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Formation of 1,2,4-triazole derivatives by oxidation of 4-phenyl-1-pivaloylsemicarbazide

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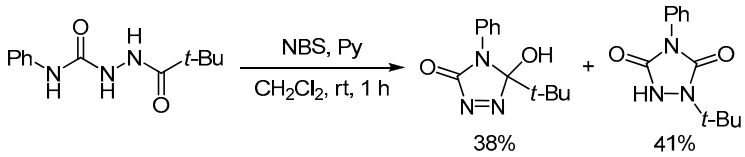


Oxidation of 4-phenyl-1-pivaloylsemicarbazide leads to the formation of two structural isomers: 5-*tert*-butyl-5-hydroxy-4-phenyl-4,5-dihydro-3*H*-1,2,4-triazol-3-one and 1-*tert*-butyl-4-phenyl-1,2,4-triazolidine-3,5-dione. Isomerization of 5-*tert*-butyl-5-hydroxy-4-phenyl-4,5-dihydro-3*H*-1,2,4-triazol-3-one to 1-*tert*-butyl-4-phenyl-1,2,4-triazolidine-3,5-dione proceeds upon heating and is accompanied by the migration of the *tert*-butyl group from the carbon atom to the nitrogen atom.

Keywords: 4-phenyl-1-pivaloylsemicarbazide, 1,2,4-triazol-3-one, 1,2,4-triazolidine-3,5-dione, C,N-migration of *tert*-butyl group, cyclization, oxidation, structural isomers.

The development of chemistry of nitrogen-containing compounds is one of the priority directions in organic chemistry, because the molecules of a significant part of drugs contain nitrogen atoms and the reactions of formation of the C–N bond play an important role in their synthesis.[1] In recent years, there has been a steady interest in studying 1,4-disubstituted semicarbazides $R^1NHC(O)NHNHR^2$ as pharmacophores responsible for the anti-inflammatory, antiviral, antibacterial, and antitumor activity of target compounds.[2] 1,4-Disubstituted semicarbazides are widely used as building blocks in synthetic organic and medicinal chemistry.[3]

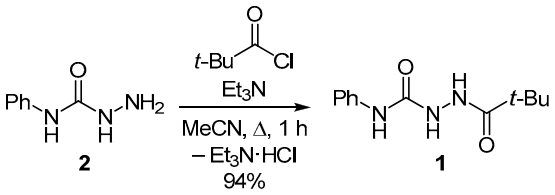
During the oxidation of substituted semicarbazides by typical oxidizing systems ($Fe(NO_3)_3·9H_2O$,[4] $Fe(NO_3)_3·9H_2O$–$NaHSO_4·H_2O$,[5] $FeCl_3·6H_2O$,[6] MnO_2–H_2SO_4–SiO_2,[7] $NaNO_2$–$NaHSO_4·H_2O$–SiO_2,[8] NBS–Py[9]), azocarboxamides (diazenecarboxamides) $R^1R^2NC(O)N=NR^3$ (R^1, R^2 = H, Alk, Ar; R^3 = Ar, $R^1R^2NC(O)$) are easily formed. Azocarboxamide molecules contain two structural fragments that determine the properties of this class of compounds – the azo group, N=N–, which can induce structural changes in azocarboxamides upon irradiation with light, and the carboxamide group, capable of forming intra- and intermolecular hydrogen bonds.[10] Unlike azobenzene, azocarboxamides are not capable of *cis-trans* photoisomerization. The results of studies of the light-driven dynamic behavior of molecular systems based on azodicarboxamide by time-resolved IR spectroscopy and quantum chemistry methods show that conformational changes in such molecules occur by a pedal-type mechanism.[11]

Azocarboxamides are universal azo ligands: the presence of several functional groups in the molecule ensures their ability to coordinate interactions of various types.[12] These compounds are convenient building blocks in synthetic chemistry, provide a simple and selective introduction of nitrogen-containing functional groups into organic compounds,[12e,13] and are successfully used in the Mitsunobu reaction.[14]

