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Synthesis and Properties of Substituted [3-(2-Hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl]acetonitriles

E. Yu. Shasheva[a], N. I. Vikrishchuk[a], L. D. Popov[a], V. I. Minkin[a], M. E. Kletskii[a], M. Yu. Antipin[b], A. D. Vikrishchuk[c], and I. E. Mikhailov[c]

[a] *Southern Federal University, ul. Zorge 7, Rostov-on-Don, 344090 Russia*
e-mail: natvi2004@mail.ru

[b] *Nesmeyanov Institute of Organometallic Compounds, Russian Academy of Sciences, ul. Vavilova 28, Moscow, 119991 Russia*

[c] *Southern Research Center, Russian Academy of Sciences, Rostov-on-Don, Russia*

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Abstract—Alkylation of 3-substituted 5-(2-hydroxyphenyl)-1*H*-1,2,4-triazoles with chloroacetonitrile gave hitherto unknown N-cyanomethyl derivatives whose structure was determined by X-ray analysis and ^{1}H and ^{13}C NMR spectroscopy. Condensation of substituted [3-(2-hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl]acetonitriles at the activated methylene group with acetone led to the formation of new 3-methyl-2-triazolylbut-2-enenitrile derivatives.

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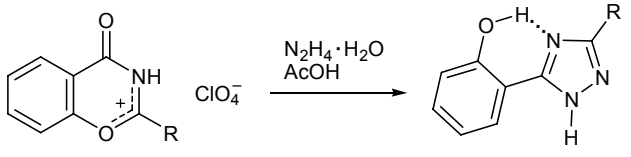
Hydroxyphenyl-substituted 1,2,4-triazoles **I** are formed via recyclization of 4-oxo-1,3-benzoxazinium perchlorates **II** [1, 2] by the action of hydrazine hydrate (Scheme 1) [3]. Their molecules possess several nucleophilic centers, and therefore their reactions with various electrophilic reagents attract interest. Substituted 1,2,4-triazoles are biologically active substances; antitumor [4, 5], antifungal [6], sedative [7], tranquilizing [8], analgesic, and antihypoxic agents [8] were found among 1,2,4-triazole derivatives.

Scheme 1.



IIa–IIf **Ia–If**

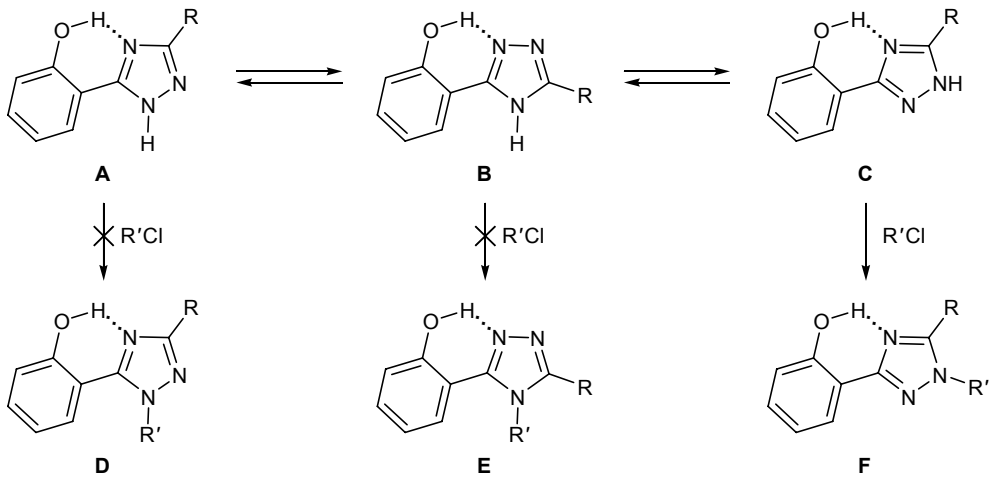
R = Me (**a**), PhCH=CH (**b**), 4-MeOC$_6$H$_4$CH=CH (**c**), 2-(2-thienyl)-vinyl (**d**), 4-BrC$_6$H$_4$CH=CH (**e**), 4-FC$_6$H$_4$CH=CH (**f**).

