Reactions of 2-arylhydrazonoacetamidoximes with orthoesters*

N. P. Belskaya,[a] A. V. Koksharov,[a] S. G. Lesogorova,[a] P. A. Slepukhin,[b] and V. A. Bakulev[a]*

[a] *Ural Federal University named after the First President of Russia B. N. Eltsyn, 19 ul. Mira, 620002 Ekaterinburg, Russian Federation. E-mail: belska@mail.ustu.ru*

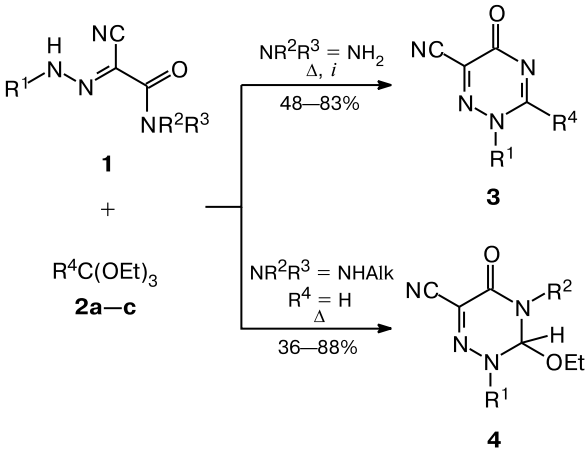
[b] *I. Ya. Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 20 ul. S. Kovalevskoi, 620041 Ekaterinburg, Russian Federation*

The reactions of 2-arylhydrazono-2-carbamoylacetamidoximes with orthoesters afford either 3-arylhydrazono-1,2,4-oxadiazoles or 1,2,3-triazoles, depending on the reactant structure.

Key words: hydrazones, amidoximes, 1,2,3-triazoles, 1,2,4-oxadiazoles, orthoesters, heterocyclization.

We have earlier[1,2] shown that the reaction of 2-arylhydrazono-2-cyanoacetamides **1** with orthoesters **2** is a convenient method for the construction of the 1,2,4-triazine system (Scheme 1). This reaction can afford 2,5-dihydrotriazinones **3** or 2,3,4,5-tetrahydrotriazinones **4**, depending on the substitution pattern in the amide fragment.

Scheme 1



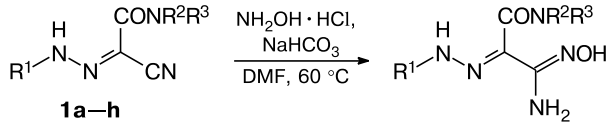
i. Xylene.

1: R^1 = Ar, NR^2R^3 = H, Alk; **2:** R^4 = H (**a**), Me (**b**), Et (**c**); **3:** R^1 = Ar, R^4 = H, Me, Et; **4:** R^1 = Ar, R^2 = Alk

We supposed that the introduction of additional functional fragments into a molecule of hydrazonoacetamides **1** can change the reaction mechanism or cyclization direction and can result in the formation of other heterocyclic compounds. Hydrazones containing amidoxime function along with the amide fragment seemed to be an interesting object for the study. Aminoximes are reactive compounds involved in a wide range of chemical transformations affording various oxygen- and nitrogen-containing heterocycles.[3] Alkyl- and arylamidoximes are the most studied representatives of this type of compounds. No reactions of hydrazones containing the amidoxime groups with orthoesters were studied earlier. Therefore, the purpose of the present work is to study the reactions of arylhydrazono amidoximes with orthoesters and to determine regularities of this reaction at various structures of the starting reactants and conditions of the process.

Hydrazones with amidoxime group **5a**—**h** were synthesized by the reaction of arylhydrazonocyanoacetamides **1a**—**h** with hydroxylamine hydrochloride in the presence of a base (Scheme 2).

Scheme 2



1, 5: R^1 = 4-ClC_6H_4, NR^2R^3 = NHMe (**a**), NHEt (**b**), *cyclo*-$C_6H_{11}NH$ (**c**), NHBn (**d**), pyrrolidin-1-yl (**e**); R^1 = 4-$MeOC_6H_4$, NR^2R^3 = NHMe (**f**), NHBn (**g**), pyrrolidin-1-yl (**h**)

The IR spectra of hydrazone derivatives **5a**—**h** exhibit intense absorption bands of stretching vibrations of the NH and OH bonds in a region of 3300—3500 cm^{-1} and the absorption band corresponding stretching vibrations of the C=O bond at 1670 cm^{-1}. The ^1H NMR spectra of compounds **5** contain two sets of signals of the proton-con-

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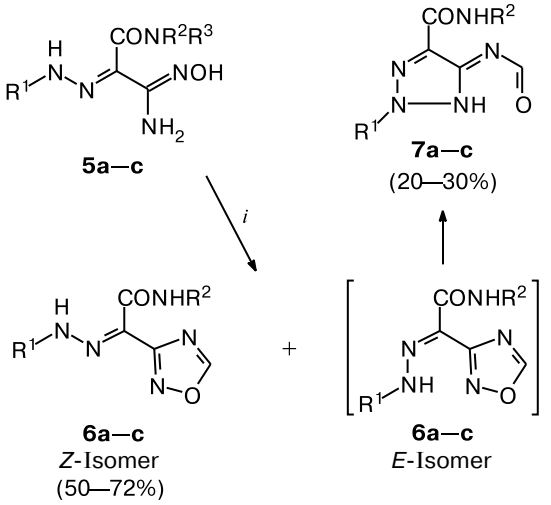
taining groups in a ratio of 1 : 1 or 3 : 2, which can be the result of formation of two geometrical isomers relative to the C=N bond of the hydrazone group or amidoxime fragment.

The reaction of arylhydrazono amidoximes **5** with triethyl orthoformate was carried out in DMF at room temperature in the presence of catalytic quantities of boron trifluoride etherate (Scheme 3). Two types of compounds were formed (TLC), which were separated by fractional crystallization from ethanol. Based on the analysis of the spectral data for one of them, we proposed the structure of 2-arylhydrazono-2-(1,2,4-oxadiazol-4-yl)acetamide **6a—c**, whose formation is the result of heterocyclization involving nucleophilic centers of the amidoxime group.

