Exceptionally Easy Ring Cleavage of Benzimidazoles by α,β-Acetylenic γ-Hydroxy Nitriles and Water

Boris A. Trofimov,* Ludmila V. Andriyankova, Lina P. Nikitina, Kseniya V. Belyaeva, Anastasiya G. Mal'kina, Andrei V. Afonin

A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences,
1 Favorsky Str., 664033 Irkutsk, Russian Federation
Fax +7(3952)419346; E-mail: boris_trofimov@irioch.irk.ru

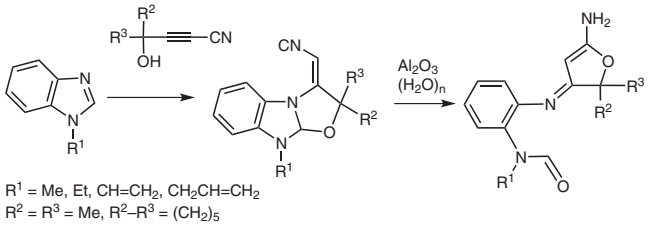
Received 27 January 2010; revised 3 February 2010

Abstract: The three-component reaction of a benzimidazole with an α,β-acetylenic γ-hydroxy nitrile and water in acetonitrile at 20–25 °C for seven days or at 45–50 °C for six hours results in cleavage of the imidazole ring to afford the corresponding (2-{[(3*E*)-5-aminofuran-3(2*H*)-ylidene]amino}phenyl)formamide exclusively in 84–99% yield. The synthesis involves multipositional cascade transformations of the intermediate hemiaminals formed from the primary zwitterions and water.

Key words: alkynes, benzimidazoles, heterocycles, multicomponent reactions, nitriles, ring opening, polycycles

The dihydrofuran ring is a key structural subunit of many natural products that have promising applications, for example, as pharmaceuticals or flavor and fragrance compounds.[1] Furthermore, highly substituted furans are of interest because they are useful and versatile intermediates for syntheses of heterocyclic or acyclic compounds.[2] The group of substituted furanones includes natural and unnatural (*Z*)-4-aryl-5-[1-(aryl)methylidene]-3-halofuran-2(5*H*)-ones[3] and nostoclides I and II,[4] which are cytotoxic against human cancer.[5] Much interest has focused on the synthesis of functionalized dihydrofuranones[6] as their tetronic, ascorbic, or penicillic acid derivatives and their metabolites, which are widespread in nature and are of special importance in human life. Tetronic acid derivatives possess antibiotic, antitumor, anticoagulant, antiepileptic, antifungal, insecticidal, analgesic, and anti-inflammatory properties and they are important as inhibitors of HIV-1 protease.[7] The pulvinic acid congeners, the 4-ylidenetetronic acids, are pigments present in lichens and in higher fungi. The chemistry of analogues of L-ascorbic acid (vitamin C) has been intensively developed to optimize their activity.[8] 3(2*H*)-Furanone derivatives have been studied as a novel selective inhibitors of cyclooxygenase-2.[9] Analogues of the naturally occurring furanones that act as inhibitors of *Serratia marcescens* chitinases have recently been synthesized.[10] The development of strategies for the synthesis of new families of functionalized dihydrofuran derivatives is therefore an interesting challenge in organic chemistry.

We recently[11] discovered a transformation of 1-substituted benzimidazoles into densely functionalized 5-amino-3-dihydrofurans by using readily available α,β-acetylenic γ-hydroxy nitriles[12] as reactants (Scheme 1). The reaction proceeds via oxazolidine dihydrobenzimidazoles as annelated intermediates that, on passage through neutral alumina, rearrange and abstract the molecules of water from the alumina to give the final products.



R^1 = Me, Et, $CH=CH_2$, $CH_2CH=CH_2$
$R^2 = R^3$ = Me, R^2–R^3 = $(CH_2)_5$

Scheme 1

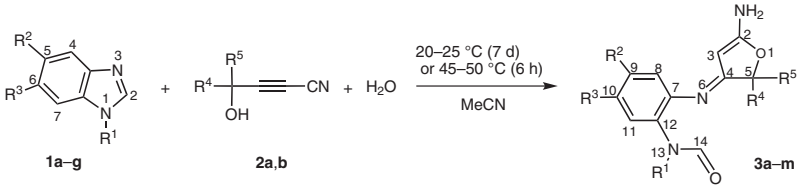
In our earlier study, we used only 1-substituted benzimidazoles, so that the scope and the synthetic impact of the reaction remained unclear, particularly in relation to substitution of the benzene ring. Of particular importance was to check the possibility of the direct synthesis of functionalized 5-amino-3-dihydrofurans from benzimidazoles, α,β-acetylenic γ-hydroxy nitriles, and water, without alumina, by a one-pot three-component reaction.