The formation of just 5-(2-hydroxyphenyl)-1*H*-1,2,4-triazoles **A** rather than other isomeric structures **B** and **C** (Scheme 2) was proved previously [9] and was confirmed by the ^{13}C NMR data and DFT B3LYP/6-31G* quantum-chemical calculations for the gas phase, according to which the most energetically favorable is tautomer **A** (the energies of formation of tautomers **A**–**C** are –609655.52, –609644.72, and –609655.02 kcal/mol, respectively).

In the present work we examined reactions of 1,2,4-triazoles **I** with chloroacetonitrile. Taking into account that triazoles **I** in solution could give rise to equilibrium mixtures of tautomers **A**–**C**, the alkylation process may involve different nitrogen atoms in molecule **I** with formation of isomeric structures **D**–**F** (Scheme 2). By treatment of 1,2,4-triazoles **Ia**–**Id** with chloroacetonitrile in acetone in the presence of potassium carbonate according to standard procedure (1.5 h under reflux) we obtained compounds **IIIa**–**IIId** (Scheme 3) whose structure was determined on the basis of their elemental compositions and IR, NMR, and mass spectra. The structure of triazole **IIIc** was unambiguously proved by X-ray analysis (Fig. 1).

The IR spectra of *N*-cyanomethyl-1,2,4-triazoles **IIIa**–**IIId** contained medium-intensity absorption bands in the region 1690–1550 cm^{-1}, which were assigned to vibrations of the triazole and benzene rings, while no absorption typical of cyano group (2100–2200 cm^{-1}) was observed. In the ^{1}H NMR spectra of **IIIa**–**IIId**, protons in the exocyclic methylene group resonated as a singlet at δ 5.62–5.81 ppm, which

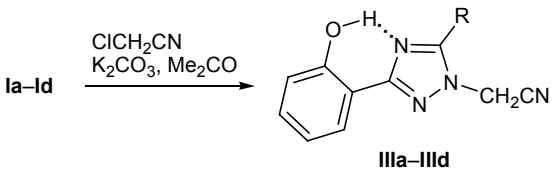
Scheme 2.



R = Me, ArCH=CH, HtCH=CH; R′ = CH_2CN.

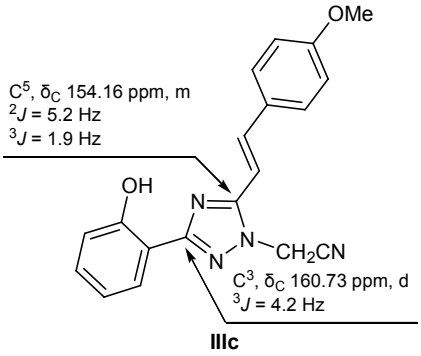
was absent in the spectra of initial triazoles **Ia**–**Id**. In the downfield region of the spectrum we observed only one singlet at δ 10.66–10.86 ppm, belonging to the phenolic hydroxy group.

Scheme 3.



R = Me (**a**), PhCH=CH (**b**), 4-$MeOC_6H_4CH$=CH (**c**), 2-(2-thienyl)vinyl (**d**).

The structure of *N*-cyanomethyl-1,2,4-triazole **IIIc** was also studied by ^{13}C NMR spectroscopy. The C^3 atom in the triazole ring displayed long-range spin–spin coupling with the 6-H proton in the hydroxyphenyl group; its signal was a doublet at δ_C 160.73 ppm (^3J = 4.2 Hz). The C^5 atom in the triazole ring gave rise to a multiplet at δ_C 154.16 ppm due to long-range couplings with the 5-CH and CH_2 protons (^2J = 5.2, ^3J = 1.9 Hz).



