167.7(18)
O7-H7…N2	2645 [a]	0.94(2)	2.598(19)	3.3683(15)	139.2(15)
N8-H8…N2	2645 [a]	0.911(18)	2.24(2)	3.0216(18)	111.9(8)
O12-H12…OW	2545 [b]	0.869(19)	1.947(18)	2.7686(19)	157.3(19)

[a] 2645 = 3/2-x, -1/2+y, 1/2-z; [b] 2545 = 1/2-x, -1/2+y, 1/2-z.

The packing of the molecules in the crystal of **4i** is determined by the net of the intermolecular hydrogen bonds with geometry and symmetry codes presented in Table 3.

In conclusion, it must be emphasized that this type of reaction of α-hydroxyacid hydrazides and orthoesters in ethanol-acetic acid solution which so far has not been described in literature, affords new potentials involving the synthesis of asymmetrically substituted 4-amino-1,2,4-triazoles.

EXPERIMENTAL

UV spectra were recorded on a Shimadzu UV-2102 spectrophotometer; Elemental analyses were carried out with a Perkin Elmer 240c analyser. The ^{1}H- and ^{13}C-nmr spectra were recorded on a Varian Inova 300 spectrometer in DMSO solution using TMS as internal standard. Thin layer chromatography was carried out on silica gel 60 F_{254} (Merck) thin layer chromatography plates using a benzene-ethyl acetate (1:3 v/v) as the mobile phase. Orthoesters were purchased from Fluka Chemie GmbH.

Synthesis of α-hydroxyacids Hydrazides (**1a-c**).

The hydrazides of α-hydroxyacids were obtained according to a standard procedure in the reaction of ethyl esters of α-hydroxyacids with hydrazine hydrate to yield: The hydrazide of lactic acid (**1a**) [14]: bp 153-156 °C/2 torr; The hydrazide of mandelic acid (**1b**) [15]: mp 151-153 °C; The hydrazide of benzilic acid (**1c**) [16]: mp 167-169 °C.

General Procedure for the Preparation of Substituted 1-(Alkanecarbonyl)-2-ethoxymethylenehydrazine Derivatives (**2**).

A solution of the appropriate hydrazide (**1**) (0.025 mole) and triethyl orthoester (20 mL) was heated under mild reflux for 24 hours. Then it was cooled giving white precipitate of **2**, which was collected by filtration and recrystallized from alcohol (methanol, ethanol). In one case the post-reaction mixture was distilled under reduced pressure to get 2-ethoxymethylenehydrazine intermediate **2a**.

1-(1-Hydroxyethanecarbonyl)-2-ethoxymethylenehydrazine (**2a**).

This compound was obtained as a yellowish liquid in 65% yield; bp 144-146 °C/20 torr; R_f: 0.38; ^{1}H nmr (DMSO-d_6, Me_4Si): δ 1.22 (t, *J* = 7.2, 3 H, OCH_2CH_3), 1.33 (d, *J* = 6.9, 3 H, CH_3), 4.12 (q, *J* = 7.2, 2 H, OCH_2CH_3), 4.42 (q, *J* = 6.9, 1 H, HC=O), 6.03 (d, 1 H, OH), 8.17 (s, 1H, HC=N), 8.51 (s, 1 H, NH) ppm; uv: λ_{max} ($\varepsilon \cdot 10^{-3}$) MeOH: 227.6 (6.93) nm.

Anal. Calcd. for $C_6H_{12}N_2O_3$: C, 45.01; H, 7.57; N, 17.49. Found: C, 45.22; H, 7.70; N, 17.56.

1-(1-Hydroxy-1-phenylmethanecarbonyl)-2-ethoxymethylenehydrazine (**2d**).

This compound was obtained as a white solid in 32% yield; mp 125-129 °C; R_f: 0.04; ^{1}H nmr (DMSO-d_6, Me_4Si): δ 1.22 (t, *J* = 7.2, 3 H, OCH_2CH_3), 4.04 (q, *J* = 7.2, 2 H, OCH_2CH_3), 4.95 (d, *J* = 4.5, 1 H, PhCH), 6.23 (d, *J* = 4.5, 1 H, OH), 7.26-7.45 (m, 5H, Ph), 8.32 (s, 1H, HC=N), 10.71 (s, 1 H, NH) ppm; uv: λ_{max} ($\varepsilon \cdot 10^{-3}$) MeOH: 205.0 (25.70), 232.0 (12.50) nm.