We now report a new one-pot version of a synthesis of (2-{[(3*E*)-5-aminofuran-3(2*H*)-ylidene]amino}phenyl)formamides substituted on both the *N*(1) atom and the benzene ring; the starting materials are a benzimidazole **1a**–**g**, an α,β-acetylenic γ-hydroxy nitrile **2a** or **2b,** and water, and the synthesis proceeds in the absence of alumina. When the three reactants in a 1:1:1 molar ratio are allowed to react at 20–25 °C for seven days or at 45–50 °C for six hours in acetonitrile, the corresponding (2-{[(3*E*)-5-aminofuran-3(2*H*)-ylidene]amino}phenyl)formamides **3a**–**m** are obtained in yields of 84–99% (Table 1).

The ^{1}H and ^{13}C NMR spectra and IR spectra of the products are similar to those of their analogues, the structures of which have been previously established unambiguously by X-ray crystal structure analysis.[11]

SYNTHESIS 2010, No. 9, pp 1536–1542
Advanced online publication: 15.03.2010
DOI: 10.1055/s-0029-1218704; Art ID: Z01610SS

Table 1 Three-Component Synthesis of (2-{[(3*E*)-5-Aminofuran-3(2*H*)-ylidene]amino}phenyl)formamides (**3a–m**) from Benzimidazoles **1a–g**, Nitrile **2a** or **2b**, and Water



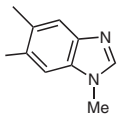
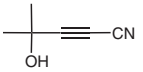
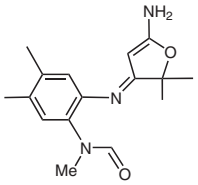
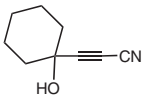
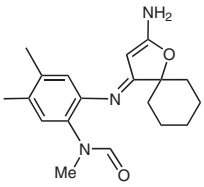
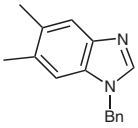
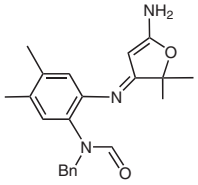
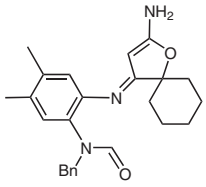
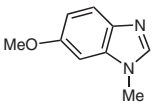
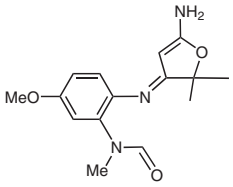
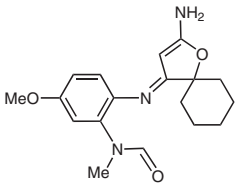
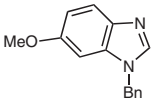
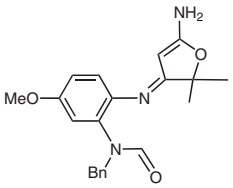
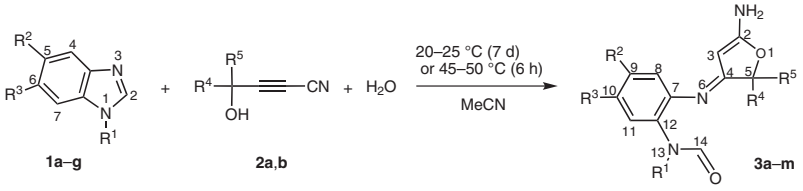
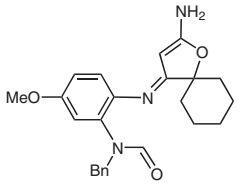
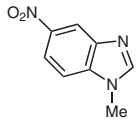
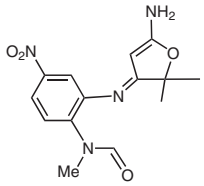
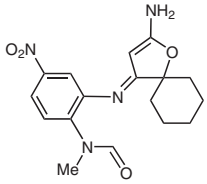
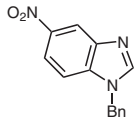
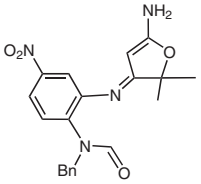
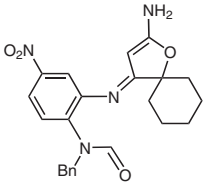
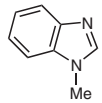
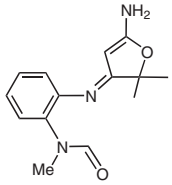
Benzimidazole		Nitrile		Product		Yield[a] (%)
1a		**2a**		**3a**		99
1a		**2b**		**3b**		96
1b		**2a**		**3c**		84
1b		**2b**		**3d**		93
1c		**2a**		**3e**		93
1c		**2b**		**3f**		91
1d		**2a**		**3g**		98

