Stereoselective annelation of 3-substituted imidazo[4,5-*b*]pyridines with cyanoacetylenic alcohols and domino rearrangement of the adducts

Boris A. Trofimov,[a,*] Ludmila V. Andriyankova,[a] Lina P. Nikitina,[a] Kseniya V. Belyaeva,[a] Anastasiya G. Mal'kina,[a] Oleg A. Dyachenko,[b] Olga N. Kazheva,[b] Anatolii N. Chekhlov,[b] and Andrei V. Afonin[a]

[a]A.E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences, 1 Favorsky Str., Irkutsk 664033, Russian Federation
[b]Institute of Problems of Chemical Physics, Russian Academy of Sciences, 1 Academician N.N. Semenov Str., Chernogolovka 142432, Russian Federation
E-mail: boris_trofimov@irioch.irk.ru

DOI: http://dx.doi.org/10.3998/ark.5550190.0013.622

Abstract
Imidazo[4,5-*b*]pyridines are readily annelated (45-50 °C, 24-30 h, MeCN) with cyanoacetylenic tertiary α-alcohols to give stereoselectively functionalized 1,3-oxazolo[3,2-*a*]imidazo[4,5-*b*]pyridines in 50-88% yields. The adducts undergo a facile stereoselective hydrolytic domino rearrangement to functionalized derivatives of 2,3-diaminopyridines.

Keywords: Annelation, formamides, imidazopyridines, rearrangement, zwitterions

Introduction

Derivatives of imidazole and pyridine are of special interest in drug design.[1,2] The condensed heterocyclic systems consisting of imidazole and pyridine rings (imidazopyridines) often possess pharmaceutically valuable properties which are not typical for either of the separate moieties. For example, a popular soporific remedy, "Zolpidem" ("Ivadal"), is a functionalized imidazo[1,2-*a*]pyridine.[2] Among other derivatives of imidazopyridines, are potent nitric-oxide synthase inhibitors of inflammatory diseases,[3] inhibitors of AKT kinase,[4] preventive and/or therapeutic agents for neutrophilic inflammation disease,[5] compounds with tuberculostatic[6] and hypoglycemic[7] activities, angiotensin II receptor antagonists,[8] and anticoccidial agents.[9] A series of imidazo[1,2-*a*]pyridines bearing sulfonylurea functions exhibit herbicidal activity.[10]

Most reported syntheses of imidazopyridines are, as a rule, laborious and multi-step (up to 6 steps). Therefore, the search for novel straightforward approaches to the synthesis of functionalized imidazopyridines remains a challenge.

The objective of this present work was to develop a straightforward efficient approach to the synthesis of new condensed functionalized heterocyclic systems combining and imidazo[4,5-*b*]pyridine skeleton and a 1,3-oxazole moiety. For this, we have studied the reaction of substituted imidazo[4,5-*b*]pyridines with readily available cyanoacetylenic tertiary α-alcohols.[11]

From out recent findings related to the annelation of the cyanoacetylenic alcohols with pyridines,[11b,12] quinoline and quinoxaline,[13] phenanthridines,[14] natural alkaloids[15] and substituted benzimidazoles[16] one might expect that either the pyridine or the imidazole (or both) components of an imidazo[4,5-*b*]pyridine would be involved in the reaction to furnish novel 1,3-oxazoloimidazopyridine tricyclic fused scaffolds. Therefore, a fundamental part of the objective is also the issue of competition between the imidazole and pyridine nitrogen atoms as nucleophiles towards the electron-deficient acetylenic bond.

Results and Discussion

The experimental results have shown that 3-substituted imidazo[4,5-*b*]pyridines **1a**,**b** are readily annelated with cyanoacetylenic tertiary α-alcohols **2a**,**b** (45-50 ºC, 24-30 h, MeCN, **1**:**2** molar ratio equals 1:1) to give (*Z*)-3-cyanomethylene-1,3-oxazolo[3,2-*a*]imidazo[4,5-*b*]pyridines **3a-d** in 50-88% yields (Table 1). No *E*-isomers of the adducts **3a-d** have been discernible in the reaction mixture, i.e. the annelation is strictly stereoselective. Neither alternative adducts **4** nor possible diadducts with participation of both imidazole and pyridine counterparts have been detected among the reaction products thus indicating that imidazole nitrogen atom *N*(1) entirely wins the competition against the pyridine nitrogen *N*(4) in the nucelophilic addition to the triple bond. In other words, the annelation is also strongly regioselective. Notably, although under the same conditions the annelation of 1-benzylimidazo[4,5-*b*]pyridine **1c** with cyanoacetylenic alcohol **2a** proceeds reluctantly to afford the corresponding adduct 1,3-oxazoloimidazopyridine **3e** (also of *Z*-configuration only) just in 18% yield, no alternative adducts are formed (Table 1).

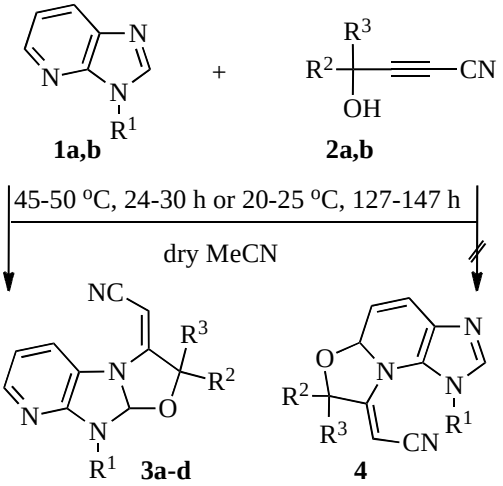
When carried out at room temperature (20-25 ºC), completion of the annelation takes a much longer time (up to 147 h), though the yields of the adducts **3a-e** increase by approximately 10% (relative to the yields shown in Table 1), obviously due to the milder reaction conditions.

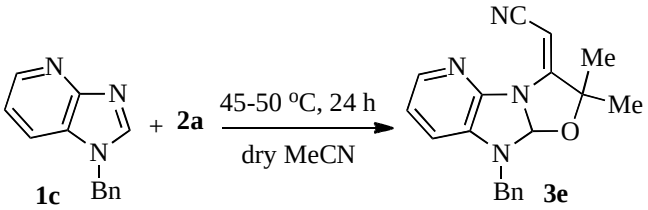
The pyridine nitrogen atom was not involved into the annelation even when adduct **3c** was allowed to react with cyanoacetylenic alcohol **2b** (20-25 ºC, 147 h). Also, no bis-adduct was isolated even when the reactants **1a** and **2b** were taken in the 1:2 molar ratio.

The structure of adducts **3a-e** was established by NMR (^{1}H, ^{13}C, 2D) and IR spectroscopy. Thus, in the ^{1}H NMR spectra of 1,3-oxazoloimidazopyridines **3a-e**, olefinic protons (H-10, the =CHCN fragment) appear as singlets in the region 4.43-4.55 ppm thus indicating to the

formation of only one isomer (NOESY). In the IR spectra, the absorption bands of the cyano groups on the double bond are observed at 2202-2213 cm^{-1}.