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.44; H, 6.36; N, 12.60. Found: C, 59.76; H, 6.22; N, 12.74.

1-(1,1-Diphenyl-1-hydroxymethanecarbonyl)-2-ethoxyethylenehydrazine (**2h**).

This compound was obtained as a white solid in 75% yield; mp 162-165 °C; R_f: 0.17, 0.50; ^{1}H nmr (DMSO-d_6, Me_4Si): δ 1.22 (t, *J* = 7.2, 3 H, OCH_2CH_3), 1.25 (t, *J* = 7.2, 3 H, OCH_2CH_3), 1.86 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 4.07 (q, *J* = 7.2, 2 H, OCH_2CH_3), 4.15 (q, *J* = 7.2, 2 H, OCH_2CH_3), 6.80 (s, 1 H, OH), 7.00 (s, 1 H, OH), 7.26-7.43 (m, 20H, Ph), 10.00 (s, 1 H, NH), 10.21 (s, 1 H, NH) ppm; uv: λ_{max} ($\varepsilon \cdot 10^{-3}$) MeOH: 208.0 (25.80), 227.0 (15.00) nm.

Anal. Calcd. for $C_{18}H_{20}N_2O_3$: C, 69.20; H, 6.46; N, 8.96. Found: C, 69.36; H, 6.52; N, 9.05.

1-(1,1-Diphenyl-1-hydroxymethanecarbonyl)-2-ethoxypropylenehydrazine (**2i**).

This compound was obtained as a white solid in 73% yield; mp 120-122 °C; R_f: 0.17, 0.54; ^{1}H nmr (DMSO-d_6, Me_4Si): δ 0.98 (t, *J*

= 7.5, 3 H, CH_2CH_3), 1.06 (t, *J* = 7.5, 3 H, CH_2CH_3) 1.22 (t, *J* = 6.9, 3 H, OCH_2CH_3), 1.25 (t, *J* = 6.9, 3 H, OCH_2CH_3), 2.25 (q, *J* = 7.5, 2H, CH_2CH_3), 2.43 (q, *J* = 7.5, 2H, CH_2CH_3), 4.07 (q, *J* = 6.9, 2 H, OCH_2CH_3), 4.14 (q, *J* = 6.9, 2 H, OCH_2CH_3), 6.82 (s, 1 H, OH), 7.01 (s, 1 H, OH), 7.24-7.43 (m, 20H, Ph), 9.98 (s, 1 H, NH), 10.27 (s, 1 H, NH) ppm; ^{13}C nmr: δ 9.4 (CH_3), 10.1 (CH_3), 14.1 (OCH_2CH_3), 15.1 (OCH_2CH_3), 21.6 (CH_2CH_3), 22.1 (CH_2CH_3), 61.9 (OCH_2CH_3), 63.8 (OCH_2CH_3), 80.4 (Ph_2COH), 80.5 (Ph_2COH), 127.2, 127.3, 127.4, 127.5, 127.6, 127.7, 143.7, 144.1 (C_{Ar}), 156.0 (C=N), 167.2 (C=N), 167.8 (C=O), 169.4 (C=O) ppm; uv: λ_{max} ($\varepsilon \cdot 10^{-3}$) MeOH: 205.0 (25.60), 232.0 (12.50) nm.

Anal. Calcd. for $C_{19}H_{22}N_2O_3$: C, 69.91; H, 6.80; N, 8.58. Found: C, 70.06; H, 6.71; N, 8.78.

The Preparation of *N,N'*-Bis(1-hydroxy-1-phenylmethanecarbonylamino)-formamidine (**3d**).

A mixture of mandelic acid hydrazide (**1b**) (1.87 g, 11.3 mmole) and 2-ethoxymetylenehydrazine intermediate (**2d**) in methanol (15 mL) was heated under reflux until the disappearance of the intermediate (**2d**) (tlc) was completed. Then methanol was removed using a rotary evaporator giving white crude product (**3d**) which was crystallized from ethyl acetate (yield: 26%); mp 155-158 °C; R_f: 0.02; ^{1}H nmr (DMSO-d_6, Me_4Si): δ 5.19 (d, *J* = 3.0, 1H, PhCH), 5.54 (d, *J* = 3.0, 1H, PhCH), 6.13 (br s, 1H, OH), 6.59 (d, *J* = 3.0, 1H, OH), 7.22-7.49 (m, 10H, Ph), 8.47 (s, 1H, HC=N), 9.81 (br s, 1H, NH), 10.38 (s, 1 H, NH), 11.65 (s, 1H, NHN=C) ppm; uv: λ_{max} ($\varepsilon \cdot 10^{-3}$) MeOH: 207.0 (21.50), 247.0 (8.80) nm.