Table 1 Three-Component Synthesis of (2-{[(3*E*)-5-Aminofuran-3(2*H*)-ylidene]amino}phenyl)formamides (**3a–m**) from Benzimidazoles **1a–g**, Nitrile **2a** or **2b**, and Water (continued)



Benzimidazole	Nitrile	Product	Yield[a] (%)
1d	**2b**	**3h** 	87
1e 	**2a**	**3i** 	99
1e	**2b**	**3j** 	95
1f 	**2a**	**3k** 	99
1f	**2b**	**3l** 	99
1g 	**2a**	**3m** 	91

[a] Isolated yield. The reaction conditions are discussed in the experimental details below.

In the ^{1}H NMR spectra of adducts **3a–m**, singlets for the NH_2 protons are observed at δ = 6.85–7.82 ppm, those for the protons of the aldehyde fragment appear at δ = 7.83–8.23 ppm, and H-3 protons of the dihydrofuran ring appear at δ = 4.13–4.90 ppm. In the ^{13}C spectra, the carbon signal for the aldehyde moiety is observed at δ = 162.7–163.9 ppm and that of the C4 atom in the dihydrofuran ring appears at δ = 177.1–179.0 ppm. The IR spectrum contains distinct absorption bands assigned to the carbonyl (1657–1688 cm^{-1}) and NH_2 fragments (3188–3395 cm^{-1}).

The *E*-configuration of the isomers was established from the two-dimensional nuclear Overhauser effect spectrum of adduct **3a**, in which a cross-peak between the signals for the H3 proton in the dihydrofuran ring and H8 proton in the phenyl fragment and a cross-peak between the sig-

nals for the proton of the aldehyde fragment and the protons of the methyl group are observed. The *Z*-configurations of the isomers is not observed (Figure 1).

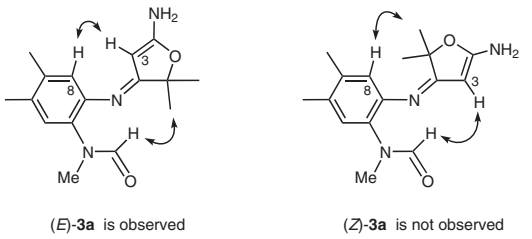
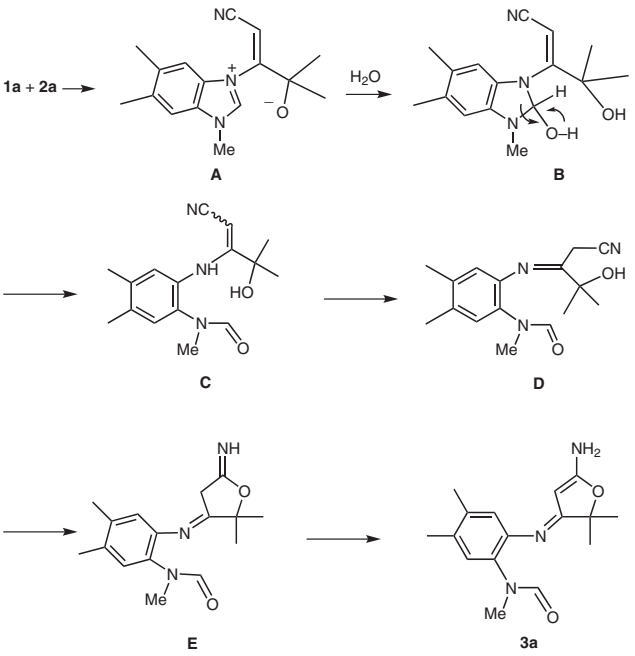