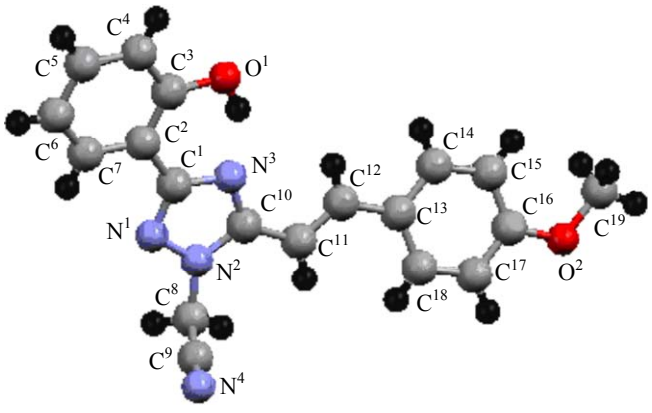


Fig. 1. Structure of the molecule of {3-(2-hydroxyphenyl)-5-[2-(4-methoxyphenyl)vinyl]-1*H*-1,2,4-triazol-1-yl}acetonitrile (**IIIc**) according to the X-ray diffraction data.

The X-ray diffraction data for a single crystal of **IIIc** indicated formation of intramolecular hydrogen bond between the N^3 atom in the triazole ring and hydrogen atom in the phenolic hydroxy group [d(H···N) = 1.77 Å], which stabilized coplanar arrangement of the 2-hydroxyphenyl substituent and 1,2,4-triazole ring plane (Fig. 1). The principal bond lengths and bond angles in molecule **IIIc** are given in table.

It is known that alkylation of 1,2,4-triazoles in alkaline medium usually gives the corresponding 1-alkyl-substituted derivatives [10], i.e., products like **D** are commonly formed from tautomer **A**. In our case, products with structure **F** were isolated exclusively (Scheme 2). Presumably, in the reactions of triazoles

Ia–**Id** with chloroacetonitrile the direction of electrophilic attack changes due to effect of substituent in the triazole ring. Insofar as the alkylation of **Ia**–**Id** was carried out in alkaline medium (Scheme 3) in the presence of 4 equiv of potassium carbonate, the substrates reacted as the corresponding anions **IVa**–**IVd**, and just the structure of the latter should be responsible for the direction of electrophilic attack. In order to verify this assumption we performed quantum-chemical calculations of the electronic and steric structure and relative stabilities of conformers of anion **IVa** in terms of the density functional theory (DFT) using B3LYP/6-311++G** basis set. The results showed that structures **IVa** and **IVa′** (Fig. 2) occupy minima on the potential energy surface (PPE). Conformers **IVa** and **IVa′** are almost equally stable: the difference in their energies calculated with correction for zero-point vibration energy was ΔE_{ZPE} = 1.26 kcal/mol, and the total energies were –368654.15 and –368655.36 kcal × mol^{-1} for compounds **IVa** and **IVa′**, respectively. The least harmonic vibration frequencies were ω_1 = 65 (**IVa**) and 66 cm^{-1} (**IVa′**). The calculated negative charge (natural bond orbital approximation) on the N^2 atom in anion **IVa** (–0.385 a.u.) is slightly greater than the charge on N^1 (–0.374 a.u.). This factor may be responsible for the alkylation at N^2. Anion **IVa′** is characterized by the opposite charge distribution over N^1 and N^2, but strong intramolecular hydrogen bond between the N^1 atom and hydroxy group ($H\cdots N^1$ 1.537 Å) is likely to hamper electrophilic substitution at that center, so that the alkylation also occurs at N^2. The alkylation of **IVa** and **IVa′** at position *4* of the triazole ring (N^3) is hardly probable; this reaction direction is not consistent with the recent data on the alkylation of 1,2,4-triazoles [10].

The alkylation of triazoles **Ie** and **If** containing a fluorine or bromine atom in the arylvinyl fragment gave mixtures of the corresponding *N*-cyanomethyl-1,2,4-triazoles **IIIe** and **IIIf** and isobutylene derivatives **Va** and **Vb**. The latter were formed as a result of condensation of acetone at the activated exocyclic methylene group in triazoles **III**. According to the ^{1}H NMR data, the product ratios were **IIIe**:**Va** = 0.40:0.60 and **IIIf**:**Vb** = 0.32:0.68. By heating mixtures **IIIe**/**Va** and **IIIf**/**Vb** in boiling acetone in the presence of potassium carbonate for an additional 1 h