Azocarboxamides exhibit biological activity and are of significant interest for medicinal chemistry.[13f,15] In addition, azocarboxamides containing substituents labeled with the isotope ^{18}F are potentially useful as radioactive tracers for positron emission tomography.[16] Some azocarboxamides have been isolated from natural products.[17] Thus, lyophyllin was isolated from the fungus *Lyophyllum shimeji* and showed antibiotic[17] and teratogenic[18] activity. 2-(4-Hydroxyphenyl)- and 2-(4-methoxyphenyl)diazenecarboxamides, which have nematicidal activity against the parasitic nematode *Meloidogyne incognita*, were isolated from the fungus *Lycoperdon pyriforme*.[17]

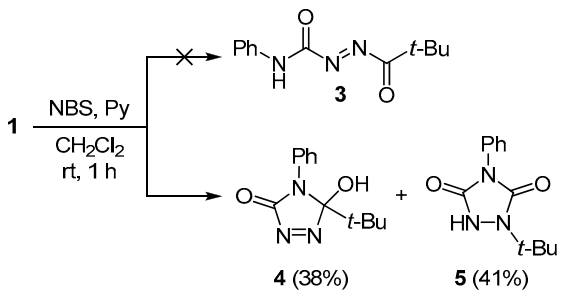
The goal of this work was to develop a method for the synthesis of 4-phenyl-1-pivaloylsemicarbazide (**1**) and to study its reactivity. 4-Phenyl-1-pivaloylsemicarbazide (**1**) was synthesized in 94% yield by acylation of 4-phenylsemicarbazide (**2**) with pivalic acid chloride in the presence of Et_3N (Scheme 1).

Scheme 1



We expected that the oxidation of compound **1** would lead to the formation of *N*-phenyl-2-pivaloyldiazenecarboxamide (**3**). For the oxidation of compound **1**, the NBS–Py system was chosen, since diazenecarboxamides ArNHC(O)N=NC(O)OAlk were obtained in 90–97% yields by the oxidation of 1,4-disubstituted semicarbazides according to this method.[9c] The reaction of semicarbazide **1** with NBS in the presence of pyridine takes place at room temperature (Scheme 2). As a result of the reaction, a yellow crystalline substance was isolated. Its ^{1}H NMR spectrum exhibits two peaks at 0.90 ppm and 1.43 ppm with a 1.75:1.00 intensity ratio corresponding to two *tert*-butyl groups, which indicates the possible formation of two products. By recrystallization from CH_2Cl_2, 5-*tert*-butyl-5-hydroxy-4-phenyl-4,5-dihydro-3*H*-1,2,4-triazol-3-one (**4**) was isolated from the resulting mixture in 38% yield (Scheme 2) in the form of yellow crystals. Heating compound **4** forms its regioisomer 1-*tert*-butyl-4-phenyl-1,2,4-triazolidine-3,5-dione (**5**) in quantitative yield. This property was used in the isolation of compound **5** from the reaction mixture. After removing the crystals of heterocycle **4**, the mother liquor containing a mixture of residual 5-*tert*-butyl-5-hydroxy-4-phenyl-4,5-dihydro-3*H*-1,2,4-triazol-3-one (**4**) and its isomer **5** was evaporated to dryness. The solid residue was heated at 130°C for 30 min. Subsequent recrystallization from Et_2O afforded 1-*tert*-butyl-4-phenyl-1,2,4-triazolidine-3,5-dione (**5**) as colorless crystals in 41% yield.

Scheme 2



Analysis of the literature data indicates that compound **4** is the first example of 4,5-dihydro-3*H*-1,2,4-triazol-3-one **A** derivatives containing an OH group at position 5. The heterocyclic system **A** remains poorly studied, in contrast to its regioisomer **B** (Fig. 1).