Figure 1 Cross-peaks in the two-dimensional nuclear Overhauser effect spectrum of adduct **3a**

The reaction is assumed to proceed via the primary zwitterion **A**, the adduct of benzimidazole with the acetylenic nitrile, as shown in Scheme 2 for the case of the reaction of benzimidazole **1a** with nitrile **2a** and water. The intermediate is further attacked by a molecule of water so that hydroxide ion adds to the C2-position, which has a cationic character, and the proton quenches the carbanionic center to give the intermediate hemiaminal **B**. This initiates a cascade sequence that includes cleavage of the C2–N3 bond and rearrangement of the benzimidazole ring to the 2-aminophenylformamide moiety. The resulting intermediate **C** undergoes a double-bond shift from the acrylonitrile moiety to the N3 atom to give the intermediate **D**, which is now capable of undergoing closure of the iminodihydrofuran ring. The intermediate **E** prototropically rearranges to give the final product **3a**.

Attention should be drawn to the extraordinary ease with which the aromatic imidazole ring is opened; this reaction occurs at room temperature in the absence of any transition-metal catalyst, acid or base. The driving force for this peculiar multipositional cascade transformation is probably the thermodynamically favored formation of systems that, in solution, possess a widespread conjugation over the entire molecule, including the phenylenediamine and aminodihydrofuran moieties.



Scheme 2 Tentative mechanism for the formation of the final product **3**

To summarize, a new, efficient, one-pot, three-component, cascade reaction between substituted benzimidazoles, α,β-acetylenic γ-hydroxy nitriles, and water to give (2-{[(3*E*)-5-aminofuran-3(2*H*)-ylidene]amino}phenyl)formamides has been discovered. The reaction proceeds at room temperature (or at 45–50 °C) and starts with the extraordinarily easy cleavage of the C2–N3 bond of the imidazole ring. This is followed by a cascade sequence of skeleton rearrangements and prototropic isomerizations. The new reaction does not require the presence of alumina, and it can be applied to benzimidazoles that are substituted in the benzene ring, thereby broadening the frontiers and the generality of our previously described two-step alumina-assisted synthesis. The results contribute substantially to the basic chemistry of benzimidazoles and electron-deficient acetylenes, as well as to the methodology of multicomponent reactions. The family of densely functionalized 3-dihydrofuran derivatives that are now available as a result of the newly developed method represent highly potent building blocks that are promising as precursors for drug design and as potential pharmaceutical candidates.

IR spectra were recorded on a Bruker IFS-25 instrument (KBr). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer at 400.13 MHz (^{1}H) or 100.62 MHz (^{13}C) by using DMSO-d_6 as a solvent; the atom numbering for the assignment of the peaks in the NMR spectra is that shown in Table 1. UV/Vis spectra were measured on a Perkin-Elmer Lambda 35 spectrometer at r.t. (EtOH, d = 0.1 cm). All melting points were determined on a Kofler micro hot stage. Elemental analyses were performed on a FLASH EA 1112 Series. MeCN solvent was dried by a standard method. The α,β-acetylenic γ-hydroxy nitriles **2a**,**b** were prepared by the procedure described in the literature.[12] Benzimidazoles **1a**–**g** were prepared by alkylation according to the literature protocol.[13] The reaction was monitored by examining the disappearance of the IR absorption bands for the starting nitrile **2a** or **2b** in the reaction mixtures.

(2-{[(3*E*)-5-Amino-2,2-dimethylfuran-3(2*H*)-ylidene]amino}-4,5-dimethylphenyl)methylformamide (3a); Typical Procedure

A mixture of 1,5,6-trimethyl-1*H*-benzimidazole (**1a**; 0.160 g, 1 mmol), nitrile **2a** (0.109 g, 1 mmol), and H_2O (0.018 g, 1 mmol) in dry MeCN (0.5 mL) was stirred at 45–50 °C for 6 h then cooled to r.t. The residue that precipitated was filtered off and recrystallized (EtOH) to give a light-yellow powder; yield: 0.286 g (99%); mp 196–198 °C.

IR: 456, 519, 571, 601, 662, 706, 755, 775, 886, 954, 1002, 1070, 1080, 1147, 1181, 1223, 1263, 1273, 1309, 1357, 1372, 1386, 1431, 1495, 1543, 1624, 1675, 2872, 2930, 2979, 2989, 3015, 3108, 3308, 3341 cm^{-1}.