Scheme 3



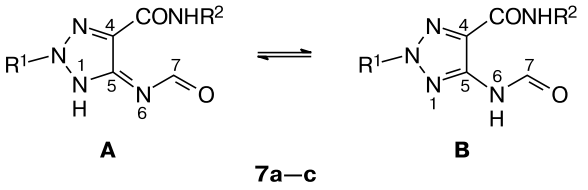
i. R^3 = H; $HC(OEt)_3$, $BF_3 \cdot OEt_2$, DMF, 20 °C
6, 7: R^1 = 4-ClC_6H_4, NR^2R^3 = NHMe (**a**), NHEt (**b**), *cyclo*-$C_6H_{11}NH$ (**c**)

As compared to the ^{1}H NMR spectra of starting compounds **5a—c**, no changes in position and multiplicity of the signals caused by resonance of the protons of the NH-hydrazone group and NH-alkylamide group are observed in the ^{1}H NMR spectra of compounds **6a—c**, but the one-proton singlet is present at δ 9.5—9.7 corresponding to the signal of the proton of the C(5)H-oxadiazole cycle and signals of the protons of the NH_2 and NOH groups are absent.

The structure of 2-aryl-5-formylimino-2,5-dihydro-1*H*-1,2,3-triazole-4-alkylcarboxamides **7a—c** was ascribed to minor products on the basis of the data of ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, mass spectrometry, and elemental analysis.

Unlike the IR spectra of oxadiazoles **6a—c**, the absorption spectra of 1,2,3-triazoles **7a—c** display a band at 1710 cm^{-1} characteristic of stretching vibrations of the C=O bond of the formyl substituent. The ^{1}H NMR spectra of 2,5-dihydro-1*H*-1,2,3-triazoles **7** in DMSO-d_6 solution contain signals of protons of the aromatic ring and the substituent in the amide fragment and two broad signals of the protons N(1)H and C(7)H of tautomeric form **A** (Scheme 4) and two broad signals from N(6)H and C(7)H corresponding to tautometric form **B**. In the ^{1}H NMR spectrum of 1,2,3-triazole **7a** in $CDCl_3$, the signals of the protons N(6)H and C(7)H are presented by the AB system.

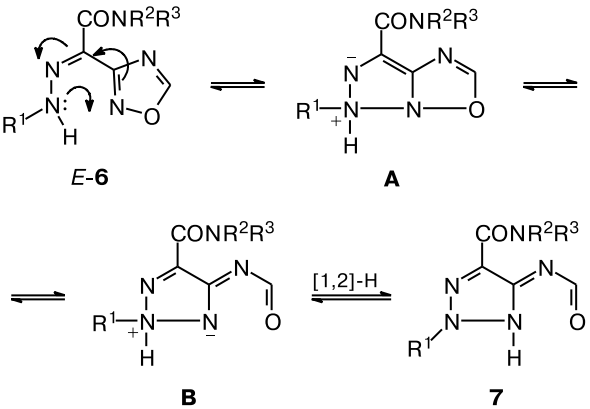
Scheme 4



The ^{13}C NMR spectrum of each triazole **7a—c** contain two broadened signals for each carbon atom C(4), C(5), and C(7)H of the formyl residue. The detection of the ^{1}H and ^{13}C NMR spectra at 30 and 100 °C showed that these double signals are brought together and form one signal. This confirms the presence of a dynamic process in the structure of compounds **7**, which is due to the tautomeric transformation between two forms.

Triazoles **7** are formed in the monocyclic variant of the Boulton—Katritzky rearrangement (MRH) of 1,2,4-oxadiazoles **6**.[4—9] These transformations are characteristic of compounds capable of forming pentalene structures in which all the three heteroatoms (in our case, N—N—O) involved in the rearrangement are almost linear. The *E*-isomer of 1,2,4-oxadiazoles **6** has a favorable spatial configuration for this rearrangement to occur, for which pentalene transition state **A** can be formed (Scheme 5) due to the nucleophilic attack of the amine nitrogen atom of the hydrazone group to the cyclic nitrogen atom N(2).

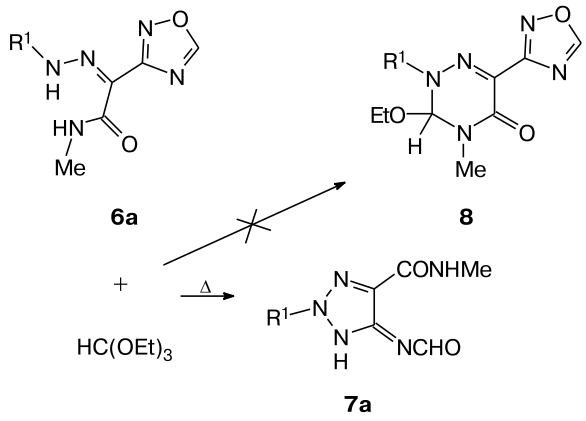
Scheme 5



The *Z*-isomer is not involved in this rearrangement and, most likely, at room temperature is isolated as hydrazone-containing oxadiazole **6**. It can be assumed that on heating the *Z*-isomer can be transformed into the *E*-isomer and then rearranged.

Indeed, reflux of compound **6a** in orthoester excess gave the same compound **7a** (Scheme 6).

Scheme 6

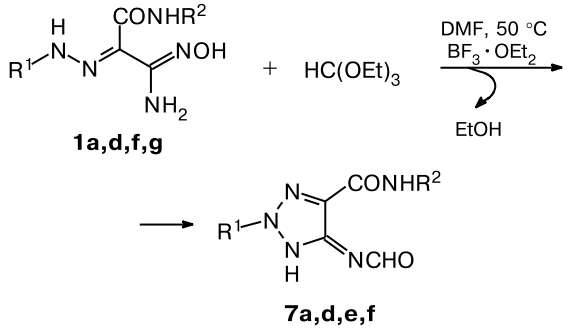


R^1 = 4-ClC_6H_4

The hydrazone group and amide fragment interact with triethyl orthoformate much more slowly and, hence, no cyclic products corresponding to tetrahydrotriazines **8** are formed involving these moieties.

The study of the temperature effect on the yield and duration of the reaction of arylhydrazono amidoximes with triethyl orthoformate showed that raising the temperature to 50 °C shortens the duration time to 3 h, and 5-formylimino-1,2,3-triazoles **7** grow as the only products (Scheme 7).

Scheme 7



7: R^1 = 4-ClC_6H_4, R^2 = Me (**a**), Bn (**d**); R^1 = 4-$MeOC_6H_4$, R^2 = Me (**e**), Bn (**f**)

The X-ray diffraction data for 2,5-dihydro-1*H*-1,2,3-triazole **7f** confirmed the structure of the compounds considered (Fig. 1).