Table 1. Formation of 1,3-oxazoloimidazopyridines **3a-e** from substituted imidazo[4,5-*b*]pyridines **1a-c** and cyanoacetylenic alcohols **2a**,**b**





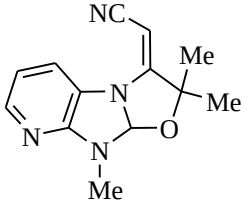
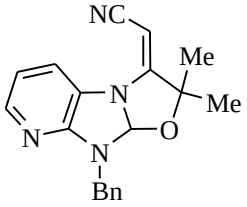
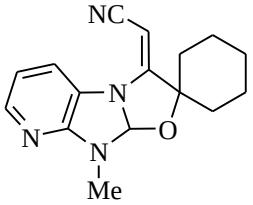
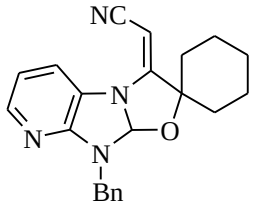
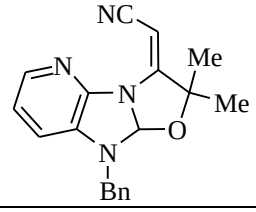
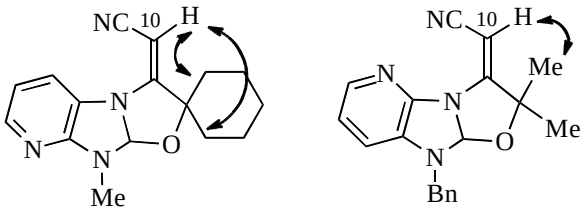
R^1	R^2	R^3	Products **3**		Yield (%)
Me	Me	Me		**3a**	88
Bn	Me	Me		**3b**	70
Me	$(CH_2)_5$			**3c**	75

Table 1. Continued

R1	R2	R3	**Products 3**	Yield (%)
Bn	$(CH_2)_5$		 **3d**	50
Bn	Me	Me	 **3e**	18

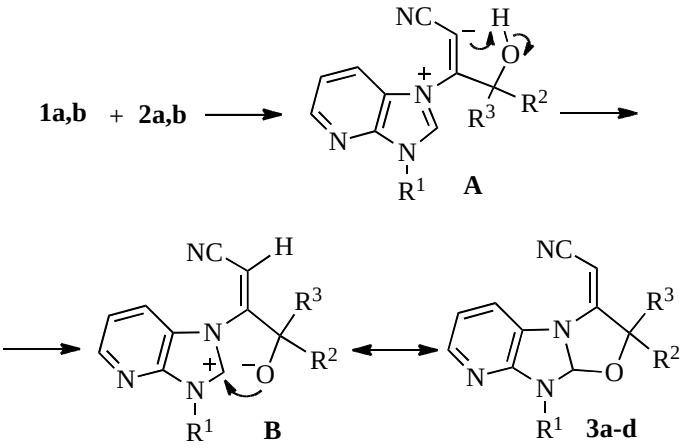
According to the NOESY spectra, the 1,3-oxazoloimidazopyridines **3a-e** are *Z*-isomers: the cross-peaks between olefinic proton H-10 and the immediately adjacent protons of cyclohexyl (for **3c**) or Me group (for **3e**) are observed (Figure 1).



Z-**3c** *Z*-**3e**

Figure 1. Cross-peaks in the 2D NOESY spectra of 1,3-oxazoloimidazopyridines **3c** and **3e**.

Apparently, the annelation is triggered by the addition of imidazopyridines **1a**,**b** *via* their imidazole nitrogen atom *N*(1) as neutral nucleophiles to cyanoacetylenic alcohols **2a**,**b** to generate zwitterions **A** having a vinyl carbanion moiety which is then converted into the oxygen-centered zwitterions **B** the proton transfer (in either an intra- or intermolecular manner) from the hydroxyl group to the carbanionic center. The secondary zwitterions **B** undergo the ring closure at the *C*(2) position of the imidazole ring to form the final annelated adducts **3a-d** (Scheme 1).



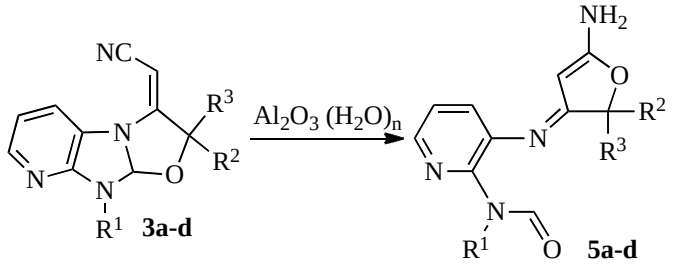
Scheme 1. Proposed mechanism of formation 1,3-oxazoloimidazopyridines **3a-d**.

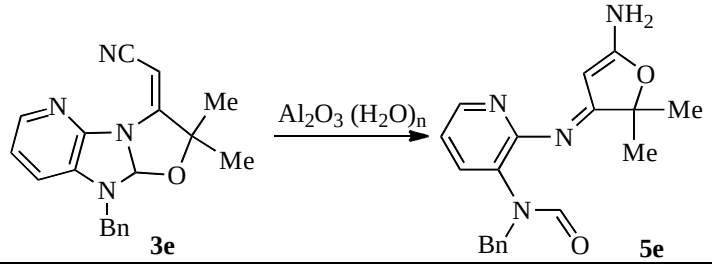
The *Z*-configuration of the final adducts **3a-d** is the expected result of the nucleophilic addition to acetylenes, which is known to proceed in a concerted *trans*-fashion.[17] Notably, the 1,3-oxazoloimidazopyridines **3a-d** retain a contribution of zwitterionic form **B** (an inner salt). A similar consideration is true also for the formation of adduct **3e**.

The regioselectivity of the annelation likely results from the steric constrains between the cyanomethylene group and the substituents R^1 at the imidazole *N*(3) atom in the possible alternative adducts **4** (cf. Table 1). Indeed, the nucleophilicities of *N*(1) of the imidazole ring and *N*(4) of the pyridine ring should not differ significantly since the basicities of pyridine and benzimidazole, an analog of the imidazopyridines **1a**,**b**, are close (pK_a = 5.20 and 5.50 for pyridine and benzimidazole, respectively[1]). This conclusion is in agreement with the low yield (18%) of adduct **3e**, in which the cyanomethylene group faces the steric repulsion from the lone electron pair of the *N*(4) pyridine atom.

1,3-Oxazoloimidazopyridines **3a-d**, when passed through a column packed with neutral alumina, or in moist ethanol, undergo the hydrolytic domino rearrangement to functionalized derivatives of 2,3-diaminopyridines conjugated with a 2-aminodihydrofuran moiety – (*E*)-*N*-(3-{[5-amino-2,2-dialkyl-3(2*H*)-furanyliden]amino}-2-pyridinyl)-*N*-alkylformamides **5a-d** in 83-98% yields (Table 2). This exceptionally facile multi-step rearrangement is rigorously stereoselective: the products **5a-d** are formed exclusively in the *E*-configuration (relative to the C=N bond). Likewise, 1,3-oxazoloimidazopyridine **3e** rearranges to a similar derivative of 2,3-diaminopyridine of *E*-configuration in 46% yield (Table 2).