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.63; H, 5.31; N, 16.35. Found: C, 59.86; H, 5.42; N, 16.50.

General Procedure for the Preparation of Substituted 4-Acylamino-1,2,4-triazoles (**4**).

The appropriate triethyl orthoester (0.06 mole) was dropped into a boiling mixture of the hydrazide (**1**) (0.02 mole) in ethanol (7 mL) and glacial acetic acid (1 mL). It was kept under reflux for about 1-2 hours. After cooling the solution a white precipitate was obtained that was collected by filtration and the crude product (**4**) was crystallized from ethyl acetate.

4-(1-Hydroxyethanecarbonylamino)-3-(1-hydroxyethyl)-1,2,4-triazole (**4a**).

This compound was obtained as a white solid in 50% yield; mp 192-194 °C; R_f: 0.08; ^{1}H nmr (DMSO-d_6, Me_4Si): δ 1.32 (d, 3H, *J* = 6.9 Hz, CH_3), 1.42 (d, 3H, *J* = 6.9 Hz, CH_3CC=O), 4.24 (q, 1H, *J* = 6.9 Hz, CH), 4.65 (q, 1H, *J* = 6.9 Hz, CHC=O), 5.50 (s, 1H, COH), 5.90 (s, 1H, O=CCOH), 8.47 (s, 1H, H-C5), 11.50 (s, 1H, NH) ppm; ^{13}C nmr: δ 18.5 (CH_3-CHOH-C3), 20.6 (CH_3-CHOHCONH), 65.4 (CH_3-CHOH-C3), 68.3 (CH_3-CHOHCONH), 143.2 (C5), 151.6 (C3), 172.0 (C=O) ppm.

Anal. Calcd. for $C_7H_{12}N_4O_3$: C, 41.99; H, 6.06; N, 27.98; O, 23.97. Found: C, 42.05; H, 6.03; N, 27.95; O, 23.90.

4-(1-Hydroxyethanecarbonylamino)-3-(1-hydroxyethyl)-5-methyl-1,2,4-triazole (**4b**).

This compound was obtained as a white solid in 64% yield; mp 227-231 °C; R_f: 0.04; ^{1}H nmr (DMSO-d_6, Me_4Si): δ 1.33 (d, 3H, *J* = 6.6 Hz, CH_3), 1.40 (d, 3H, *J* = 6.9 Hz, CH_3CC=O), 2.12 (s, 3H, CH_3C=N), 4.20-4.38 (m, 1H, CH), 4.50-4.70 (m, 1H, CHC=O), 5.35 (d, 1H, *J* = 6.0 Hz, COH), 5.89 (d, 1H, *J* = 5.1 Hz, O=CCOH), 11.20 (s, 1H, NH) ppm; ^{13}C nmr: δ 8.0 (CH_3-C5), 18.5 (CH_3-CHOH-C3), 20.5 (CH_3-CHOHCONH), 65.3 (CH_3-CHOH-C3), 68.3 (CH_3-CHOHCONH), 151.6 (C3), 152.3 (C5), 171.8 (C=O) ppm.

Anal. Calcd. for: $C_8H_{14}N_4O_3$: C, 44.85; H, 6.59; N, 26.15; O, 22.41. Found: C, 44.86; H, 6.41; N, 26.31; O, 22.42.

4-(1-Hydroxyethanecarbonylamino)-3-(1-hydroxyethyl)-5-ethyl-1,2,4-triazole (**4c**).

This compound was obtained as a white solid in 48% yield; mp 240-243 °C; R_f: 0.10; ^{1}H nmr (DMSO-d_6, Me_4Si): δ 1.16 (t, 3H, *J* = 7.6 Hz, CH_2CH_3), 1.32 (d, 3H, *J* = 6.9 Hz, CH_3), 1.40 (d, 3H, *J* = 6.6 Hz, CH_3CC=O), 2.46 (q, 2H, *J* = 7.6 Hz, CH_2CH_3), 4.20-4.40 (m, 1H, CH), 4.50-4.78 (m, 1H, CHC=O), 5.34 (d, 1H, *J* = 5.4 Hz, COH), 5.85 (d, 1H, *J* = 4.8 Hz, O=CCOH), 11.19 (s, 1H, NH) ppm; ^{13}C nmr: δ 7.8 (CH_3CH_2-C5), 16.0 (CH_3CH_2-C5), 18.5 (CH_3-CHOH-C3), 20.5 (CH_3-CHOHCONH), 65.3 (CH_3-CHOH-C3), 68.4 (CH_3-CHOHCONH), 151.7 (C-3), 153.5 (C5), 171.7 (C=O) ppm.