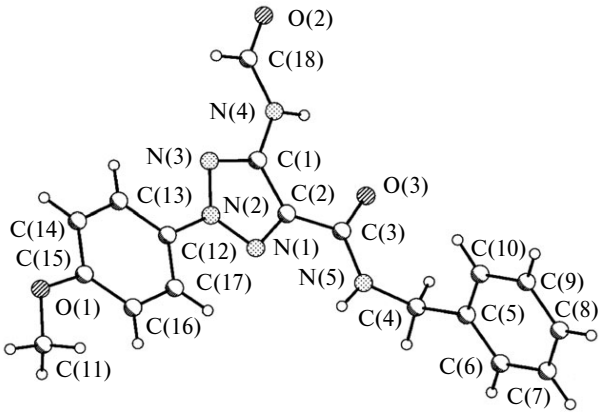


Fig. 1. General view of molecule **7f** and the numeration of atoms accepted in structural experiments.

The X-ray diffraction results show that compound **7f** crystallize in the centrosymmetric symmetry space group. The bond lengths and bond angles of the compounds are close to standard values. The aryl substituent of triazole lies almost in the heterocycle plane, and the angle between the root-mean-square planes is 6.5(2)°. At the same time, the phenyl substituent of the benzyl fragment is unfolded almost perpendicularly to the triazole plane (the angle between the root-mean-squares is 89.0(2)°). Except for the atoms of the phenyl ring, the deviation of the atoms from the root-mean-square plane of the azole cycle does not exceed 0.305(2) Å (deviation of the O(2) atom of the terminal carbonyl group), and the molecule as a whole can be considered planar. The crystal packing is characterized by the presence of planar dimers formed by intermolecular hydrogen bonds N(4)H(4)..O(2) [$-x$, $-y + 1$, $-z - 1$] between the formamide fragments (Table 1). In addition to this, intermolecular hydrogen bonds N(5)H(5)...O(3) [x, $-y + 3/2$, $z + 1/2$] occur between the amide fragments binding the molecules into polymer chains in which the planes of the triazole rings are oriented relatively to each other at an angle of 75.0(2)° and the phenyl substituents are oriented almost in parallel (the dihedral angle between the rings is 10.9(2)°, and the distance between the centroids C(5)C(6)C(7)C(8)C(9)—C(10)...C(5)C(6)C(7)C(8)C(9)C(10) [x, $-y + 3/2$, $z + 1/2$] is 4.605(2) Å).

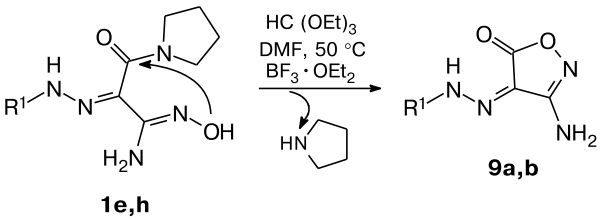
The molecular packing contains no pronounced π—π-contacts. As a result, the molecular packing has a complicated motif in which the ladder-parquet packing of zones of polar contacts of the triazole fragments is supplemented by the stack packing of the nonpolar aryl substituents.

Hydrazonoacetamidoximes **1e,h** containing the *N*,*N*-disubstituted carbamoyl group at the carbon atom of the hydrazone group react with orthoesters in different manner: their heating with triethyl orthoformate affords products of intramolecular cyclization, *viz.*, aminoisoxazoles **9a,b** (Scheme 8).

Table 1. Hydrogen bonds with H...A < *r*(A) + 2.000 Å and angle D—H—A > 110°

D—H	*d*/Å			Angle D—H—A /deg	A
	D—H	H...A	D...A		
N(4)—H(4)	0.852(15)	2.273(15)	3.029(2)	148(1)	O(2) [$-x$, $-y+1$, $-z-1$]
N(4)—H(4)	0.852(15)	2.322(15)	2.908(2)	126(1)	O(3)
N(5)—H(5)	0.835(14)	2.150(15)	2.887(2)	147(1)	O(3) [x, $-y+3/2$, $z+1/2$]

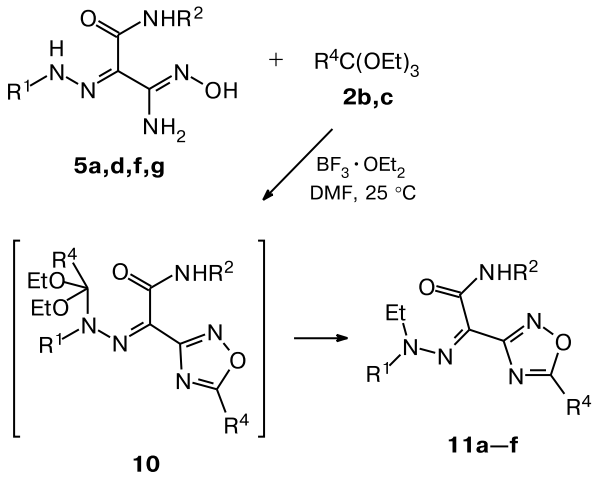
Scheme 8



9: R^1 = 4-ClC_6H_4 (**a**), 4-$MeOC_6H_4$ (**b**)

The reaction of arylhydrazonoamidoximes **5a**,**d**,**f**,**g** with triethyl orthoacetate **2b** and triethyl orthopropionate **2c** (Scheme 9) afford only 1,2,4-oxadiazoles **11a**—**f**, and the alkylation of the hydrazone nitrogen atom occurs along with heterocyclization.

Scheme 9



11: R^1 = 4-ClC_6H_4, R^4 = Me, R^2 = Me (**a**), Bn (**b**); R^4 = Et, R^2 = Me (**c**); R^1 = 4-$MeOC_6H_4$, R^4 = R^2 = Me (**d**), Bn (**e**); R^4 = Et, R^2 = Bn (**f**)

The structure of compounds **11a—f** was confirmed by spectral methods and elemental analysis.

Thus, the studies showed that arylhydrazonoamidoximes **5** are very reactive compounds. Unlike arylhydrazonoacetamides **1**, they undergo intramolecular cyclization or react with orthoesters already at room temperature. The results obtained make it possible to perform the target synthesis of various types of azoles by the variation of the structure of the starting reactants or temperature conditions of the process.