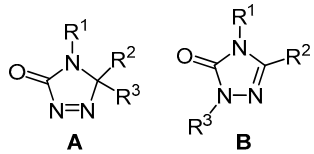
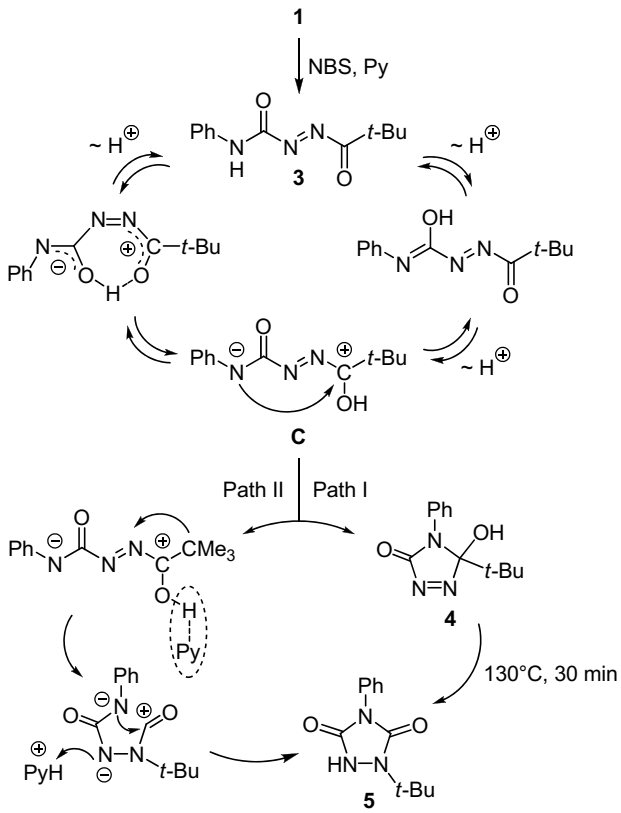


Figure 1. Derivatives of 4,5-dihydro-3*H*-1,2,4-triazol-3-one **A** and 2,4-dihydro-3*H*-1,2,4-triazol-3-one **B**.

To date, only a few type **A** heterocycles (Fig. 1) containing alkyl groups at position 5 have been investigated.[19] However, we have not found compounds containing any heteroatoms at position 5. Compound **5** was first synthesized in the reaction of 4-phenylurazole with isobutylene (61% yield).[20] 1,2,4-Triazole derivatives **4** and **5** are stable at room temperature for several months, although, as noted above, compound **4** quantitatively transforms upon heating into its regioisomer **5**.

The mechanism for the formation of heterocycles **4** and **5** requires further study. At present, based on the analysis of the literature data and the obtained results, one can suggest a possible route for their formation. *N*-Phenyl-2-pivaloyldiazenecarboxamide (**3**) and heterocycles **4**, **5** are structural isomers, and the prototropic tautomerism of *N*-phenyl-2-pivaloyldiazenenecarboxamide (**3**) can lead to the formation of compounds **4** and **5**. Diazenecarboxamide **3** is probably formed during the oxidation of semicarbazide **1**; however, under the reaction conditions, it easily cyclizes with the formation of a mixture of compounds **4** and **5**. The

Scheme 3



key intermediate of this reaction is tautomer **C**, and its cyclization can occur *via* two different routes. The first of them (path I) is a kinetically controlled one-step process of intramolecular cyclization with the formation of compound **4**. Path II is accompanied by an extraordinary process of migration of the *tert*-butyl group from the carbon atom to the nitrogen atom and ends with the formation of a thermodynamically more stable product **5**. This rearrangement is most likely catalyzed by pyridine and proceeds concertedly (Scheme 3).

The structures of compounds **1**, **4**, and **5** were proved by NMR spectroscopy and X-ray structural analysis, as well as by elemental analysis. The unit cell contains four independent molecules of 4-phenyl-1-pivaloylsemicarbazide (**1**). Figure 2 shows only one of four crystallographically independent molecules. The molecules of compound **1** form a chain with an alternating "head to head" and "head to tail" arrangement of molecules, bonded by two types of intermolecular hydrogen bonds. Intermolecular three-center hydrogen bonds are formed between the carbonyl group of the PhNHC=O fragment and two NH groups of the urea fragment PhHNC(O)NH of the neighboring molecule. In addition, an intermolecular hydrogen bond exists between the *t*-BuC=O group and the *t*-BuC(O)NH fragment of the neighboring molecule (Fig. 3*a*). These hydrogen bonds lead to the formation of an infinite helical structure (Fig. 3*b*). It should be noted that the lengths of these bonds are somewhat different for molecules with the "head to head" and "head to tail" arrangement (Table 1).