Principal bond lengths (*d*) in the molecule of {3-(2-hydroxyphenyl)-5-[2-(4-methoxyphenyl)vinyl]-1*H*-1,2,4-triazol-1-yl}acetonitrile (**IIIc**) according to the X-ray diffraction data and quantum-chemical calculations (italic numbers)

Bond	*d*, Å	Bond	*d*, Å	Bond	*d*, Å
N^4–C^9	1.144(4) *1.160*	C^5–C^6	1.389(4) *1.402*	C^{13}–C^{14}	1.386(3) *1.404*
C^8–C^9	1.467(4) *1.474*	C^4–C^5	1.380(4) *1.388*	C^{14}–C^{15}	1.391(3) *1.394*
N^2–C^8	1.445(3) *1.450*	C^3–C^4	1.394(4) *1.404*	C^{15}–C^{16}	1.385(4) *1.400*
N^1–N^2	1.365(3) *1.364*	C^2–C^3	1.400(3) *1.417*	C^{16}–C^{17}	1.391(4) *1.407*
N^1–C^1	1.326(3) *1.331*	O^1–C^3	1.361(3) *1.351*	C^{17}–C^{18}	1.378(4) *1.383*
N^3–C^1	1.371(3) *1.371*	O^1–H	0.9405	C^{13}–C^{18}	1.403(4) *1.412*
N^3–C^{10}	1.333(3) *1.331*	C^{10}–C^{11}	1.442(3) *1.450*	O^2–C^{16}	1.367(3) *1.359*
N^2–C^{10}	1.361(3) *1.367*	C^{11}–C^{12}	1.328(3) *1.352*	O^2–C^{19}	1.431(3) *1.359*
C^1–C^2	1.458(3) *1.463*	C^{11}–H	0.9300	C^{19}–H	0.9600
C^2–C^7	1.409(3) *1.407*	C^{12}–C^{13}	1.459(3) *1.459*	C^8–H	0.9700
C^6–C^7	1.378(4) *1.387*	C^{12}–H	0.9300	C^{14}–H	0.9300

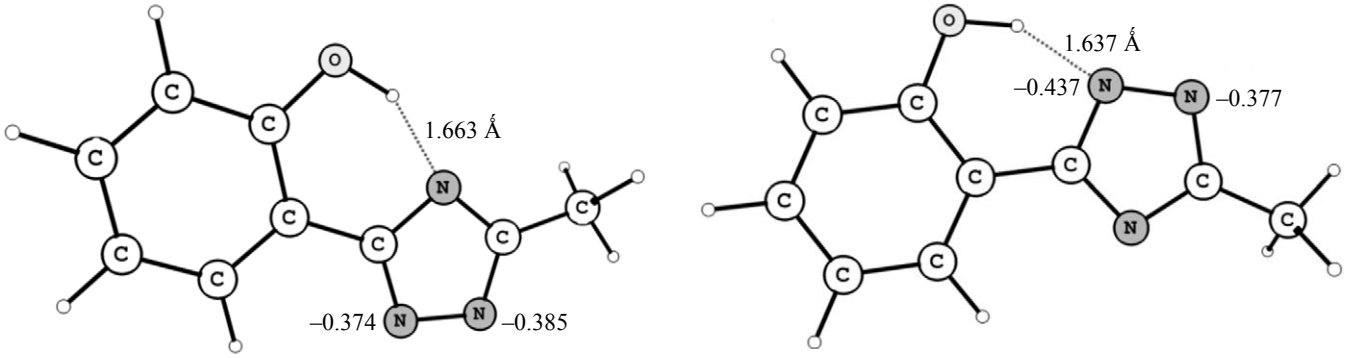
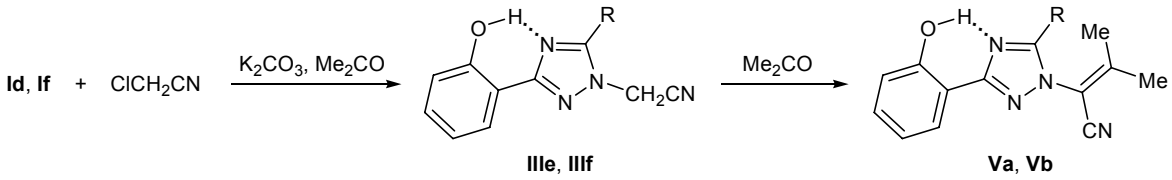


Fig. 2. Structures of conformers **IVa** and **IVa′** and charges on some atoms, according to quantum-chemical calculations.