Anal. Calcd. for: $C_9H_{16}N_4O_3$: C, 47.36; H, 7.08; N, 24.53; O, 21.03. Found: C, 47.30; H, 7.10; N, 24.57; O, 20.96.

4-(1-Hydroxy-1-phenylmethanecarbonylamino)-3-(1-hydroxy-1-phenylmethyl)-1,2,4-triazole (**4d**).

This compound was obtained as a white solid in 51% yield; mp 244-245 °C; R_f: 0.06; ^{1}H nmr (DMSO-d_6, Me_4Si): δ 4.92 (d, 1H, *J* = 5.2 Hz, CH), 5.01 (d, 1H, *J* = 5.5 Hz, CHC=O), 5.96 (d, 1H, *J* = 5.2 Hz, COH), 6.12 (d, 1H, *J* = 5.5 Hz, O=CCOH), 7.23-7.47 (m, 10H, Ph), 9.96 (s, 1H, H-C5), 11.40 (s, 1H, NH) ppm; ^{13}C nmr: δ 66.3 (Ph*C*HOH-C3), 70.8 (Ph*C*HOHCONH), 126.5-129.1, 139.5, 141.4 (C_{Ar}), 145.1 (C5), 153.5 (C3), 171.1 (C=O) ppm.

Anal. Calcd. for $C_{17}H_{16}N_4O_3$: C, 62.96; H, 4.98; N, 17.28; O, 14.78. Found: C, 62.98; H, 4.99; N, 17.30; O, 14.72.

4-(1-Hydroxy-1-phenylmethanecarbonylamino)-3-(1-hydroxy-1-phenylmethyl)-5-methyl-1,2,4-triazole (**4e**).

This compound was obtained as a white solid in 41% yield; mp 231-232°C; R_f: 0.04; ^{1}H nmr (DMSO-d_6, Me_4Si): δ 2.00 (s, 3H, CH_3), 5.12 (s, 1H, CH), 5.52 (s, 1H, CHC=O), 5.16 (d, 1H, *J* = 5.7 Hz, COH), 6.71 (d, 1H, *J* = 4.2 Hz, O=CCOH), 7.25-7.52 (m, 10H, Ph), 11.49 (s, 1H, NH) ppm; ^{13}C nmr: δ 8.4 (CH_3-C5), 66.4 (Ph*C*HOH-C3), 70.8 (Ph*C*HOHCONH), 126.5-128.3, 139.2, 141.3 (C_{Ar}), 152.6 (C5), 153.7 (C3), 171.1 (C=O) ppm.

Anal. Calcd. for $C_{18}H_{18}N_4O_3$: C, 63.89; H, 5.33; N, 16.56; O, 14.19. Found: C, 63.27; H, 5.37; N, 16.42; O, 14.94.

4-(1-Hydroxy-1-phenylmethanecarbonylamino)-3-(1-hydroxy-1-phenylmethyl)-5-ethyl-1,2,4-triazole (**4f**).

This compound was obtained as a white solid in 32% yield; mp 211-213°C; R_f: 0.07; ^{1}H nmr (DMSO-d_6, Me_4Si): δ 1.02 (t, 3H, *J* = 7.2 Hz, CH_2CH_3), 2.32 (q, 2H, *J* = 7.2 Hz, CH_2CH_3), 5.22 (d, 1H, COH), 5.50 (s, 1H, CHC=O), 6.12 (s, 1H, COH), 6.62 (s, 1H, O=CCOH), 7.26-7.52 (m, 10H, Ph), 11.53 (s, 1H, NH) ppm; ^{13}C nmr: δ 8.3 (CH_3CH_2-C5), 16.5 (CH_3CH_2-C5), 66.3 (Ph*C*HOH-C3), 70.9 (Ph*C*HOHCONH), 126.8-129.1, 139.0, 141.6 (C_{Ar}), 153.7 (C3), 154.0 (C5), 171.1 (C=O) ppm.

Anal. Calcd. for $C_{19}H_{20}N_4O_3$: C, 64.75; H, 5.73; N, 15.90; O, 13.62. Found: C, 64.77; H, 5.75; N, 15.85; O, 13.59.