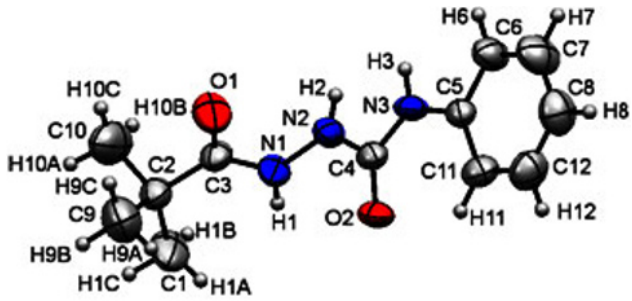


Figure 2. Molecular structure of compound **1** with atoms represented as thermal vibration ellipsoids of 50% probability.

The molecular structure of compound **4** is shown in Figure 4*a*, the geometric parameters of this heterocycle are close to those of 1,2,4-triazol-3-one derivatives.[19a,b] In the solid state, compound **4** has an intermolecular bifurcation hydrogen bond as a result of the interaction of the C=O group with the OH groups of two neighboring molecules. A short OH···O=C bond (*l* 2.034 Å) leads to the formation of di-

Table 1. Lengths of hydrogen bonds (Å) between the molecules of compound **1**

Hydrogen bond	The arrangement of molecules in the solid state	
	"head to head"	"head to tail"
PhNHC=O···HN(Ph)C(O)NH	1.985	1.999
PhNHC=O···HNC(O)NHPh	2.430	2.421
t-BuC=O···HNC(O)*t*-Bu	2.034	2.018

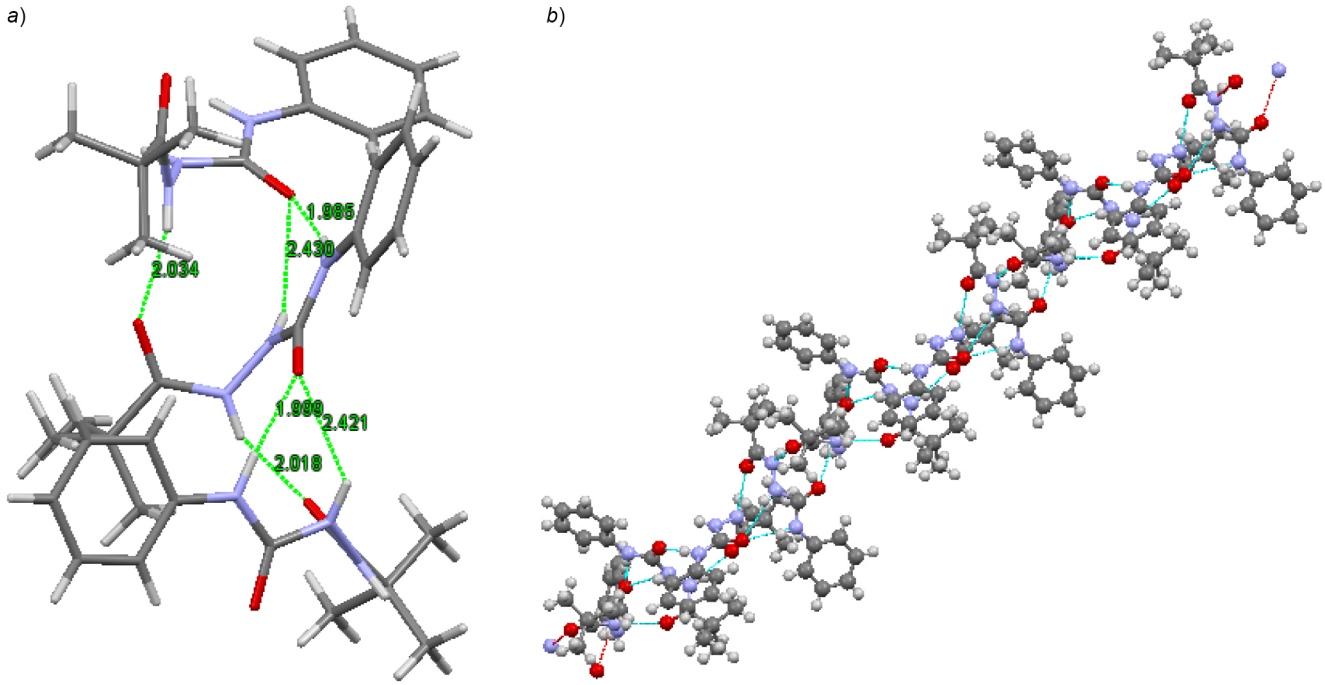


Figure 3. Hydrogen bonds in the solid state of compound **1**: *a*) intermolecular bonds between three semicarbazide molecules **1**, *b*) an infinitive helical structure composed of hydrogen-bonded molecules of semicarbazide **1** (*l*, Å).