Experimental

^{1}H and ^{13}C NMR spectra were obtained on Bruker WM-250 and Bruker AVANCE II 400 instruments (250.13 and 400.00 MHz for ^{1}H and 100.00 MHz for ^{13}C) in DMSO-d_6 or $CDCl_3$ solutions using Me_4Si as an internal standard. IR spectra were measured on a Bruker Alpha FT-IR spectrometer (NPVO, ZnSe). Mass spectra were recorded on a Varian MAT 311A instrument at an ionization energy of 70 eV. The reaction course and individual character of the synthesized substances were monitored by TLC on Sorbfil UV-254 plates in ethyl acetane—hexane (1 : 1), chloroform—acetone (30 : 1), and chloroform—hexane—acetone (5 : 4 : 1) systems. DMF was purified according to a standard procedure. Arylhydrazonocyanacetamides were synthesized according to a method described previously.[1,2]

3-Amino-3-hydroxyimino-2-arylhydrazono-*N*-alkylpropanamides 5 (general procedure). A solution of $NH_2OH \cdot HCl$ (0.25 g, 3.6 mmol) and $NaHCO_3$ (0.3 g, 3.6 mmol) in water (20 mL) was added to a suspension of hydrazone **1** (3 mmol) in DMF (50 mL), and the mixture was stored for 4.5—5 h at 60 °C, cooled, and diluted with water. The precipitate was filtered off and recrystallized from EtOH.

3-Amino-2-(4-chlorophenylhydrazono)-3-hydroxyimino-*N*-methylpropanamide (5a). The yield was 0.62 g (78%), m.p. 170—171 °C. IR, ν/cm^{-1}: 1670 (CO); 3310, 3350, 3430, 3440, 3510 (NH, OH). ^{1}H NMR (DMSO-d_6), δ: 2.75 (d, 3 H, NHC$\underline{H}_3$, J = 4.9 Hz); 5.58, 6.70 (both s, 2 H, NH_2); 7.36—7.40 (m, 4 H, Ar); 8.20, 9.40 (both q, 1 H, N$\underline{H}$Me, J = 4.9 Hz); 10.07, 10.19 (both s, 1 H, OH); 13.24, 13.40 (both s, 1 H, NH). A mixture of *E*- and *Z*-isomers in a ratio of 1 : 1. Found (%): C, 44.78; H, 4.56; N, 25.84. $C_{10}H_{12}ClN_5O_2$. Calculated (%): C, 44.54; H, 4.48; N, 25.97.

3-Amino-2-(4-chlorophenylhydrazono)-*N*-ethyl-3-hydroxyiminopropanamide (5b). The yield was 0.75 g (88%), m.p. 140—141 °C. IR, ν/cm^{-1}: 1665 (CO); 3310, 3340, 3445, 3550 (NH, OH). ^{1}H NMR (DMSO-d_6), δ: 1.28 (t, 3 H, $CH_2C\underline{H}_3$, J = 6.9 Hz); 4.22 (dq, 2 H, NHC$\underline{H}_2$Me, J = 7.0 Hz, J = 5.5 Hz); 5.56, 6.68 (both s, 2 H, NH_2); 7.35—7.41 (m, 4 H, Ar); 8.33 (t, 1 H, N$\underline{H}CH_2$, J = 5.5 Hz); 10.05, 10.17 (both s, 1 H, OH); 13.23, 13.38 (both s, 1 H, NH). A mixture of *E*- and *Z*-isomers in a ratio of 1 : 1. Found (%): C, 46.65; H, 4.63; N, 24.43. $C_{11}H_{14}ClN_5O_2$. Calculated (%): C, 46.57; H, 4.97; N, 24.68.

3-Amino-2-(4-chlorophenylhydrazono)-*N*-cyclohexyl-3-hydroxyiminopropanamide (5c). The yield was 0.76 g (75%), m.p.

160—161 °C. IR, ν/cm^{-1}: 1670 (CO); 3310, 3350, 3430, 3440, 3510 (NH, OH). ^{1}H (DMSO-d$_6$), δ: 1.22—1.95 (m, 10 H, 5 CH$_2$); 3.72—3.84 (m, 1 H, CH); 5.59, 6.69 (both s, 2 H, NH$_2$); 7.34—7.42 (m, 4 H, Ar); 8.35 (d, 1 H, NHCH, J = 7.2 Hz); 10.09, 10.17 (both s, 1 H, OH); 13.22, 13.38 (both s, 1 H, NH). A mixture of *E*- and *Z*-isomers in a ratio of 2 : 3. Found (%): C, 53.26; H, 5.87; N, 20.82. $C_{15}H_{20}ClN_5O_2$. Calculated (%): C, 53.33; H, 5.97; N, 20.73.

3-Amino-*N*-benzyl-2-(4-chlorophenylhydrazono)-3-hydroxyiminopropanamide (5d). The yield was 0.82 g (82%), m.p. 152—153 °C. IR, ν/cm^{-1}: 1680 (CO); 3300, 3345, 3570 (NH, OH). ^{1}H NMR (DMSO-d$_6$), δ: 4.15, 4.49 (both d, 2 H, NHCH$_2$, J = 6.4 Hz); 5.52, 6.61 (both s, 2 H, NH$_2$); 7.12—7.37 (m, 9 H, Ar); 8.57, 10.14 (both t, 1 H, NHCH$_2$, J = 6.4 Hz); 9.90, 10.06 (both s, 1 H, NOH); 13.56, 13.87 (both s, 1 H, NH). A mixture of *E*- and *Z*-isomers in a ratio of 1 : 1. MS, m/z (I_{rel} (%)): 345 [M]$^+$ (25). Found (%): C, 55.39; H, 4.59; N, 20.81. $C_6H_{16}ClN_5O_2$. Calculated (%): C, 55.58; H, 4.66; N, 20.25.

2-(4-Chlorophenylhydrazono)-*N*-hydroxy-3-oxo-3-(pyrrolidin-1-yl)propanamidine (5e). The yield was 0.74 (80%), m.p. 185—186 °C. ^{1}H NMR (DMSO-d$_6$), δ: 1.85—1.90 (m, 4 H, CH$_2$); 3.23—3.28 (m, 2 H, CH$_2$); 3.43—3.50 (m, 2 H, CH$_2$); 5.27, 6.28 (both s, 2 H, NH$_2$); 7.12 (d, 2 H, Ar, J = 8.4 Hz); 7.30—7.45 (m, 2 H, Ar); 9.69, 9.99 (both s, 1 H, NOH); 12.43, 15.78 (both s, 1 H, NH). A mixture of *E*- and *Z*-isomers in a ratio of 1 : 5. MS, m/z (I_{rel} (%)): 309 [M]$^+$ (46). Found (%): C, 50.55; H, 5.27; N, 22.70. $C_{13}H_{16}ClN_5O_2$. Calculated (%): C, 50.41; H, 5.21; N, 22.61.