Table 2. Rearrangement of 1,3-oxazoloimidazopyridines **3a-e** to pyridinyl-*N*-substituted formamides **5a-e**





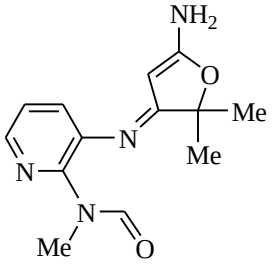
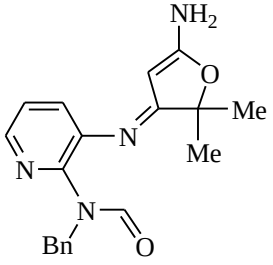
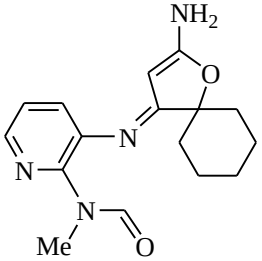
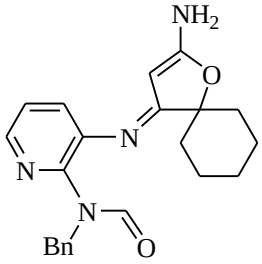
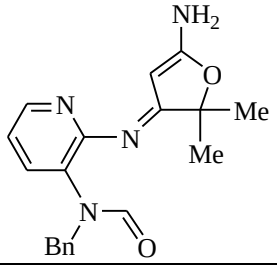
R^1	R^2	R^3	Products **5**		Yield (%)
Me	Me	Me		**5a**	83
Bn	Me	Me		**5b**	98
Me	$(CH_2)_5$			**5c**	91

Table 2. Continued

R1	R2	R3	**Products 5**	Yield (%)
Bn	$(CH_2)_5$			**5d** 93
Bn	Me	Me		**5e** 46

(*E*)-Pyridinyl-*N*-substituted formamides **5a-e** were isolated as crystals. Their structures are based on analogy with that of formamide **5c**, which was established by X-ray diffraction analysis, and confirmed using ^{1}H and ^{13}C NMR, UV and IR techniques.

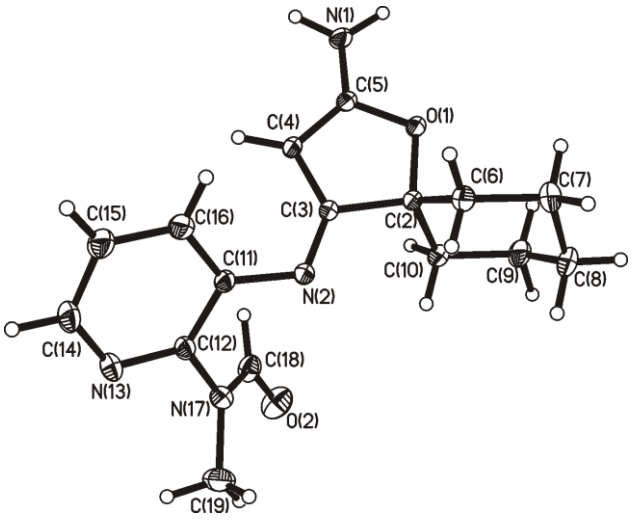


Figure 2. Molecular structure of (*E*)-pyridinyl-*N*-methylformamide **5c**.

Crystal structure of formamide **5c** is formed by one crystallographically independent molecule (Figure 2) taking a general position. The cyclohexane ring has a chair conformation. The furan and pyridine heterocycles are almost planar, maximum deviation of atoms from their average planes do not exceed 0.02 Å (*C*(2) and *C*(12) atoms). The dihedral angle between these planes is 125.4°. Deviations of the *N*(1) and *N*(2) atoms from plane of the furan cycle are

insignificant (0.01 and 0.03 Å, respectively). The *N*(2) and *N*(17) atoms deviate from the plane of the pyridine ring by 0.23 and 0.10 Å. The fragment formed by the *O*(2)*C*(18)*N*(17)*C*(19) atoms is practically planar, maximum deviation of atoms from its average plane being 0.02 Å (*C*(18) atom). This plane forms with planes of the furan and pyridine moieties the dihedral angles of 117.4 and 130.5°, respectively.

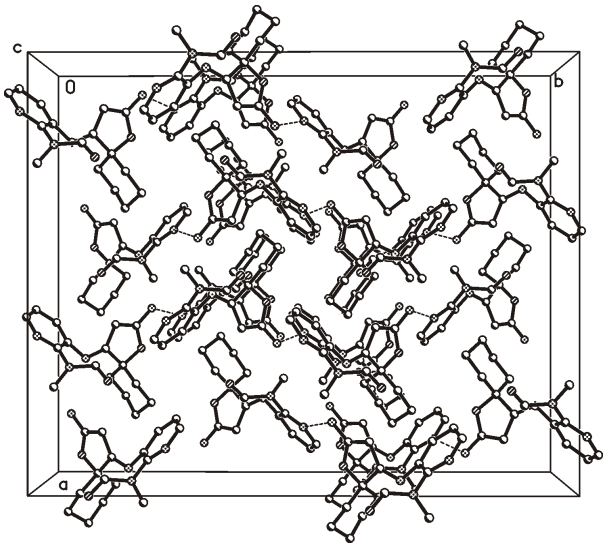
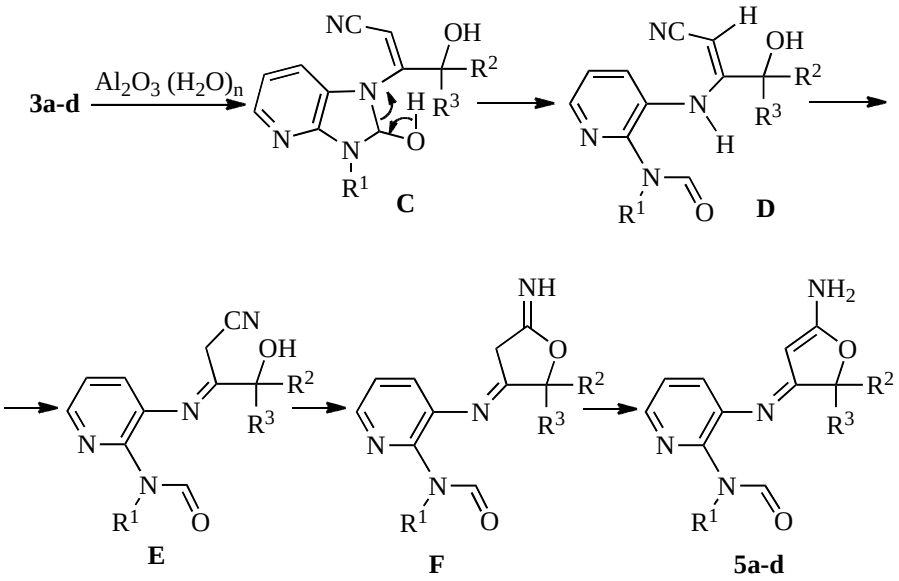


Figure 3. Crystal structure of formamide **5c**.

Crystal structure of formamide **5c** is given in Figure 3. In this compound, the molecules are bonded in chains (shorten distances along the axis *b*) via hydrogen bonding *N*-H…*N*: *N*(1)…*N*(2) – 3.026(2) Å, *N*(1)-H(1A) – 0.93(2) Å, N(2)… H(1A) – 2.14(2) Å, *N*(1)-H(1A)…*N*(2) – 159(2)°, *N*(1')…*N*(13) – 2.999(2) Å, *N*(1')-H(1B') – 0.95(3) Å, *N*(13)…H(1B') – 2.09(3) Å, *N*(1')-H(1B')…*N*(13) – 160(2)° (sum of van-der-Waals radii *N*…H – 2.75 Å, *N*…*N* is 3.10 Å[18]).