4-(1,1-Diphenyl-1-hydroxymethanecarbonylamino)-3-(1,1-diphenyl-1-hydroxymethyl)-1,2,4-triazole (**4g**).

This compound was obtained as a white solid in 25% yield; mp 209-211°C; R_f: 0.07; ^{1}H nmr (DMSO-d_6, Me_4Si): δ 6.70 (s, 1H,

COH), 6.80 (s, 1H, O=CCOH), 7.26-7.42 (m, 20H, Ph), 9.82 (s, 1H, H-C5), 11.22 (s, 1H, NH) ppm; ^{13}C nmr: δ 76.8 (Ph_2*C*OH-C3), 80.8 (Ph_2(OH)*C*ONH), 126.6-128.6, 142.9-143.3 (C_{Ar}), 155.7 (C3), 156.1 (C5), 171.2 (C=O) ppm.

Anal. Calcd. for $C_{29}H_{24}N_4O_3$: C, 73.09; H, 5.08; N, 11.75. Found: C, 73.20; H, 4.99; N, 11.93.

4-(1,1-Diphenyl-1-hydroxymethanecarbonylamino)-3-(1,1-diphenyl-1-hydroxymethyl)-5-methyl-1,2,4-triazole (**4h**).

This compound was obtained as a white solid in 82% yield; mp 205-207°C; R_f: 0.03; ^{1}H nmr (DMSO-d_6, Me_4Si): δ 1.73 (s, 3H, CH_3), 6.60 (s, 1H, COH), 6.90 (s, 1H, O=CCOH), 7.00-7.28 (m, 20H, Ph), 10.99 (s, 1H, NH) ppm; ^{13}C nmr: δ 8.9 (CH_3-C5), 76.7 (Ph_2*C*OH-C3), 80.8 (Ph_2(OH)*C*ONH), 127.0-127.6, 142.8-144.3 (C_{Ar}), 152.7 (C5), 155.7 (C3), 171.2 (C=O) ppm.

Anal. Calcd. for $C_{30}H_{26}N_4O_3$: C, 73.44; H, 5.35; N, 11.41. Found: C, 73.57; H, 5.50; N, 11.49.

4-(1,1-Diphenyl-1-hydroxymethanecarbonylamino)-3-(1,1-diphenyl-1-hydroxymethyl)-5-ethyl-1,2,4-triazole (**4i**).

This compound was obtained as a white solid in 48% yield; mp 213-215°C; R_f: 0.02; ^{1}H nmr (DMSO-d_6, Me_4Si): δ 0.88 (t, 3H, *J* = 7.5 Hz, CH_2CH_3), 2.02 (q, 2H, *J* = 7.5 Hz, CH_2CH_3), 6.56 (s, 1H, COH), 6.87 (s, 1H, O=CCOH), 7.03-7.28 (m, 20H, Ph), 11.00 (s, 1H, NH) ppm; ^{13}C nmr: δ 8.6 (CH_3CH_2-C5), 16.6 (CH_3CH_2-C5), 76.7 (Ph_2*C*OH-C3), 80.7 (Ph_2(OH)*C*ONH), 126.8-127.9, 142.6-143.5 (C_{Ar}), 155.1 (C5), 155.5 (C3), 171.0 (C=O) ppm.

Anal. Calcd. for $C_{31}H_{28}N_4O_3$: C, 73.78; H, 5.60; N, 11.10. Found: C,73.85; H, 5.71; N, 11.24.

Crystal Data for **4i**.