3-Amino-3-hydroxyimino-2-(4-methoxyphenylhydrazono)-*N*-methylpropanamide (5f). The yield was 0.60 g (75%), m.p. 135—136 °C. ^{1}H NMR (DMSO-d$_6$ + CCl$_4$), δ: 2.77 (d, 3 H, NHCH$_3$, J = 4.8 Hz); 3.74 (s, 3 H, OMe); 5.45 (s, 1 H, NH$_2$); 6.60 (br.s, 1 H, NH$_2$); 6.83, 7.24, 6.83, 7.27 (two AA´XX´ systems, 4 H, Ar, J = 8.5 Hz); 7.83, 9.00 (both q, 1 H, NHMe, J = 4.8 Hz); 9.75, 9.88 (both s, 1 H, NOH); 13.37, 13.85 (both s, 1 H, NH). A mixture of *E*- and *Z*-isomers in a ratio of 2 : 3. MS, m/z (I_{rel} (%)): 265 [M]$^+$ (58). Found (%): C, 49.72; H, 5.66; N, 26.54. $C_{11}H_{15}N_5O_3$. Calculated (%): C, 49.81; H, 5.70; N, 26.40.

3-Amino-*N*-benzyl-3-hydroxyimino-2-(4-methoxyphenylhydrazono)propanamide (5g). The yield was 0.70 g (68%), m.p. 105—106 °C. ^{1}H NMR (DMSO-d$_6$ + CCl$_4$), δ: 3.74 (s, 3 H, OMe); 4.43, 4.48 (both d, 2 H, CH$_2$, J = 6.4 Hz); 5.51, 6.60 (both s, 2 H, NH$_2$); 6.84 (d, 2 H, Ar, J = 9.2 Hz); 7.17—7.33 (m, 7 H, Ar); 8.53, 10.10 (both t, 1 H, NHCH$_2$, J = 6.4 Hz); 9.81, 9.95 (both s, 1 H, NOH); 13.48, 13.88 (both s, 1 H, NH). A mixture of *E*- and *Z*-isomers in a ratio of 2 : 3. MS, m/z (I_{rel} (%)): 341 [M]$^+$ (31). Found (%): C, 59.57; H, 5.50; N, 20.80. $C_{17}H_{19}N_5O_3$. Calculated (%): C, 59.81; H, 5.61; N, 20.52.

***N*-Hydroxy-2-(4-methoxyphenylhydrazono)-3-oxo-3-(pyrrolidin-1-yl)propionamidine (5h).** The yield was 0.64 g (70%), m.p. 190—191 °C. ^{1}H NMR (DMSO-d$_6$), δ: 1.87—1.91 (m, 4 H, CH$_2$); 3.24—3.29 (m, 2 H, CH$_2$); 3.42—3.50 (m, 2 H, CH$_2$); 3.72, 3.73 (both s, 3 H, OMe); 5.12, 5.94 (both s, 2 H, NH$_2$); 6.75, 7.04, 6.84, 7.19 (two AA´XX´ systems, 4 H, Ar, J = 9.2 Hz); 9.36, 10.03 (both s, 1 H, NOH); 9.86, 12.89 (both s, 1 H, NH). A mixture of *E*- and *Z*-isomers in a ratio of 1 : 3. MS, m/z (I_{rel} (%)): 305 [M]$^+$ (20). Found (%): C, 54.95; H, 6.25; N, 22.98. $C_{14}H_{19}N_5O_3$. Calculated (%): C, 55.07; H, 6.27; N, 22.94.

Reactions of arylhydrozonoacetamidoximes 5 with orthoesters (general procedures). Method *A*. Triethyl orthoformate (2 mL) and 1—2 droplets of $BF_3 \cdot OEt_2$ were added to a solution of amidoxime **5** (1.0 mmol) in DMF (10 mL). The reaction mixture was stored for 20—24 h at ~20 °C and diluted with 100 mL of water, and the precipitate was filtered off and crystallized from EtOH. After crystallization, the filtrate was diluted with water, and the precipitate that formed was filtered off.

Method *B*. Triethyl orthoformate (2 mL) and 1 droplet of $BF_3 \cdot OEt_2$ were added to a solution of amidoxime **5** (1.0 mmol) in DMF (10 mL). The reaction mixture was stored for 3—4 h at 50 °C and diluted with water. The precipitate that formed was filtered off and recrystallized from ethanol.

2-(4-Chlorophenylhydrazono)-*N*-methyl-2-(1,2,4-oxadiazol-3-yl)acetamide (6a). Method *A*, the yield was 0.14 g (50%), m.p. 110—111 °C. IR, ν/cm^{-1}: 1680 (CO); 3330, 3370 (NH). ^{1}H NMR (DMSO-d$_6$), δ: 2.78, 2.87 (both d, 3 H, NHCH$_3$, J = 4.8 Hz); 7.30, 7.37 (AA´XX´ system, 4 H, Ar, J = 8.5 Hz); 8.31, 8.37 (both q, 1 H, NHMe, J = 4.8 Hz); 9.57, 9.67 (both br.s, 1 H, CH); 13.58 (br.s, 1 H, NH). Found (%): C, 47.11; H, 3.73; N, 25.34. $C_{11}H_{10}ClN_5O_2$. Calculated (%): C, 47.24; H, 3.60; N, 25.04.

2-(4-Chlorophenylhydrazono)-*N*-ethyl-2-(1,2,4-oxadiazol-3-yl)acetamide (6b). Method *A*, the yield was 0.19 g (65%), m.p. 135—136 °C. IR, ν/cm^{-1}: 1640 (CO); 2845, 2930 (CH); 3210, 3280, 3315 (NH). ^{1}H NMR (DMSO-d$_6$), δ: 1.21 (t, 3 H, CH$_2$CH$_3$, J = 7.0 Hz); 3.37 (dq, 2 H, NHCH$_2$CH$_3$, J = 7.1 Hz, J = 5.1 Hz); 7.29, 7.39 (AA´XX´ system, 4 H, Ar, J = 9.2 Hz); 8.43 (t, 1 H, NHCH$_2$, J = 5.1 Hz); 9.48 (s, 1 H, CH); 14.00 (s, 1 H, NH). Found (%): C, 48.93; H, 3.85; N, 24.57. $C_{12}H_{12}ClN_5O_2$. Calculated (%): C, 49.07; H, 4.12; N, 23.84.