Scheme 4.



IIIe, **Va**, R = 4-BrC_6H_4CH=CH; **IIIf**, **Vb**, R = 4-FC_6H_4CH=CH.

we obtained pure compounds **Va** and **Vb** (Scheme 4). Isobutylene derivative **Vc** (R = 4-$MeOC_6H_4CH$=CH) having an electron-donating group in the arylvinyl fragment was obtained by heating triazole **Ic** in boiling acetone in the presence of potassium carbonate over a period of 1.5 h.

With a view to elucidate specificities of the structure and mechanism of formation of isobutylene derivatives **Va**–**Vc** (Scheme 5), compounds **Ic** (R = 4-$MeOC_6H_4CH$=CH) and **If** (R = 4-FC_6H_4CH=CH) and products of their transformations were analyzed by DFT quantum-chemical calculations using B3LYP/6-31G* basis set. The calculations revealed some differences in the thermodynamics of the transformation **I**→**III** (Scheme 5) for triazoles having different arylvinyl substituents. The substitution reaction **Ic**→**IIIc** (R = 4-$MeOC_6H_4CH$=CH) is exothermic, while analogous transformation **If**→**IIIf** (R = 4-FC_6H_4CH=CH) is endothermic (Fig. 3). The same results were obtained by *ab initio* calculations with 6-31G* basis set. Presumably, this is the reason why we failed to isolate fluoro derivative **IIIf** as individual substance. The subsequent addition of acetone to compounds **III** with formation of adducts **VI** is exothermic in both cases (Fig. 4).

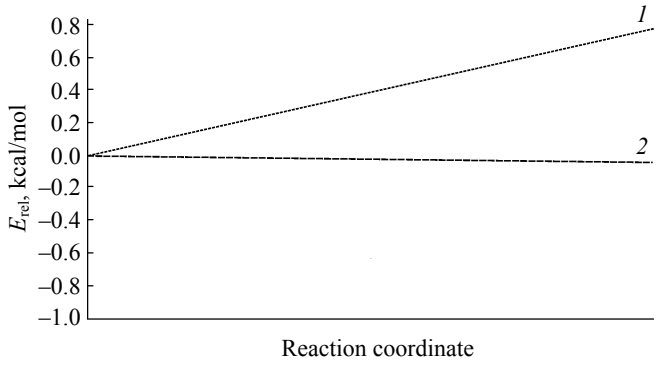


Fig. 3. Thermodynamic effects in the transformations **I**→**III** (Scheme 5) according to quantum-chemical calculations: (*1*) R = 4-FC_6H_4CH=CH, (2) R = 4-$MeOC_6H_4CH$=CH.

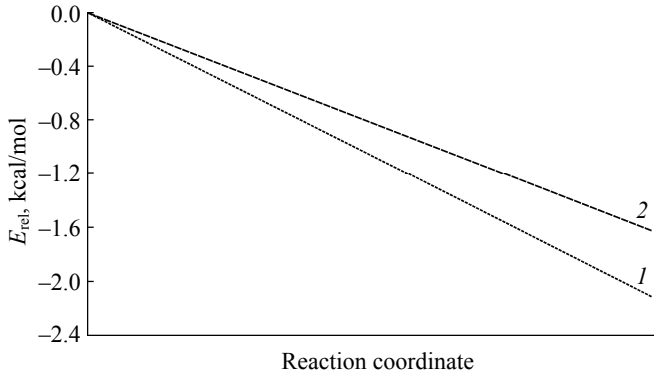
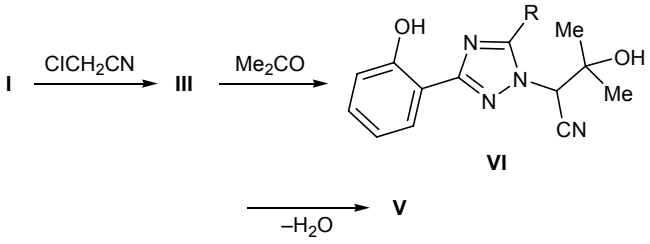


Fig. 4. Thermodynamic effects in the transformations **III**→**V** (Scheme 5) according to quantum-chemical calculations: (*1*) R = 4-FC_6H_4CH=CH, (*2*) R = 4-$MeOC_6H_4CH$=CH.