mers, which are linked into a continuous polymeric chain as a result of a longer OH···O=C bonding (*l* 2.541 Å) (Fig. 4*b*).

The molecular structure of compound **5** is shown in Figure 5*a*. The existence of an intermolecular hydrogen bond NH···O=C (*l* 1.898 Å) leads to the formation of dimers (Fig. 5*b*). Similar structural assemblies are described for 4-phenylurazole derivatives containing an unsubstituted NH group.[21]

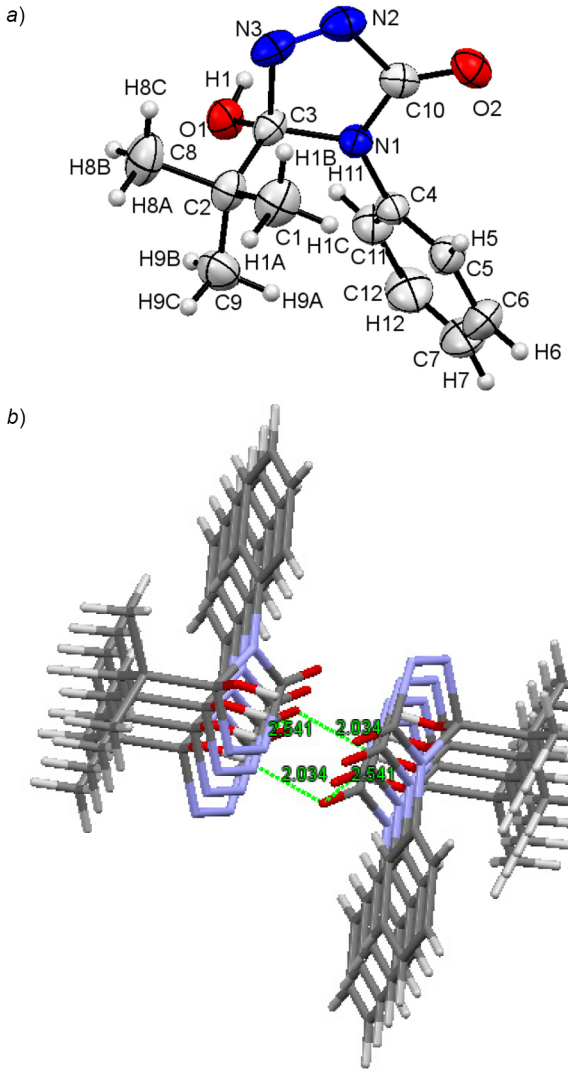


Figure 4. *a*) Molecular structure of compound **4** with atoms represented as thermal vibration ellipsoids of 50% probability and *b*) hydrogen bonds in the solid state of compound **4** (*l*, Å).

To conclude, a previously unknown 4-phenyl-1-pivaloylsemicarbazide was synthesized. Its oxidation by the NBS–pyridine system led to the formation of two heterocycles, 5-*tert*-butyl-5-hydroxy-4-phenyl-4,5-dihydro-3*H*-1,2,4-triazol-3-one and 1-*tert*-butyl-4-phenyl-1,2,4-triazolidine-3,5-dione in a 1.75:1.00 ratio according to ^{1}H NMR spectroscopy. The structure of the compounds has been proven by NMR spectroscopy and X-ray structural analysis. Each of these heterocycles is of interest for synthetic organic chemistry and medicinal chemistry. 5-*tert*-