Obviously, the rearrangement of 1,3-oxazoloimidazopyridines **3a-d** starts with the cleavage of polar C(2)-O bond by water to deliver the intermediates **C** (Scheme 2) which further rearrange to the intermediates **D** having a formamide function, probably stabilized by intramolecular H-bonding between the NH moiety and the carbonyl oxygen. The latter, being an NH vinylamine, undergoes a 1,3-hydrogen shift to produce the imine intermediates **E**, in which the free rotation of the CN function is allowed. By virtue of this, the ring closure by addition of hydroxyl function to the CN bond to furnish the iminodihydrofuran intermediates **F** becomes possible. The 1,3-hydrogen shift in the intermediates **F** to form iminodihydrofuranylidene moiety in final products **5a-d** completes the domino sequence.

The rearrangement of **3e** to **5e** would pass through similar steps.



Scheme 2. Probable steps of the rearrangement of (*Z*)-1,3-oxazoloimidazopyridines **3a-d** to (*E*)-pyridinyl-*N*-alkylformamides **5a-d**.

The driving force of this multi-step rearrangement is plausibly the formation of a long-range through-conjugated system of the push-pull type, accomplished in the final products **5a-d**. Despite the distorted coplanarity of the pyridine and furan rings in the crystal state (the corresponding dihedral angle is 125.4°, Figure 2), the conjugation can still be partly realized, particularly in solution, or in excited or transition states (during certain reactions).

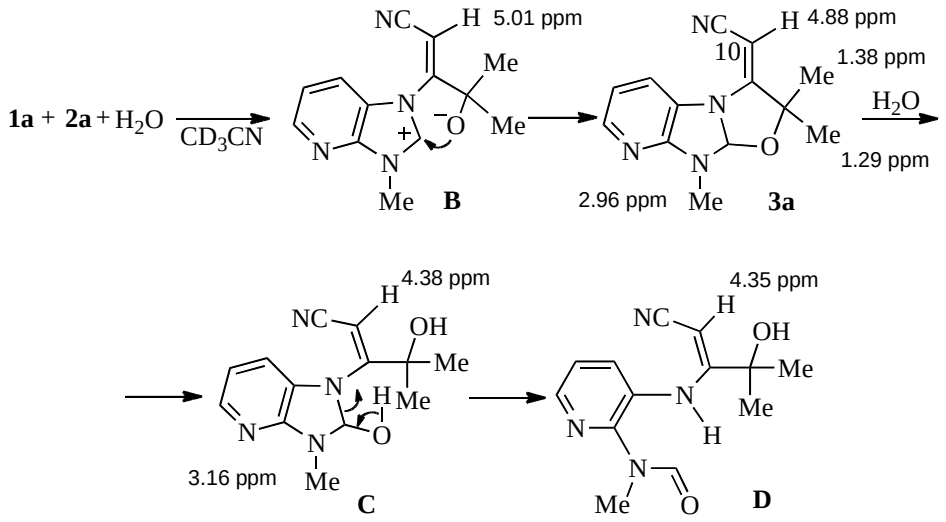
Easrlier, a simlar deep rearrangement was observed for the adducts of benzimidazoles with cyanoacetylenic tertiary α-alcohols.[16a]

The rearrangement products **5a-e** can be prepared directly from reactants **1** and **2** avoiding the isolation of annelated species **3a-e** by passing the reaction mixture through a layer of alumina.

An attempt to obtain a monocrystal of 1,3-oxazoloimidazopyridine **3c** [where R^1 = Me, R^2-R^3 = $(CH_2)_5$] from moist ethanol ends up with the formation of crystalline rearrangement product **5c**.

In the ^{1}H NMR spectra of (*E*)-pyridinyl-*N*-substituted formamides **5a-e**, the proton of the formamide fragment (H-14) is observed in the region 8.23-8.78 ppm. In the ^{13}C NMR spectra, carbonyl carbon resonates at 163.2-169.8 ppm. In the IR spectra, the absorption bands of the C=O group are present at 1659-1684 cm^{-1}.

The direct synthesis of the rearrangement products **5a-e** was monitored as an example of a three-component reaction, between imidazopyridine **1a**, cyanoacetylenic tertiary α-alcohol **2a** and water (1:1:1 molar ratio) in CD_3CN solution (room temperature, NMR tube). The reaction was followed by the methyl and olefin proton signals in the ^{1}H NMR spectra (Scheme 3).



Scheme 3. Monitoring of the three-component reaction of imidazopyridine **1a** with cyanoacetylenic alcohol **2a** and water.

After 1 h, in the spectrum, along with the signals of starting materials [1.48 (Me in cyanoacetylenic α-alcohol **2a**) and 3.83 (*N*-Me in imidazopyridine **1a**) ppm], weak singlets at 2.96, 4.88 and 5.01 ppm assignable to *N*-Me, olefinic proton H-10 in cyanomethylene group (in annelated product **3a**) and olefinic proton in the zwitterion **B** (Schemes 1, 3) respectively, appeared. During the next three days the intensities of these signals gradually increased and singlets at 1.29 and 1.38 ppm become observable. After 11 days, signals for the annelated adduct **3a** were considerably augmented and weak signals at 3.16 and 4.38 ppm emerged attributable to *N*-Me and olefinic proton in the intermediate **C** (Schemes 2, 3). After 20 days, the intensities of these signals rose with a simultaneous decrease of the intensity of the olefinic proton signal in the zwitterion **B** (5.01 ppm). Finally, after 35 days, the singlet at 5.01 ppm disappeared and the signal intensities of annelated adduct **3a** (1.29, 1.38, 2.96 and 4.88 ppm) fell sharply. In this spectrum, the signals of intermediates **C** (3.16 and 4.38 ppm) and **D** (4.35 ppm) dominated. When the reaction mixture was passed through the column packed with alumina (chloroform/benzene/ethanol, 20:4:1, mixture as eluent), the final rearrangement products **5a** was isolated (Scheme 2).

Thus, the monitoring confirms Schemes 1 and 2, though under the conditions employed, the combined rearrangement annelation sequence proceeds only slowly and did not reach completion, so that even after 35 days the reaction mixture consisted of intermediates **C** and **D**.

Conclusions

In conclusion, a novel one-pot efficient methodology for the stereoselective synthesis of previously unknown imidazo[4,5-*b*]pyridine derived tricyclic fused functionalized systems – (*Z*)-

1,3-oxazolo[3,2-*a*]imidazo[4,5-*b*]pyridines, has been developed (yields up to 88%). The methodology represents an exceptionally facile (20-50 ºC) metal-free stereoselective (relative to the cyanomethylene function) annelation of imidazo[4,5-*b*]pyridines with cyanoacetylenic tertiary α-alcohols, involving intermediate zwitterions. The 1,3-oxazolo[3,2-*a*]imidazo[4,5-*b*]pyridines, when passed through alumina, or in aqueous solvents at room temperature, undergo an easy hydrolytic multi-step domino rearrangement to functionalized derivatives of 2,3-diaminopyridines – (*E*)-pyridinyl-*N*-alkylformamides, in excellent to quantitative yields. The principal steps of the rearrangement were verified by NMR monitoring to show that initially the cleavage of the C(2)-O bond of the oxazole cycle by the molecule of water occurs. Then follows the rearrangement of the semi-aminal moiety forking the formamide function and a sequence of 1,3-prototropic shifts and the iminodihydrofuran ring closure. A straightforward three-component access to derivatives of 2,3-diaminopyridines conjugated with 2-aminodihydrofurans directly from imidazo[4,5-*b*]pyridine, cyanoacetylenic tertiary *α*-alcohols and water has been elaborated. The results contribute to the fundamental chemistry of imidazole, pyridine and acetylenes as well as to the development of novel imidazo[4,5-*b*]pyridines.