Scheme 5.



Comparison of the results of quantum-chemical calculations on *N*-cyanomethyl-1,2,4-triazole **IIIc** with the X-ray diffraction data (see table) showed a good agreement between the calculated and experimental geometric parameters, indicating proper choice of the calculation scheme.

The structure of compounds **Va**–**Vc** was confirmed by the data of elemental analysis and IR and ^{1}H NMR spectroscopy. The IR spectra of **Va**–**Vc** contained absorption bands in the region 1730–1500 cm^{-1} due to stretching vibrations of the C=C bond in the isobutylene fragment, C=C bond conjugated with the phenyl group, and double bonds in the azole and benzene rings. Unlike *N*-cyanomethyl-1,2,4-triazoles **IIIa**–**IIIf**, compounds **Va**–**Vc** displayed in the ^{1}H NMR spectra two three-proton singlets from methyl groups in the region δ 1.79–2.34 ppm, while no singlet at δ 5.62–5.81 ppm was present (CH_2).

Apart from activated methylene group, 1,2,4-triazoles **IIIa**–**IIIf** possess a cyano group whose functionalization could lead to novel polyheterocyclic systems. However, our attempt to effect condensations of *N*-cyanomethyl-1,2,4-triazoles at the cyano group with *o*-phenylenediamine or carboxylic acid hydrazides under standard conditions were unsuccessful, and the initial reactants were recovered from the reaction mixtures.

EXPERIMENTAL

The IR spectra were recorded on a Specord 75IR spectrometer from samples dispersed in mineral oil. The ^{1}H and ^{13}C NMR spectra were measured on a Varian Unity-300 instrument (300 MHz) at 20°C using DMSO-d_6 as solvent. The mass spectra (electron impact, 70 eV) were obtained on a VG 7070E mass spectrometer.

The synthesis of perchlorates **IIa**–**IIf** was described previously [1, 2], and 1,2,4-triazoles **Ia**–**If** were prepared according to the procedure reported in [3].

2-(3-Methyl-1*H*-1,2,4-triazol-5-yl)phenol (Ia) was obtained by heating 2-methyl-4-oxo-1,3-benzoxazinium perchlorate with hydrazine hydrate in glacial acetic acid according to the procedure described in [2]. ^{13}C NMR spectrum, δ_C, ppm: 12.92 q (Me, J = 129.2 Hz), 114.51 m (C_{arom}), 117.6 m (C_{arom}), 120.05 m (C_{arom}), 127.08 d (C_{arom}, J = 5.6 Hz), 131.58 m (C_{arom}), 155.09 q (C^3, J = 7.3 Hz), 157.10 m (C_{arom}), 158.55 m (C^5, ^2J = 5.2 Hz).

[3-(2-Hydroxyphenyl)-5-methyl-1*H*-1,2,4-triazol-1-yl]acetonitrile (IIIa). *a*. Triazole **Ia**, 1.75 g (10 mmol), was dissolved in 30 ml of acetone, 5.52 g (40 mmol) of calcined potassium carbonate was added, the mixture was heated for 20–25 min and cooled, 0.76 g (10 mmol) of chloroacetonitrile was added, and the mixture was heated for 1.5 h under reflux and diluted with water. The precipitate was filtered off and recrystallized. Yield 3.92 g (58%), colorless crystals, mp 140–142°C (from 1-BuOH). IR spectrum, ν, cm^{-1}: 1660, 1620, 1595 (C=C_{arom}, C=N). ^{1}H NMR spectrum, δ, ppm: 2.59 s (3H, CH_3), 5.62 s (2H, CH_2), 6.92–7.78 m (4H, H_{arom}), 10.80 s (1H, OH). Mass spectrum, m/z (I_{rel}, %): 214 (77) $[M]^+$, 186 (5), 145 (36), 119 (15), 105 (49) , 91 (34) ,76 (56), 63 (32), 50 (35), 42 (70), 39 (100). Found, %: C 62.00; H 4.90; N 25.80. $C_{11}H_{10}N_4O$. Calculated, %: C 61.68; H 4.67; N 26.17. M 214.14.