2-(4-Chlorophenylhydrazono)-*N*-cyclohexyl-2-(1,2,4-oxadiazol-3-yl)acetamide (6c). Method *A*, the yield was 0.25 g (72%), m.p. 115—116 °C. IR, ν/cm^{-1}: 1630 (CO); 2850, 2930 (CH); 3210, 3280, 3310 (NH). ^{1}H NMR (DMSO-d$_6$), δ: 1.24—1.93 (m, 10 H, CH$_2$); 3.83—3.91 (m, 1 H, CH); 7.32, 7.36 (AA´BB´ system, 4 H, Ar, J = 9.2 Hz); 8.39 (d, 1 H, NHCH, J = 7.3 Hz); 9.57 (s, 1 H, CH); 13.98 (br.s, 1 H, NH). Found (%): C, 55.49; H, 5.10; N, 20.3. $C_{15}H_{18}ClN_5O_2$. Calculated (%): C, 55.25; H, 5.22; N, 20.14.

2-(4-Chlorophenyl)-5-formylimino-*N*-methyl-2,5-dihydro-1*H*-1,2,3-triazole-4-carboxamide (7a). Method *A*, the yield was 0.08 (30%); method *B*, the yield was 0.19 (68%), m.p. 230—231 °C. IR, ν/cm^{-1}: 1650, 1710 (CO); 3060, 3100 (CH); 3280, 3380, 3500 (NH). ^{1}H NMR (CDCl$_3$), δ: 3.04 (d, 3 H, NHCH$_3$, J = 5.2 Hz); 6.73, 6.83 (both br.q, 1 H, NHMe, J = 5.2 Hz); 7.47, 7.95 (AA´XX´ system, 4 H, Ar, J = 8.7 Hz); 8.52 and 9.17 (s and d, 1 H, CHO, J = 10.8 Hz); 9.03 and 9.68 (br.d and br.s, 1 H, NH, J = 10.8 Hz). Found (%): C, 47.12; H, 3.55; N, 24.88. $C_{11}H_{10}ClN_5O$. Calculated (%): C, 47.24; H, 3.60; N, 25.04.

2-(4-Chlorophenyl)-*N*-ethyl-5-formylimino-2,5-dihydro-1*H*-1,2,3-triazole-4-carboxamide (7b). Method *A*, the yield was 0.60 g (20%), m.p. 172—173 °C. IR, ν/cm^{-1}: 1650, 1710 (CO); 2850, 2920, 2980 (CH); 3380; 3280 (NH). ^{1}H NMR (T = 373 K, DMSO-d$_6$), δ: 1.19 (t, 3 H, CH$_2$CH$_3$, J = 7.2 Hz); 3.36 (dq, 2 H, NHCH$_2$CH$_3$, J = 7.2 Hz, J = 5.3 Hz); 7.60, 8.00 (AA´XX´ system, 4 H, Ar, J = 8.9 Hz); 8.26 (s, 1 H, CHO); 8.73 (t, 1 H, NHCH$_2$, J = 5.3 Hz); 9.71 (s, 1 H, NH). ^{1}H NMR (T = 303 K, DMSO-d$_6$), δ: 1.17 (t, 3 H, CH$_2$CH$_3$, J = 7.2 Hz); 3.34 (dq, 2 H, CH$_2$CH$_3$ J = 7.2 Hz, J = 5.3 Hz); 7.67, 8.02 (AA´XX´ system, 4 H, Ar, J = 8.9 Hz); 8.74 (br.t, 1 H, NHCH$_2$, J = 5.3 Hz); 8.44 and 8.92 (br.s and br.s, 1 H, CHO); 9.94 and 10.37 (br.s and br.s, 1 H, NH). ^{13}C NMR (T = 373 K, DMSO-d$_6$), δ: 13.8 (Me); 33.0 (CH$_2$); 119.8; 129.0; 132.2; 137.1 (C$_{arom}$); 131.1 (C(5)$_{triaz}$); 144.5

($C(4)_{triaz}$); 159.1 (CO); 159.9 (CHO). ^{13}C NMR (T = 313 K, DMSO-d_6), δ: 14.6 (Me); 33.4 (CH_2); 120.0; 129.9, 132.5; 137.3 (C_{arom}); 130.9, 131.88 (br.s, $C(5)_{triaz}$); 144.1, 145.5 (br.s, $C(4)_{triaz}$); 159.4 (CO); 159.4, 162.1 (br.s, CHO). Found (%): C, 48.92; H, 4.02; N, 23.75. $C_{12}H_{12}ClN_5O_2$. Calculated (%): C, 49.07; H, 4.12; N, 23.84.

2-(4-Chlorophenyl)-*N*-cyclohexyl-5-formylimino-2,5-dihydro-1*H*-1,2,3-triazole-4-carboxamide (7c). Method *A*, the yield was 0.07 g (20%), m.p. 115—116 °C. ^1H (DMSO-d_6), δ: 1.24—1.93 (m, 10 H, 5 CH_2); 3.73—3.83 (m, 1 H, CH); 7.32, 7.36 (AA´BB´ system, 4 H, Ar, J = 9.2 Hz); 8.39 (d, 1 H, N<u>H</u>CH, J = 7.3 Hz); 8.65, 9.57 (both br.s, 1 H, CHO); 10.15, 13.98 (both br.s, 1 H, NH). MS, m/z (I_{rel} (%)): 347 $[M]^+$ (6). Found (%): C, 55.35; H, 5.30; N, 20.15. $C_{16}H_{18}ClN_5O_2$. Calculated (%): C, 55.25; H, 5.22; N, 20.14.

***N*-Benzyl-2-(4-chlorophenyl)-5-formylimino-2,5-dihydro-1*H*-1,2,3-triazole-4-carboxamide (7d).** Method *B*, the yield was 0.25 g (70%), m.p. 153—154 °C. ^1H NMR (DMSO-d_6), δ: 4.50 (d, 2 H, NHC<u>H</u>$_2$, J = 6.0 Hz); 7.00—7.37 (m, 5 H, Ph); 7.34, 7.39 (AA´BB´ system, 4 H, Ar, J = 8.8 Hz); 8.35, 9.09 (both br.s, 1 H, CHO); 9.60 (br.t, 1 H, N<u>H</u>CH$_2$, J = 6.0 Hz); 10.30, 10.80 (both br.s, 1 H, NH). MS, m/z (I_{rel} (%)): 355 $[M]^+$ (6). Found (%): C, 57.35; H, 3.50; N, 19.45. $C_{17}H_{14}ClN_5O_2$. Calculated (%): C, 57.39; H, 3.97; N, 19.68.