Experimental Section

General. NMR spectra were run on a Bruker DPX-400 spectrometer with HMDS as an internal standard. UV-VIS spectra were measured on a Perkin-Elmer Lambda 35 spectrometer at room temperature (EtOH, d = 0.1 cm). IR spectra were recorded on a IFS 25 instrument. Column and thin-layer chromatography was carried out on neutral Al_2O_3 with chloroform/benzene/ethanol (20:4:1) mixture as eluent (length of column = 35 cm, Ø = 0.8 cm). The reaction was monitored by the disappearance of absorption bands of initial acetylenes **2a**,**b** in the reaction mixture (IR spectroscopy). Alkylation of imidazo[4,5-*b*]pyridines **1a**,**b** was carried out according to the procedures:[19] mp **1a** 56 ºC (hexane) [mp 76-78 ºC[20]]; mp **1b** 79-81 ºC (hexane) [mp 83 ºC[21]]; mp **1c** 134-135 ºC (acetone) [mp 119 ºC[21]]. Cyanoacetylenic tertiary α-alcohols **2a**,**b** were prepared by the method.[11] Labeling of hydrogen and carbon atoms in compounds **3a-e** and **5a-e** are given in Figure 4.

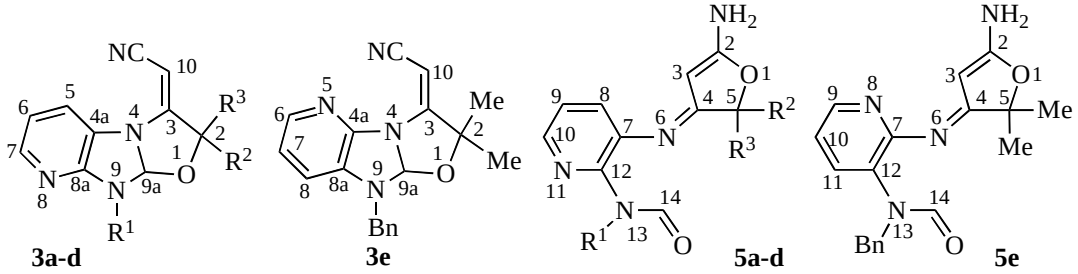


Figure 4. Labeling of hydrogen and carbon atoms in compounds **3a-e** and **5a-e**.

X-ray diffraction. The X-ray diffraction study of compound **5c** was carried out on an Enraf-Nonius CAD-4 diffractometer at room temperature (ω/2θ-scans, Mo-K_α radiation, graphite monochromator). The crystal structure was solved by direct methods followed by Fourier-syntheses using SHELXS-97 programs.[22] The structure refined by a full matrix least-squares anisotropic procedure using SHELXTL-97 programs.[23] The parameters of hydrogen atoms were defined experimentally and refined anisotropically, except for parameters of hydrogen of the methyl group which were calculated geometrically. These data are available via www.ccdc.cam.uk/contsretrieving.html (or from CCDC, 12 Union Cambrige CB2 1EZ, UK, fax: +44 (0) 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number CCDC 826322 (for **5c**).

General synthetic procedure for the preparation of products 3, exemplified by (*Z*)-3-cyanomethylene-2,3,9,9a-tetrahydro-9-methyl-2,2-dimethyl-1,3-oxazolo[3,2-*a*]-imidazo[4,5-*b*]pyridine (3a)

A mixture of 3-methyl-3*H*-imidazo[4,5-*b*]pyridine (**1a**) (0.133 g, 1 mmol) and cyanoacetylenic alcohol **2a** (0.109 g, 1 mmol) in dry MeCN (0.2 mL) was stirred at 45-50 ºC for 30 h. The solvent was removed and the residue was washed with anhydrous Et_2O (5 × 0.3 mL) to give 1,3-oxazoloimidazopyridine **3a**, yield 88%, 0.212 g, light-pink powder, mp 98-101 ºC; IR (ν_{max}, cm^{-1}): 1060, 1081, 1123 (C-O-C), 1652 (C=C), 2202 (=CH-*CN*), 3024 (=*CH*-CN). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ_H 1.29, 1.38 (6H, 2 × s, 2 × CH_3), 2.96 (3H, s, NCH_3), 4.43 (1H, s, H-10), 6.28 (1H, s, H-9a), 6.48 (1H, dd, H-6), 7.63 (1H, d, $^3J_{H6,H7}$ = 5.2 Hz, H-7), 7.68 (1H, d, $^3J_{H5,H6}$ = 7.7 Hz, H-5). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ_C 26.5, 28.0 (2 × CH_3), 29.1 (NCH_3), 70.0 (C-10), 83.6 (C-2), 105.4 (C-9a), 113.8 (C-6), 118.6 (CN), 120.7 (C-5), 128.9 (C-4a), 142.3 (C-7), 153.8 (C-8a), 167.9 (C-3); Anal. Calcd for $C_{13}H_{14}N_4O$ (242.20): C, 64.45; H, 5.82; N, 23.12%. Found: C, 64.60; H, 5.89; N, 23.10%.

(*Z*)-3-Cyanomethylene-2,3,9,9a-tetrahydro-9-benzyl-2,2-dimethyl-1,3-oxazolo[3,2-*a*]-imidazo[4,5-*b*]pyridine (3b). Light-yellow powder, yield 70%, 0.256 g, mp 102-104 ºC; IR (ν_{max}, cm^{-1}): 1108, 1136, 1156 (C-O-C), 1650 (C=C), 2213 (=CH-*CN*), 3066 (=*CH*-CN). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ_H 1.39, 1.43 (6H, 2 × s, 2 × CH_3), 4.53, 4.97 (2H, 2 × d, $^2J_{H,H}$ = 15.6 Hz, CH_2 from *N*-benzyl), 4.54 (1H, s, H-10), 6.39 (1H, s, H-9a), 6.65 (1H, dd, H-6), 7.24-7.30 (5H, m, Ph from *N*-benzyl), 7.78 (1H, d, $^3J_{H6,H7}$ = 5.4 Hz, H-7), 7.84 (1H, d, $^3J_{H5,H6}$ = 7.7 Hz, H-5). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ_C 26.5, 28.1 (2 × CH_3), 43.1 (CH_2 from *N*-benzyl), 70.7 (C-10), 83.3 (C-2), 103.4 (C-9a), 114.2 (C-6), 118.6 (CN), 120.8 (C-5), 127.7, 128.1, 128.7 (*m*,*o*,*p*-C, Ph from *N*-benzyl), 128.9 (C-4a), 136.4 (*i*-C, Ph from *N*-benzyl), 142.4 (C-7), 153.2 (C-8a), 168.2 (C-3); Anal. Calcd for $C_{19}H_{18}N_4O$ (318.38): C, 71.68; H, 5.70; N, 17.60%. Found: C, 71.95; H, 5.42; N, 17.85%.