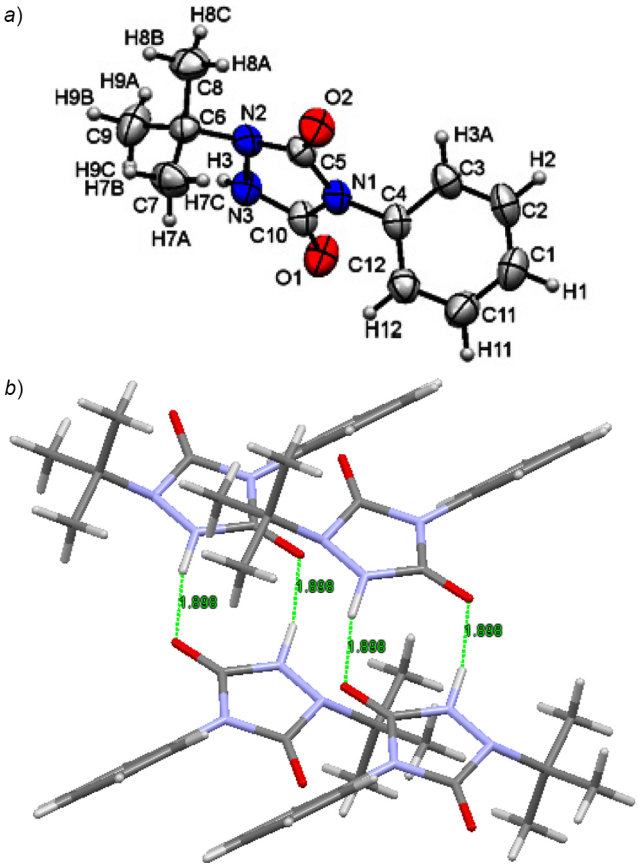


Figure 5. *a*) Molecular structure of compound **5** with atoms represented as thermal vibration ellipsoids of 50% probability and *b*) hydrogen bonds in the solid state of compound **5** (*l*, Å).

Butyl-5-hydroxy-4-phenyl-4,5-dihydro-3*H*-1,2,4-triazol-3-one is the first example of 1,2,4-triazol-3-ones containing the OH group in position 5. Its rearrangement into the thermodynamically more stable 1-*tert*-butyl-4-phenyl-1,2,4-triazolidine-3,5-dione is accompanied by an extraordinary migration of the *tert*-butyl group from the carbon atom to the nitrogen atom.

Experimental

IR spectra were registered on a Varian 3100 spectrometer in petroleum jelly. ^{1}H and ^{13}C NMR spectra were acquired on Bruker DPX-400 and Bruker AV-400 spectrometers (400 and 100 MHz, respectively) in DMSO-d_6 (compound **1**) and CD_3CN (compounds **4** and **5**), with TMS as internal standard. Elemental analysis was performed on a Thermo Scientific Flash 2000 CHNS-analyzer. Melting points were determined on a Boetius heating bench.

Before use, solvents and reagents were prepared according to standard procedures.[22]

***N*-Phenyl-2-pivaloylhydrazine-1-carboxamide (1)**. A solution of pivaloyl chloride (5.58 g, 46.3 mmol) in anhydrous MeCN (10 ml) was added dropwise over 3 h to a solution of 4-phenylsemicarbazide (**2**) (7.00 g, 46.3 mmol) and Et_3N (9.37 g, 92.6 mmol) in MeCN (40 ml). The

reaction mixture was heated under reflux for 1 h. Volatile organic compounds were removed under reduced pressure, and the white solid was stirred with H_2O (50 ml). The precipitate was filtered off, washed with H_2O (3×20 ml), dried under reduced pressure, and recrystallized from *i*-PrOH. Yield 10.20 g (94%), white powder, mp 217–218°C. IR spectrum, ν, cm^{-1}: 3325 (NH), 3215, 3148, 3108, 1693 (C=O), 1643. ^1H NMR spectrum, δ, ppm: 1.16 (9H, s, $C(CH_3)_3$); 6.94–7.00 (1H, m, H-4); 7.24–7.30 (2H, m, H-3,5); 7.42–7.44 (2H, m, H-2,6); 7.81 (1H, br. s, PhNHC(O)N<u>H</u>); 8.71 (1H, s, PhNH); 9.34 (1H, br. s, *t*-BuC(O)NH). ^{13}C NMR spectrum, δ, ppm: 27.2 ($C(\underline{C}H_3)_3$); 37.5 ($\underline{C}Me_3$); 118.3 (C-2,6); 122.1 (C-4); 128.8 (C-3,5); 139.6 (C-1); 155.7 (PhNH<u>C</u>=O); 178.0 (*t*-Bu<u>C</u>=O). Found, %: C 61.30; H 7.32; N 17.80. $C_{12}H_{17}N_3O_2$. Calculated, %: C 61.26; H 7.28; N 17.86.