Compounds **IIIb**–**IIId** were synthesized in a similar way.

b. Potassium hydroxide, 0.56 g (10 mmol), was added to a solution of 1.75 g (10 mmol) of compound **Ia** in 3 ml of DMF, the mixture was heated for 1.5 h on a water bath and diluted with water, and the precipitate was filtered off and purified by recrystallization. Yield 2.57 g (38%), colorless crystals, mp 140–142°C (from butan-1-ol). IR spectrum, ν, cm^{-1}: 1660, 1620, 1590 (C=C_{arom}, C=N). ^{1}H NMR spectrum, δ, ppm: 2.59 s (3H, CH_3), 5.62 s (2H, CH_2), 6.92–7.78 m (4H, H_{arom}), 10.80 s (1H, OH). Found, %: C 61.30; H 4.80; N 25.60. $C_{11}H_{10}N_4O$. Calculated, %: C 61.68; H 4.67; N 26.17.

[3-(2-Hydroxyphenyl)-5-(2-phenylvinyl)-1*H*-1,2,4-triazol-1-yl]acetonitrile (IIIb). Yield 1.69 g (56%). Colorless crystals, mp 170–172°C (from 1-BuOH). IR spectrum, ν, cm^{-1}: 1610, 1600, 1590 (C=C_{arom}, C=N). ^{1}H NMR spectrum, δ, ppm: 5.81 s (2H, CH_2), 6.92 d and 7.78 d (2H, CH=CH, J = 8.6 Hz), 6.89–7.98 m (9H, H_{arom}), 10.74 s (1H, OH). Mass spectrum, m/z (I_{rel}, %): 302 (99) $[M]^+$, 233 (5), 204 (3), 155 (4), 147 (10), 128 (34), 115 (72), 105 (35), 91 (67), 76 (76), 63 (51), 51 (94), 38 (62). Found, %: C 71.90; H 4.20; N 18.10. $C_{18}H_{14}N_4O$. Calculated, %: C 71.52; H 4.64; N 18.54. M 302.22.

{3-(2-Hydroxyphenyl)-5-[2-(4-methoxyphenyl)-vinyl]-1*H*-1,2,4-triazol-1-yl}acetonitrile (IIIc). Yield 1.83 g (55%). Colorless crystals, mp 175°C (from toluene). IR spectrum, ν, cm^{-1}: 1670, 1610, 1510 (C=C, C=C_{arom}, C=N). ^{1}H NMR spectrum, δ, ppm: 3.82 s (3H, OCH_3), 5.69 s (2H, CH_2), 6.89–8.00 m (10H, H_{arom}, CH=CH), 10.86 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 37.27 t (1C, CH_2, J = 151.1 Hz), 56.18 q (1C, OCH_3, J = 144.6 Hz), 108.46 d (1C, CH=CH, J = 7.1 Hz), 114.32 d (1C, C_{arom}, J = 7.7 Hz), 115.23 t (1C, CH, J = 8.81 Hz), 115.24 m (1C, C_{arom}), 116.05 m (1C, C_{arom}), 117.96 m (1C, C_{arom}), 120.43 m (1C, C_{arom}), 127.55 t (1C, C_{arom}, J = 6.8 Hz), 128.57 m (1C, C_{arom}), 130.49 m (2C, C_{arom}), 132.31 m (1C, C_{arom}), 139.57 m (1C, CH=CH), 154.16 m (1C, C^5, ^2J = 5.2, ^3J = 1.9 Hz), 157.28 m (1C, **C**OMe), 160.73 d (1C, C^3, J = 4.21 Hz), 161.55 m (1C, COH). Mass spectrum, m/z (I_{rel}, %): 331 (100) $[M]^+$, 317 (5), 301 (7), 292 (20), 159 (18), 145 (24), 119 (25), 105 (31), 77 (38), 51 (33). Found, %: C 68.10; H 5.20; N 16.30. $C_{19}H_{16}N_4O_2$. Calculated, %: C 68.67; H 4.82; N 16.87. M 331.23.