(*Z*)-Spiro-1,3-oxazolo[3,2-*a*]imidazo[4,5-*b*]pyridine (3c). Red powder, yield 75%, 0.212 g, mp 103-105 ºC; IR (ν_{max}, cm^{-1}): 1052, 1074, 1125, 1148, 1167 (C-O-C), 1644 (C=C), 2206 (=CH-*CN*), 3077 (=*CH*-CN). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ_H 1.10-1.90 (10H, m, cyclohexyl), 3.14 (3H, s, NCH_3), 4.55 (1H, s, H-10), 6.42 (1H, s, H-9a), 6.63 (1H, dd, H-6), 7.78 (1H, d, $^3J_{H6,H7}$ =

5.4 Hz, H-7), 7.83 (1H, d, $^3J_{H5,H6}$ = 7.8 Hz, H-5). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ_C 21.3-36.2 (5 × CH_2, cyclohexyl), 28.6 (NCH_3), 70.3 (C-10), 84.9 (C-2), 105.2 (C-9a), 113.3 (C-6), 118.2 (CN), 120.3 (C-5), 128.7 (C-4a), 141.8 (C-7), 153.4 (C-8a), 167.6 (C-3); Anal. Calcd for $C_{16}H_{18}N_4O$ (282.34): C, 68.06; H, 6.43; N, 19.84%. Found: C, 68.33; H, 6.56; N, 19.55%.

(*Z*)-Spiro-1,3-oxazolo[3,2-*a*]imidazo[4,5-*b*]pyridine (3d). Light-yellow powder, yield 50%, 0.197 g, mp 108-110 ºC; IR (ν_{max}, cm^{-1}): 1064, 1082, 1105, 1130, 1159, 1174 (C-O-C), 1647 (C=C), 2209 (=CH-*CN*), 3066 (=*CH*-CN). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ_H 1.10-1.90 (10H, m, cyclohexyl), 4.57 (1H, s, H-10), 4.67, 4.92 (2H, 2 × d, $^2J_{H,H}$ = 15.5 Hz, CH_2 from *N*-benzyl), 6.41 (1H, s, H-9a), 6.65 (1H, dd, H-6), 7.25-7.40 (5H, m, Ph from *N*-benzyl), 7.80 (1H, d, $^3J_{H6,H7}$ = 5.5 Hz, H-7), 7.82 (1H, d, $^3J_{H5,H6}$ = 7.8 Hz, H-5). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ_C 21.6-24.7 (5 × CH_2, cyclohexyl), 46.2 (CH_2 from *N*-benzyl), 71.5 (C-10), 84.9 (C-2), 103.7 (C-9a), 114.0 (C-6), 118.5 (CN), 120.6 (C-5), 127.2, 128.2, 128.5 (*m*,*o*,*p*-C, Ph from *N*-benzyl), 129.2 (C-4a), 136.4 (*i*-C, Ph from *N*-benzyl), 142.2 (C-7), 153.1 (C-8a), 168.4 (C-3); Anal. Calcd for $C_{22}H_{22}N_4O$ (358.44): C, 73.72; H, 6.19; N, 15.63%. Found: C, 73.45; H, 5.99; N, 15.37%.

(*Z*)-2-[9-Benzyl-2,2-dimethyl-9,9a-dihydro[1,3]oxazolo[2',3':2,3]imidazo[4,5-*b*]pyridin-3(2*H*)-yliden]acetonitrile (3e). Light-brown powder, yield 18%, 0.057 g, mp 121-124 ºC; IR (ν_{max}, cm^{-1}): 1079, 1155 (C-O-C), 1634 (C=C), 2204 (=CH-*CN*), 3063 (=*CH*-CN). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ_H 1.39, 1.45 (6H, 2 × s, 2 × CH_3), 4.15, 4.55 (2H, 2 × d, $^2J_{H,H}$ = 15.5 Hz, CH_2 from *N*-benzyl), 4.51 (1H, s, H-10), 6.44 (1H, s, H-9a), 6.73 (1H, dd, H-7), 7.20-7.50 (5H, m, Ph from *N*-benzyl), 7.55 (1H, d, $^3J_{H7,H8}$ = 7.7 Hz, H-8), 7.75 (1H, d, $^3J_{H6,H7}$ = 5.5 Hz, H-6). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ_C 25.5, 27.5 (2 × CH_3), 44.1 (CH_2 from *N*-benzyl), 62.7 (C-10), 79.4 (C-2), 101.0 (C-9a), 114.0 (C-7), 118.5 (CN), 123.0 (C-8), 126.6, 127.9, 128.6 (*m*,*o*,*p*-C, Ph from *N*-benzyl), 130.2 (C-8a), 141.1 (*i*-C, Ph from *N*-benzyl), 142.1 (C-6), 145.1 (C-4a), 160.5 (C-3); Anal. Calcd for $C_{19}H_{18}N_4O$ (318.38): C, 71.86; H, 5.70; N, 17.60%. Found: C, 71.89; H, 5.52; N, 17.68%.

General synthetic procedure for the preparation of products 5, exemplified by (*E*)-*N*-(3-{[5-amino-2,2-dimethyl-3(2*H*)-furanyliden]amino}-2-pyridinyl)-*N*-methylformamide (5a)

1,3-Oxazoloimidazopyridine **3a** (0.145 g, 0.6 mmol) was dissolved in a mixture of $CHCl_3$-benzene-EtOH (20:4:1, 5 mL). Column chromatography on Al_2O_3 was employed to afford formamide **5a**, yield 83%, 0.130 g, light-yellow powder, mp 183-184 ºC; IR (ν_{max}, cm^{-1}): 1066, 1097, 1122, 1135 (C-O-C), 1676 (C=O), 3294, 3361 (NH_2). ^{1}H NMR (400.13 MHz, DMSO-d_6): δ_H 1.40 (6H, s, 2 × CH_3), 3.13 (3H, s, NCH_3), 4.31 (1H, s, H-3), 7.18 (1H, dd, H-9), 7.32 (1H, d, $^3J_{H8,H9}$ = 7.7 Hz, H-8), 7.50 (2H, s, NH_2), 8.01 (1H, d, $^3J_{H9,H10}$ = 4.6 Hz, H-10), 8.26 (1H, s, H-14). ^{13}C NMR (100.62 MHz, DMSO-d_6): δ_C 25.3 (2 × CH_3), 30.2 (NCH_3), 69.6 (C-3), 89.0 (C-5), 122.1 (C-9), 130.7 (C-8), 141.0 (C-10), 142.8 (C-2), 147.1 (C-7), 163.2 (C-14), 173.9 (C-2), 178.1 (C-4). UV/Vis (EtOH): λ_{max} (log ε) = 298 (4.42) nm; Anal. Calcd for $C_{13}H_{16}N_4O_2$ (260.30): C, 59.99; H, 6.20; N, 21.52%. Found: C, 59.69; H, 6.47; N, 21.48%.