5-Formylimino-2-(4-methoxyphenyl)-*N*-methyl-2,5-dihydro-1*H*-1,2,3-triazole-4-carboxamide (7e). Method *B*, the yield was 0.19 g (70%), m.p. 121—122 °C. ^1H NMR (DMSO-d_6), δ: 3.04 (d, 3 H, NHC<u>H</u>$_3$, J = 4.3 Hz); 3.84 (s, 3 H, OMe); 7.05, 7.95 (AA´BB´ system, 4 H, Ar, J = 8.8 Hz); 8.40 (br.q, 1 H, N<u>H</u>CH$_3$, J = 4.3 Hz); 8.95, 9.35 (both br.s, 1 H, CH); 9.50, 9.75 (both br.s, 1 H, NH). MS, m/z (I_{rel} (%)): 275 $[M]^+$ (10). Found (%): C, 52.33; H, 4.50; N, 25.34. $C_{12}H_{13}N_5O_3$. Calculated (%): C, 52.36; H, 4.76; N, 25.44.

***N*-Benzyl-5-formylimino-2-(4-methoxyphenyl)-2,5-dihydro-1*H*-1,2,3-triazole-4-carboxamide (7f).** Method *B*, the yield was 0.22 g (63%), m.p. 123—124 °C. ^1H NMR (DMSO-d_6), δ: 3.84 (s, 3 H, OMe); 4.49 (d, 2 H, NHC<u>H</u>$_2$, J = 7.5 Hz); 7.05, 7.94 (AA´XX´ system, 4 H, Ar, J = 9.3 Hz); 7.18—7.32 (m, 5 H, Ph); 8.40, 8.95 (both br.s, 1 H, CH); 9.01 (br.t, 1 H, N<u>H</u>CH$_2$, J = 7.5 Hz); 9.55, 10.25 (both br.s, 1 H, NH). MS, m/z (I_{rel} (%)): 351 $[M]^+$ (5). Found (%): C, 61.48; H, 4.10; N, 19.53. $C_{18}H_{17}N_5O_3$. Calculated (%): C, 61.53; H, 4.88; N, 19.93.

3-Amino-4-(4-chlorophenylhydrazono)-4*H*-isoxazol-5-one (9a). Method *A*, the yield was 0.17 g (72%), m.p. 124—125 °C. ^1H NMR (DMSO-d_6), δ: 6.09 (br.s, 2 H, NH_2); 7.28, 7.41 (AA´XX´ system, 4 H, Ar, J = 7.0 Hz); 12.27 (br.s, 1 H, NH). MS, m/z (I_{rel} (%)): 238 $[M]^+$ (1). Found (%): C, 45.33; H, 3.00; N, 23.25. $C_9H_7ClN_4O_2$. Calculated (%): C, 45.30; H, 2.96; N, 23.48.

3-Amino-4-(4-methoxyphenylhydrazono)-4*H*-isoxazol-5-one (9b). Method *A*, the yield was 0.19 g (83%), m.p. 198—199 °C. ^1H NMR (DMSO-d_6), δ: 3.77 (s, 3 H, OMe); 6.07 (br.s, 2 H, NH_2); 6.91, 7.61 (AA´BB´ system, 4 H, Ar, J = 8.8 Hz); 12.25 (br.s, 1 H, NH). MS, m/z (I_{rel} (%)): 234 $[M]^+$ (83). Found (%): C, 51.33; H, 4.43; N, 23.75. $C_{10}H_{10}N_4O_3$. Calculated (%): C, 51.28; H, 4.30; N, 23.92.

2-[2-(4-Chlorophenyl)-2-ethylhydrazono]-*N*-methyl-2-(5-methyl-1,2,4-oxadiazol-3-yl)acetamide (11a). Method *A*, the yield was 0.20 g (87%), m.p. 125—126 °C. IR, ν/cm^{-1}: 1680 (CO); 2980, 2940 (CH); 3340 (NH). ^1H NMR (DMSO-d_6), δ: 1.32 (t, 3 H, CH$_2$C<u>H</u>$_3$, J = 7.0 Hz); 2.39 (s, 3 H, Me); 2.82 (d, 3 H, NHC<u>H</u>$_3$, J = 4.8 Hz); 4.26 (q, 2 H, C<u>H</u>$_2$CH$_3$, J = 7.0 Hz); 7.49, 7.78 (AA´XX´ system, 4 H, Ar, J = 9.2 Hz); 8.10 (q, 1 H, N<u>H</u>Me, J = 4.8 Hz). Found (%): C, 52.02; H, 5.11; N, 21.42. $C_{14}H_{16}ClN_5O_2$. Calculated (%): C, 52.26; H, 5.01; N, 21.77.

***N*-Benzyl-2-[2-(4-chlorophenyl)-2-ethylhydrazono]-2-(5-methyl-1,2,4-oxadiazol-3-yl)acetamide (11b).** Method *A*, the yield was 0.32 g (80%), m.p. 142—143 °C. ^1H DMSO-d_6), δ: 1.30 (t, 3 H, CH$_2$C<u>H</u>$_3$, J = 7.2 Hz); 2.37 (s, 3 H, Me); 4.20 (q, 2 H, C<u>H</u>$_2$CH$_3$, J = 7.2 Hz); 4.50 (d, 2 H, NHC<u>H</u>$_2$, J = 6.0 Hz); 7.00, 7.20 (AA´BB´ system, 4 H, Ar, J = 8.5 Hz); 7.30—7.48 (m, 5 H, Ph); 8.63 (t, 1 H, N<u>H</u>CH$_2$, J = 6.0 Hz). Found (%): C, 60.28; H, 5.37; N, 17.35. $C_{20}H_{20}ClN_5O_2$. Calculated (%): C, 60.38; H, 5.07; N, 17.60.

2-[2-(4-Chlorophenyl)-2-ethylhydrazono]-2-(5-ethyl-1,2,4-oxadiazol-3-yl)-*N*-methylacetamide (11c). Method *A*, the yield was 0.21 g (63%), m.p. 72—73 °C. ^1H NMR (DMSO-d_6), δ: 1.10 (t, 3 H, CH$_2$C<u>H</u>$_3$, J = 7.3 Hz); 1.27 (t, 3 H, CH$_2$C<u>H</u>$_3$, J = 7.0 Hz); 2.72 (q, 2 H, C<u>H</u>$_2$CH$_3$, J = 7.3 Hz); 2.79 (d, 3 H, NHC<u>H</u>$_3$, J = 4.7 Hz); 4.24 (q, 2 H, C<u>H</u>$_2$CH$_3$, J = 7.0 Hz); 7.61, 7.76 (AA´XX´ system, 4 H, Ar, J = 8.6 Hz); 8.45 (q, 1 H, N<u>H</u>Me, J = 4.7 Hz). ^{13}C NMR (DMSO-d_6), δ: 14.3 (Me), 19.3 (Me), 26.2 (Me), 63.7 (CH_2), 125.4, 129.5, 132.7, 136.1, 155.0, 155.1, 159.7, 171.1 (CO). Found (%): C, 53.52; H, 5.11; N, 20.40. $C_{15}H_{18}ClN_5O_2$. Calculated (%): C, 53.65; H, 5.40; N, 20.86.