Oxidation of compound 1. NBS (3.72 g, 21.0 mmol) was gradually with vigorous stirring added over 1 h to a mixture of compound **1** (4.72 g, 20.0 mmol), pyridine (3.16 g, 40.0 mmol), and CH_2Cl_2 (70 ml). The reaction mixture was stirred at room temperature for 1 h, and then H_2O (80 ml) and concentrated HCl (32 ml) were added. The bottom organic layer was separated and sequentially treated with a solution of $Na_2S_2O_3 \cdot 6H_2O$ (2 g) in H_2O (100 ml) and saturated aqueous $NaHCO_3$ (100 ml). Then the organic phase was washed with H_2O (100 ml) and dried over anhydrous Na_2SO_4.

5-*tert*-Butyl-5-hydroxy-4-phenyl-4,5-dihydro-3*H*-1,2,4-triazol-3-one (4). The yellow crystalline substance (3.96 g) obtained by oxidation of compound **1** was recrystallized from CH_2Cl_2. Yield 1.77 g (38%), yellow crystals, mp 127–128°C. IR spectrum, ν, cm^{-1}: 3351 (OH), 1756 (C=O). ^1H NMR spectrum, δ, ppm: 0.90 (9H, s, $C(CH_3)_3$); 5.91 (1H, s, OH); 7.38–7.49 (5H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 25.3 ($C(\underline{C}H_3)_3$); 39.9 ($\underline{C}Me_3$); 121.2 (C-5); 127.1 (C-2',6'); 129.1 (C-4'); 130.3 (C-3',5'); 136.4 (C-1'); 158.5 (C=O). Found, %: C 61.92; H 6.84; N 18.09. $C_{12}H_{15}N_3O_2$. Calculated, %: C 61.79; H 6.48; N 18.01.

1-*tert*-Butyl-4-phenyl-1,2,4-triazolidine-3,5-dione (5). The mother liquor remaining after the isolation of compound **4** was evaporated under reduced pressure, and the solid residue was heated at 130°C for 30 min in an argon atmosphere in the Schlenk apparatus. The resulting product was recrystallized from Et_2O. Yield 1.92 g (41%), white crystals, mp 154–155°C (mp 153–154°C[20]). IR spectrum, ν, cm^{-1}: 3166 (NH), 3060, 1761 (C=O), 1697. ^1H NMR spectrum, δ, ppm: 1.43 (9H, s, $C(CH_3)_3$); 7.37–7.50 (5H, m, H Ph); 8.20 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 27.2 ($C(\underline{C}H_3)_3$); 60.2 ($\underline{C}Me_3$); 127.4 (C-2,6); 129.1 (C-4); 129.9 (C-3,5); 132.8 (C-1); 154.7; 154.8 (HNC=O, *t*-BuNC=O).

X-ray structural analysis of compounds 1, 4, and 5 was performed on a Bruker D8 Venture diffractometer, MoKα radiation (λ 0.71073 Å) using scanning at angles φ and ω. Crystals suitable for X-ray structural analysis were obtained by recrystallization from MeOH (compound **1**) or according to the isolation and purification procedures outlined above (compounds **4** and **5**). Structures were solved and refined by the direct method using the SHELX software package.[23] The positions of non-hydrogen atoms were refined in the anisotropic approximation using the SHELX program.[23] The full set of X-ray structural data for compounds **1**, **4**, and **5** was deposited at the Cambridge Crystallographic Data Center (deposits CCDC 1922936, CCDC 1922937, and CCDC 1922938, respectively).

Supplementary information file containing ^1H and ^{13}C NMR spectra, as well as X-ray structural analysis data for compounds **1**, **4**, and **5**, can be accessed at the journal website at http://link.springer.com/journal/10593.

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