(*E*)-*N*-(3-{[5-Amino-2,2-dimethyl-3(2*H*)-furanyliden]amino}-2-pyridinyl)-*N*-benzylformamide (5b). White powder, yield 98%, 0.206 g, mp 160-161 ºC; IR (ν_{max}, cm^{-1}): 1076, 1106

(C-O-C), 1676 (C=O), 3331, 3356 (NH_2). ^{1}H NMR (400.13 MHz, DMSO-d_6): δ_H 1.45 (6H, s, 2 × CH_3), 4.41 (1H, s, H-3), 5.09 (2H, s, CH_2 from *N*-benzyl), 7.14 (1H, dd, H-9), 7.14 (1H, d, $^3J_{H8,H9}$ = 7.6 Hz, H-8), 7.20-7.35 (5H, m, Ph from *N*-benzyl), 7.57 (2H, s, NH_2), 7.99 (1H, d, $^3J_{H9,H10}$ = 4.4 Hz, H-10), 8.40 (1H, s, H-14). ^{13}C NMR (100.62 MHz, DMSO-d_6): δ_C 25.4 (2 × CH_3), 45.5 (CH_2 from *N*-benzyl), 69.8 (C-3), 89.3 (C-5), 122.2 (C-9), 126.6, 126.9, 128.0 (*m*,*o*,*p*-C, Ph from *N*-benzyl), 130.3 (C-8), 137.9 (*i*-C, Ph from *N*-benzyl), 141.0 (C-10), 143.0 (C-12), 146.4 (C-7), 163.5 (C-14), 174.2 (C-2), 178.1 (C-4); Anal. Calcd for $C_{19}H_{20}N_4O_2$ (336.39): C, 67.84; H, 5.99; N, 16.66%. Found: C, 68.10; H, 5.87; N, 16.87%.

(*E*)-*N*-{3-[(2-Amino-1-oxaspiro[4,5]dec-2-en-4-yliden)amino]-2-pyridinyl}-*N*-methyl-formamide (5c). Red powder, yield 91%, 0.272 g, mp 219-221 ºC; IR (ν_{max}, cm^{-1}): 1072, 1107 (C-O-C), 1684 (C=O), 3216, 3352 (NH_2). ^{1}H NMR (400.13 MHz, DMSO-d_6): δ_H 1.50-1.70 (10H, m, cyclohexyl), 3.11 (3H, s, NCH_3), 4.29 (1H, s, H-3), 7.16 (1H, dd, H-9), 7.28 (1H, d, $^3J_{H8,H9}$ = 7.8 Hz, H-8), 7.48 (2H, s, NH_2), 8.01 (1H, d, $^3J_{H9,H10}$ = 4.5 Hz, H-10), 8.23 (1H, s, H-14). ^{13}C NMR (100.62 MHz, DMSO-d_6): δ_C 21.8-33.8 (5 × CH_2, cyclohexyl), 30.4 (NCH_3), 70.3 (C-3), 90.5 (C-5), 122.3 (C-9), 131.0 (C-8), 141.1 (C-10), 142.9 (C-12), 147.2 (C-7), 163.3 (C-14), 174.3 (C-2), 178.2 (C-4); Anal. Calcd for $C_{16}H_{20}N_4O_2$ (300.36): C, 63.98; H, 6.43; N, 18.65%. Found: C, 63.68; H, 6.74; N, 18.36%.

(*E*)-*N*-{3-[(2-Amino-1-oxaspiro[4,5]dec-2-en-4-yliden)amino]-2-pyridinyl}-*N*-benzyl-formamide (5d). Similar to the synthesis of formamide **5b**, from 1,3-oxazolidino-imidazopyridine **3d** (0.093 g, 0.3 mmol) was prepared formamide **5d**, yield 93%, 0.094 g, light-brown powder, mp 158-160 ºC; IR (ν_{max}, cm^{-1}): 1059, 1112 (C-O-C), 1659 (C=O), 3284, 3335 (NH_2). ^{1}H NMR (400.13 MHz, DMSO-d_6): δ_H 1.55-1.80 (10H, m, cyclohexyl), 4.39 (1H, s, H-3), 5.06 (2H, s, CH_2 from *N*-benzyl), 7.13 (1H, d, H-8), 7.17 (1H, dd, $^3J_{H8,H9}$ = 7.6 Hz, H-9), 7.30-7.40 (5H, m, Ph from *N*-benzyl), 7.55 (2H, s, NH_2), 7.98 (1H, d, $^3J_{H9,H10}$ = 4.4 Hz, H-10), 8.37 (1H, s, H-14). ^{13}C NMR (100.62 MHz, DMSO-d_6): δ_C 21.7-33.8 (5 × CH_2, cyclohexyl), 45.6 (CH_2 from *N*-benzyl), 70.3 (C-3), 90.6 (C-5), 122.2 (C-9), 126.6, 126.9, 128.0 (*m*,*o*,*p*-C, Ph from *N*-benzyl), 130.4 (C-8), 137.8 (*i*-C, Ph from *N*- benzyl), 140.9 (C-10, C-12), 146.3 (C-7), 163.4 (C-14), 174.4 (C-2), 178.1 (C-4); Anal. Calcd for $C_{22}H_{24}N_4O_2$ (376.46): C, 70.19; H, 6.43; N, 14.88%. Found: C, 69.99; H, 6.62; N, 14.56%.

(*E*)-*N*-(2-{[5-Amino-2,2-dimethyl-3(2*H*)-furanyliden]amino}-3-pyridinyl)-*N*-benzyl-formamide (5e). Analogously, from 1-benzyl-1*H*-imidazo[4,5-*b*]pyridine **1c** (0.080 g, 0.25 mmol) was prepared formamide **5e**, yield 46%, 0.039 g, light-brown powder, mp 107-110 ºC; IR (ν_{max}, cm^{-1}): 1076, 1181 (C-O-C), 1664 (C=O), 3283, 3338 (NH_2). ^{1}H NMR (400.13 MHz, DMSO-d_6): δ_H 1.37 (6H, s, 2 × CH_3), 4.59 (1H, s, H-3), 5.39 (2H, s, CH_2 from *N*-benzyl), 6.54 (1H, dd, H-10), 7.03 (1H, d, $^3J_{H10,H11}$ = 7.2 Hz, H-11), 7.30-7.40 (5H, m, Ph from *N*-benzyl), 7.50 (2H, s, NH_2), 7.68 (1H, d, $^3J_{H9,H10}$ = 5.9 Hz, H-9), 8.78 (1H, s, H-14). ^{13}C NMR (100.62 MHz, DMSO-d_6): δ_C 25.0 (2 × CH_3), 54.3 (CH_2 from *N*-benzyl), 70.4 (C-3), 89.4 (C-5), 110.4 (C-10), 126.2 (C-11), 127.5, 127.6, 128.5 (*m*,*o*,*p*-C, Ph from *N*-benzyl), 132.1 (C-9), 136.8 (*i*-C, Ph from *N*-benzyl), 143.8 (C-7), 154.5 (C-12), 169.8 (C-14), 174.0 (C-2, C-4); Anal. Calcd for $C_{19}H_{20}N_4O_2$ (336.39): C, 67.84; H, 5.99; N, 16.66%. Found: C, 68.08; H, 5.67; N, 16.56%.

Acknowledgements

This work was supported by Russian Fund for Basic Research (Grant No. 11-03-00203), Presidium of RAS (Program 25) and Presidium of Department of Chemical Sciences and Materials RAS (Grant No. 5.1.3.).