{3-(2-Hydroxyphenyl)-5-[2-(2-thienyl)vinyl]-1*H*-1,2,4-triazol-1-yl}acetonitrile (IIId). Yield 1.51 g (49%). Colorless crystals, mp 169–171°C (from toluene). IR spectrum, ν, cm^{-1}: 1630, 1590, 1520 (C=C, C=C_{arom}, C=N). ^{1}H NMR spectrum, δ, ppm: 5.71 s

(2H, CH_2), 6.81–7.99 m (9H, H_{arom}, CH=CH), 10.66 s (1H, OH). Found, %: C 62.10; H 3.20; N 18.30. $C_{16}H_{12}N_4OS$. Calculated, %: C 62.34; H 3.90; N 18.18.

2-{5-[2-(4-Bromophenyl)vinyl]-3-(2-hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl}-3-methylbut-2-enenitrile (Va). 2-{3-[2-(4-Bromophenyl)vinyl]-1*H*-1,2,4-triazol-5-yl}phenol (**Id**), 3.43 g (10 mmol), was dissolved in 30 ml of acetone, 5.52 g (40 mmol) of calcined potassium carbonate was added, the mixture was heated for 15 min under reflux and cooled, 0.76 g (10 mmol) of chloroacetonitrile was added, and the mixture was heated for 2.5 h under reflux and diluted with water. The colorless precipitate was filtered off and recrystallized. Yield 2.74 g (65%), mp 196–198°C (from MeCN). IR spectrum, ν, cm^{-1}: 1690 (Me_2C=C); 1650, 1550, 1500 (C=C, C=C_{arom}, C=N). ^{1}H NMR spectrum, δ, ppm: 1.79 s (3H, Me), 2.34 s (3H, Me), 6.87–7.98 m (10H, H_{arom}, CH=CH), 10.65 s (1H, OH). Found, %: C 59.60; H 4.20; N 13.50. $C_{21}H_{17}BrN_4O$. Calculated, %: C 59.86; H 4.04; N 13.30.

2-{5-[2-(4-Fluorophenyl)vinyl]-3-(2-hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl}-3-methylbut-2-enenitrile (Vb) was synthesized in a similar way. Yield 2.14 g (59%), colorless crystals, mp 198–200°C (from MeCN). IR spectrum, ν, cm^{-1}: 1690 (C=C); 1640, 1560, 1500 (C=C, C=C_{arom}, C=N). ^{1}H NMR spectrum, δ, ppm: 1.79 s and 2.34 s (3H each, Me), 6.79–7.97 m (10H, H_{arom}, CH=CH), 10.57 s (1H, OH). Found, %: C 70.10; H 4.20; N 15.30. $C_{21}H_{17}FN_4O$. Calculated, %: C 70.00; H 4.72; N 15.56.

2-{3-(2-Hydroxyphenyl)-5-[2-(4-methoxyphenyl)vinyl]-1*H*-1,2,4-triazol-1-yl}-3-methylbut-2-enenitrile (Vc). Compound **IIIc**, 10 mmol, was dissolved in 30 ml of acetone, 5.52 g (40 mmol) of potassium carbonate was added, the mixture was heated for 1.5 h under reflux and diluted with water, and the precipitate was filtered off and recrystallized. Yield 1.61 g (43%), light brown crystals, mp 186–187°C (from 1-BuOH). IR spectrum, ν, cm^{-1}: 1730 (Me_2C=C); 1640, 1610, 1510 (C=C, C=C_{arom}, C=N). ^{1}H NMR spectrum, δ, ppm: 2.34 s and 2.48 s (3H each, Me), 3.82 s (3H, OMe), 6.91–8.00 m (10H, H_{arom}, CH=CH), 10.87 s (1H, OH). Found, %: C 71.10; H 5.00; N 15.20. $C_{21}H_{18}N_4O_3$. Calculated, %: C 70.97; H 5.38; N 15.05.

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