2-[2-(4-Methoxyphenyl)-2-ethylhydrazono]-*N*-methyl-2-(5-methyl-1,2,4-oxadiazol-3-yl)acetamide (11d). Method *A*, the yield was 0.23 g (72%), m.p. 124—125 °C. IR, ν/cm^{-1}: 1670 (CO); 2945, 2985 (CH); 3330 (NH). ^1H NMR (DMSO-d_6), δ: 1.30 (t, 3 H, CH$_2$C<u>H</u>$_3$, J = 7.2 Hz); 2.35 (s, 3 H, Me); 2.80 (d, 3 H, NHC<u>H</u>$_3$, J = 4.7 Hz); 3.80 (s, 3 H, OMe); 4.20 (q, 2 H, C<u>H</u>$_2$CH$_3$, J = 7.2 Hz); 7.45, 7.75 (AA´XX´ system, 4 H, Ar, J = 9.0 Hz); 8.05 (br.q, 1 H, N<u>H</u>Me, J = 4.7 Hz). Found (%): C, 56.72; H, 6.15; N, 22.27. $C_{15}H_{19}N_5O_3$. Calculated (%): C, 56.77; H, 6.03; N, 22.07.

***N*-Benzyl-2-(5-methyl-1,2,4-oxadiazol-3-yl)-2-[2-(4-methoxyphenyl)-2-ethylhydrazono]acetamide (11e).** Method *A*, the yield was 90%, m.p. 142—143 °C. IR, ν/cm^{-1}: 1675 (CO); 2930, 2970 (CH); 3345 (NH). ^1H NMR (DMSO-d_6), δ: 1.29 (t, 3 H, CH$_2$C<u>H</u>$_3$, J = 7.0 Hz); 2.35 (s, 3 H, Me); 3.83 (s, 3 H, OMe); 4.22 (q, 2 H, C<u>H</u>$_2$CH$_3$, J = 7.0 Hz); 4.47 (d, 2 H, NHC<u>H</u>$_2$, J = 5.8 Hz); 6.98, 7.60 (AA´XX´ system, 4 H, Ar, J = 8.8 Hz); 7.20—7.38 (m, 5 H, Ph); 8.62 (t, 1 H, N<u>H</u>CH$_2$, J = 5.8 Hz). MS, m/z (I_{rel} (%)): 393 $[M]^+$ (78). Found (%): C, 64.44; H, 5.70; N, 17.54. $C_{21}H_{23}N_5O_3$. Calculated (%): C, 64.11; H, 5.89; N, 17.80.

***N*-Benzyl-2-[2-(4-methoxyphenyl)-2-ethylhydrazono]-2-(5-ethyl-1,2,4-oxadiazol-3-yl)acetamide (11f).** Method *A*, the yield was 0.35 g (90%), m.p. 142—143 °C. IR, ν/cm^{-1}: 1670 (CO); 2945, 2985 (CH); 3335 (NH). ^1H NMR (DMSO-d_6), δ: 1.18 (t, 3 H, CH$_2$C<u>H</u>$_3$, J = 7.0 Hz); 1.30 (t, 3 H, CH$_2$C<u>H</u>$_3$, J = 6.9 Hz); 2.72 (q, 2 H, C<u>H</u>$_2$CH$_3$, J = 7.0 Hz); 3.79 (s, 3 H, OMe); 4.23 (q, 2 H, C<u>H</u>$_2$CH$_3$, J = 7.0 Hz); 4.48 (d, 2 H, NHC<u>H</u>$_2$, J = 6.0 Hz); 7.00, 7.58 (AA´XX´ system, 4 H, Ar, J = 9.2 Hz); 7.18—7.57 (m, 5 H, Ar); 8.55 (t, 1 H, N<u>H</u>CH$_2$, J = 6.0 Hz). MS, m/z (I_{rel} (%)): 407 $[M]^+$ (50). Found (%): C, 64.72; H, 6.38; N, 17.25. $C_{22}H_{25}N_5O_3$. Calculated (%): C, 64.85; H, 6.18; N, 17.19.

X-ray diffraction study of compound 7f was carried out according to a standard procedure on an Xcalibur 3 diffractometer equipped with a CCD detector (λ(Mo-Kα) = 0.71073 Å, graphite monochromator, 295(2) K, ω scan mode, scanning increment 1°, time of frame measurement 20 s). A piece of colorless crystal 0.48×0.31×0.19 mm in size was used, and no absorption correction was applied because it is negligible. The structure was

solved by a direct method and refined by the least-squares method in the anisotropic full-matrix approximation for non-hydrogen atoms using the SHELXTL97 program package.[11] The hydrogen atoms of the C—H bonds were added to the geometrically calculated positions and included into refinement in the isotropic approximation with dependent thermal parameters in the riding model, while the hydrogen atoms of the N—H groups were refined in the isotropic approximation. According to the X-ray diffraction results, crystal **7f** is monoclinic, space group $P2_1/s$, a = 14.374(3) Å, b = 14.1218(17) Å, c = 8.6374(6) Å, β = 96.323(10)°, V = 1742.7(4), Z = 4, empirical formula $C_{18}H_{17}N_5O_3$, d_{calc} = 1.339 g cm^{-3}, μ = 0.095 mm^{-1}, $F(000)$ = 736. At scanning angles 2.78° < θ < 26.38°, 13 115 reflections were collected, of which 3457 were independent reflections (R_{int} = 0.0335), 1665 with $I > 2\sigma(I)$, completeness for θ = 26.38° is 97%. The final parameters are R_1 = 0.0350, wR_2 = 0.0499 (for reflections with $I > 2\sigma(I)$), R_1 = 0.1029, wR_2 = 0.0541 (for all reflections) at the goodness-of-fit S = 1.000. The residual electron density is ρ_{max}/ρ_{min} = 0.122/−0.126 e·Å^{-3}.

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