References

1. *General Organic Chemistry*; Kochetkov, N. K. Ed.; Khimiya: Moscow, 1985; Vol. 8, 752 (In Russian) [*Comprehensive Organic Chemistry*; Barton, S. D.; Ollis, W. D.; Sammes, P. G. Eds; Pergamon Press: Oxford, 1979; Vol. 4].
2. (a) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances: Syntheses, Patents, Applications*; Thieme: Stuttgart-New York, 2001; 70, 2207. (b) Mashkovsky, M. D. *Drugs*; Divov, S. B. Ed.; Novaya Volna: Moscow, 2003; Vol. 1, 540; Vol. 2, 608 (In Russian).
3. (a) Lehner, M. D.; Marx, D.; Boer, R.; Strub, A.; Hesslinger, C.; Eltze, M.; Ulrich, W.-R.; Schwoebel, F.; Schermuly, R. T.; Barsig, J. *J. Pharmacol. Exp. Ther.* **2006**, *317*, 181. (b) Strub, A.; Ulrich, W.-R.; Hesslinger, C.; Eltze, M.; Fuchβ, T.; Strassner, J.; Strand, S.; Lehner, M. D.; Boer, R. *Mol. Pharmacol*. **2006**, *69*, 328. (c) Tiso, M.; Strub, A.; Hesslinger, C.; Kenney, C. T.; Boer, R.; Stuehr, D. J. *Mol. Pharmacol.* **2008**, *73*, 1244.
4. Heerding, D. A.; Rhodes, N.; Leber, J. D.; Clark, T. J.; Keenan, R. M.; Lafrance, L. V.; Li, M.; Safonov, I. G.; Takata, D. T.; Venslavsky, J. W.; Yamashita, D. S.; Choudhry, A. E.; Copeland, R. A.; Lai, Z.; Schaber, M. D.; Tummino, P. J.; Strum, S. L.; Wood, E. R.; Duckett, D. R.; Eberwein, D.; Knick, V. B.; Lansing, T. J.; McConnel, R. T.; Zhang, S. Y.; Minthorn, E. A.; Concha, N. O.; Warren, G. L.; Kumar, R. *J. Med. Chem.* **2008**, *51*, 5663.
5. Kyochiro, I.; Nobumasa, O.; Takeshi, K.; Hitoshi, A.; Akihiro, W.; Mayumi, S.; Naoko, H.; Haruhiko, M.; Hidenori, T.; Jun, S. Eur. Pat. Appl. 2006, (JP). EP 1 724 271 A1, 05719958.0, PCT/JP2005/003656. 22.11.2006, *Bulletin* 2006, 47.
6. (a) Bukowski, L. *Chem. Heterocycl. Compd.* **2002**, *38*, 828. (b) Bukowski, L.; Zwolska, Z.; Augustynowicz-Kopec, E. *Chem. Heterocycl. Compd.* **2006**, *42*, 1358.
7. Oguchi, M.; Wada, K.; Honma, H.; Tanaka, A.; Kaneko, T.; Sakakibara, S.; Ohsumi, J.; Serizawa, N.; Fujiwara, T.; Horikoshi, H.; Fujita, T. *J. Med. Chem.* **2000**, *43*, 3052.
8. (a) Chakravarty, P. K.; Naylor, E. M.; Chen, A.; Chang, R. S. L.; Chen, T.-B.; Faust, K. A.; Lotti, V. J.; Kivlighn, S. D.; Gable, R. A.; Zingaro, G. J.; Schorn, T. W.; Schaffer, L. W.; Broten, T. P.; Siegl, P. K. S.; Patchett, A. A.; Greenlee, W. J. *J. Med. Chem.* **1994**, *37*, 4068. (b) Cappelli, A.; Mohr, G. P.; Giuliani, G.; Galeazzi, S.; Anzini, M.; Mennuni, L.; Ferrari, F.; Makovec, F.; Kleinrath, E. M.; Langer, T.; Valoti, M.; Giorgi, G.; Vomero, S. *J. Med. Chem.* **2006**, *49*, 6451.

9. Scribner, A.; Dennis, R.; Hong, J.; Lee, S.; McIntyre, D.; Perrey, D.; Feng, D.; Fisher, M.; Wyvratt, M.; Leavitt, P.; Liberator, P.; Gurnett, A.; Brown, C.; Mathew, J.; Thompson, D.; Schmatz, D.; Biftu, T. *Eur. J. Med. Chem.* **2007**, *42*, 1334.
10. Ishida, Y.; Ohta, K.; Iton, S.; Nakahama, T.; Miki, H.; Yoshikawa, H. *J. Pesticide Sci*. **1993**, *18*, 175.
11. (a) Landor, S. R.; Demetriou, B.; Grzeskowiak, R.; Pavey, D. *J. Organomet. Chem.* **1975**, *93*, 129. (b) Trofimov, B. A.; Andriyankova, L. V.; Shaikhudinova, S. I.; Kazantseva, T. I.; Mal'kina, A. G.; Afonin, A. V. *Synthesis* **2002**, 853.
12. Trofimov, B. A.; Andriyankova, L. V.; Zhivet'ev, S. A.; Mal'kina, A. G.; Voronov, V. K. *Tetrahedron Lett.* **2002**, *43*, 1093.
13. Andriyankova, L. V.; Mal'kina, A. G.; Afonin, A. V.; Trofimov, B. A. *Mendeleev Commun*. **2003**, 186.
14. Andriyankova, L. V.; Mal'kina, A. G.; Nikitina, L. P.; Belyaeva, K. V.; Ushakov, I. A.; Afonin, A. V.; Nikitin, M. V.; Trofimov, B. A. *Tetrahedron* **2005**, *61*, 8031.
15. Trofimov, B. A.; Andriyankova, L. V.; Tlegenov, R. T.; Mal'kina, A. G.; Afonin, A. V.; Il'icheva, L. N.; Nikitina, L. P. *Mendeleev Commun*. **2005**, 33.
16. (a) Trofimov, B. A.; Andriyankova, L. V.; Mal'kina, A. G.; Belyaeva, K. V.; Nikitina, L. P.; Dyachenko, O. A.; Kazheva, O. N.; Chekhlov, A. N.; Shilov, G. V.; Afonin, A. V.; Ushakov, I. A.; Baikalova, L. V. *Eur. J. Org. Chem*. **2007**, 1018. (b) Andriyankova, L. V.; Belyaeva, K. V.; Nikitina, L. P.; Mal'kina, A. G.; Afonin, A. V.; Trofimov, B. A. *Synthesis* **2010**, 2828.
17. (a) Miller, S. I.; Tanaka, R. In *Selective Organic Transformation*; Thyagarajan, B. S. Ed.; Wiley-Interscience: New York, 1970; Vol. 1, 143. (b) Dickstein, J. I.; Miller, S. I. In *The Chemistry of the Carbon-Carbon Triple Bond*; Patai, S. Ed.; Wiley: New York, 1978; Vol. 2, 814.
18. Bondi, A. *J. Phys. Chem*. **1964**, *68*, 441.
19. Starikova, O. V.; Dolgushin, G. V.; Larina, L. I.; Komarova, T. N.; Lopyrev, V. A. *Arkivoc* **2003**, *xiii*, 119.
20. Mizuno, Y.; Ikehara, M.; Iton, T.; Saito, K. *J. Org. Chem*. **1963**, *28*, 1837.
21. Khanna, I. K.; Weier, R. M.; Lentz, K. T.; Swenton, L.; Lankin, D. C. *J. Org. Chem*. **1995**, *60*, 960.
22. Sheldrick, G. M. *SHELXS-97*: *Program for crystal structure determination*; University of Göttingen: Göttingen, Germany, 1997.
23. Sheldrick, G. M. *SHELXL-97*: *Program for the refinement of crystal structures*; University of Göttingen: Göttingen, Germany, 1997.