Compound **4i** has $C_{31}H_{28}N_4O_3 \cdot H_2O$, *FW* = 522.59, monoclinic, space group $P2_1/n$, *a* = 15.210(3) Å, *b* = 8.8730(18) Å, *c* = 21.519(4) Å, *β* = 109.77(3)°, *V* = 2733.1(9) Å^3, *Z* = 4, d_{calcd} = 1.270 gcm^{-3}, *F(000)* = 1104, μ(CuKα) = 0.690 mm^{-1}. Colorless prismatic crystals suitable for X-ray diffraction analysis were grown by slow evaporation of an ethanol solution. X-ray data were collected on the Bruker SMART APEX CCD diffractometer at room temperature using CuKα radiation (λ = 1.54178 Å); crystal size: 0.10 x 0.09 x 0.04, ω scans, no. of measured reflection 30346 (θ range 3.12 – 70.04°, index ranges -18 ≤h ≤ 18, -10 ≤ k ≤ 9, -26 ≤ l ≤ 26), no. of independent reflection 5186 (R_{int} = 0.0275), absorption correction: multi-scan, Tmin/Tmax = 0.529 [17]. The structure was solved by direct methods using SIR92 [18] and refined by full-matrix least-squares with SHELXL97 [19]. All hydrogen atoms were located from Δρ map and their coordinates were refined with isotropic displacement parameters taken as 1.5 times those of the respective parent atoms. The final *R* = 0.0390, *wR* = 0.1132 for 4429 reflections with $I > 2\sigma(I)$ and 443 parameters, *S* = 1.067, an extinction coefficient κ = 0.0023(2), $(\Delta/\sigma)_{max}$ = 0.000, $(\Delta\rho)_{max}$ = 0.200 and $(\Delta\rho)_{min}$ = -0.210 eÅ^{-3}. Molecular graphics were prepared using ORTEP3 for Windows [20], PARST [21] and PLATON/PLUTON [22] were used for geometrical calculations. All calculations were performed using WINGX ver. 1.64.05 package [23]. CCDC 270400 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.ac.uk/conts/retrieving.html.

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REFERENCES AND NOTES

[1] L. Echegoyen, M. V. Martinez-Diaz, J. de Mendoza and T. Torres, *Tetrahedron*, **48**, 9545 (1992).

[2] M. V. Martinez-Diaz, J. de Mendoza, F. Santos and T. Torres, *Tetrahedron Asymmetry*, **5**, 1291 (1994).

[3] M. V. Martinez-Diaz, J. de Mendoza and T. Torres, *Synthesis*, **1994**, 1091.

[4] A. R. Katritzky, S. R. El-Zemity, P. Leeming, C. M. Hartshorn and P. J. Steel, *Tetrahedron Asymmetry*, **7**, 1621 (1996).

[5] J. de Mendoza, J. M. Ontoria, C. Ortega and T. Torres, *Synthesis*, **1992**, 398.

[6] A. A. Ikizler and N. Yildirim, *J. Het. Chem*., **35**, 377 (1998).

[7] C. Ainsworth and R. E. Hackler, *J. Org. Chem*., **31**, 3442 (1966).

[8] A. P. Grekov, O. P. Schwayka and L. M. Eugunova, *Zh. Obsc. Chim*., **29**, 2027 (1959).

[9] P. S. Lobanov, A. L. Grebionkin, D. J. Zaicew, W. A. Ginolin and A. A. Potechin, *Khim. Gieterotsikl. Soedin.*, **1991**, 1388.

[10] D. J. Collins, T. C. Hughesand W. M. Johnson, *Aust. J. Chem.*, **52**, 379 (1999).

[11] F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen and R. Taylor, *Typical interatomic distances: organic compounds,* in: International Tables for Crystallography, Vol. **C**, Kluwer Academic Publishers, Dordrecht/Boston/London, 1995, pp. 685-706.

[12] K. Chinnakali, H. K. Fun, A. Senthilvelan, K. Sriraghavan and V. T. Ramakrishnan, *Acta Cryst*., **C55**, 1136 (1999).

[13] A. Mrozek, J. Karolak-Wojciechowska, P. Amiel and J. Barbe, *J. Mol. Struct*., **524**, 151 (2000).

[14] A. A. Potechin and W. M. Karelskij, *Zh. Org. Khim*., **7**, 2100 (1971).

[15] E. M. Luis and A. McKenzie, *J. Chem. Soc*., **98**, 647 (1941).

[16] H. Aspelund, *Acta Acad. Aboensis Math. at Phys. 6*, **12**, 8 (1932).

[17] G. M. Sheldrick, SADABS, ver. 2.06. University of Göttingen: Germany, 2002.

[18] A. Altomare, G. Cascarano, C. Giacovazzo and A. Guagliardi, *J. Appl. Cryst.,* **26**, 343 (1993).

[19] G. M. Sheldrick, SHELX97 (Includes SHELXS97, SHELXL97, CIFTAB). Programs for Crystal Structure Analysis (Release 97-2). University of Göttingen: Germany, 1997.

[20] L. J. Farrugia, ORTEP3 for Windows, *J. Appl. Cryst.*, **30**, 565 (1997).

[21] M. Nardelli, PARST, *Comput. Chem*., **7**, 95 (1983).

[22] A. L. Spek, PLATON/PLUTON, *Acta Cryst.,* **A46**, C34 (1990).

[23] L. J. Farrugia, WINGX, *J. Appl. Cryst.,* **32**, 837 (1999).