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 1.38 (s, 6 H, 2 Me5), 2.16 (s, 6 H, 2 Me9,10), 2.97 (s, 3 H, *N*-Me), 4.15 (s, 1 H, H3), 6.65 (s, 1 H, H11), 6.95 (s, 1 H, H8), 7.20 (s, 2 H, NH_2), 7.87 (s, 1 H, H14).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 19.0 (Me10), 19.5 (Me9), 25.9 (2 Me5), 32.6 (*N*-Me), 70.3 (C3), 88.7 (C5), 123.8 (C11), 128.1 (C8), 130.3 (C9), 131.8 (C10), 136.2 (C12), 147.7 (C7), 163.1 (C14), 173.6 (C2), 177.4 (C4).

UV/Vis (EtOH): λ_{max} (log ε) = 283 (4.41) nm.

Anal. Calcd for $C_{16}H_{21}N_3O_2$ (287.36): C, 66.88; H, 7.37; N, 14.62. Found: C, 66.56; H, 7.22; N, 14.50.

(2-{[(4*E*)-2-Amino-1-oxaspiro[4.5]dec-2-en-4-ylidene]amino}-4,5-dimethylphenyl)methylformamide (3b)

This was prepared analogously from 1,5,6-trimethylbenzimidazole (**1a**; 0.160 g, 1 mmol), nitrile **2b** (0.149 g, 1 mmol), and H_2O (0.018 g, 1 mmol) as a white powder; yield: 0.314 g (96%); mp 249–250 °C.

IR: 494, 612, 663, 747, 769, 801, 841, 888, 936, 954, 993, 1024, 1064, 1112, 1141, 1192, 1233, 1255, 1304, 1349, 1379, 1436, 1454, 1539, 1620, 1666, 2718, 2767, 2859, 2892, 2931, 3104, 3313, 3357 cm^{-1}.

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 1.50–2.00 (m, 10 H, cyclohexyl), 2.15 (s, 6 H, 2 Me9,10), 2.96 (s, 3 H, *N*-Me), 4.13 (s, 1 H, H3), 6.62 (s, 1 H, H11), 6.94 (s, 1 H, H8), 7.20 (s, 2 H, NH_2), 7.86 (s, 1 H, H14).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 19.1 (Me9), 19.5 (Me10), 22.2, 24.7 (4 CH_2, cyclohexyl), 32.6 (*N*-Me), 34.3 (1 CH_2, cyclohexyl), 70.6 (C3), 89.6 (C5), 123.8 (C11), 128.3 (C8), 130.0 (C9), 130.4 (C10), 136.1 (C12), 147.4 (C7), 163.2 (C14), 173.8 (C2), 177.1 (C4).

Anal. Calcd for $C_{19}H_{25}N_3O_2$ (327.43): C, 69.70; H, 7.70; N, 12.83. Found: C, 69.42; H, 7.88; N, 12.80.

(2-{[(3*E*)-5-Amino-2,2-dimethylfuran-3(2*H*)-ylidene]amino}-4,5-dimethylphenyl)benzylformamide (3c)

This was prepared analogously from 1-benzyl-5,6-dimethylbenzimidazole (**1b**; 0.236 g, 1 mmol), nitrile **2a** (0.109 g, 1 mmol), and H_2O (0.018 g, 1 mmol) as a light-brown powder; yield: 0.305 g (84%); mp 187–189 °C.

IR: 495, 518, 576, 592, 611, 628, 636, 659, 696, 705, 729, 741, 756, 770, 846, 887, 957, 972, 998, 1020, 1074, 1110, 1139, 1183, 1205, 1231, 1264, 1295, 1319, 1329, 1345, 1364, 1372, 1435, 1454, 1498, 1544, 1620, 1659, 1673, 2874, 2925, 2968, 3028, 3064, 3084, 3318, 3361 cm^{-1}.

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 1.43 (s, 6 H, 2 Me5), 2.07 (s, 3 H, Me9), 2.11 (s, 3 H, Me10), 4.23 (s, 1 H, H3), 4.80 (s, 2 H, CH_2 from *N*-benzyl), 6.65 (s, 1 H, H11), 6.84 (s, 1 H, H8), 7.20 (s, 2 H, NH_2), 7.20–7.40 (m, 5 H, Ph from *N*-benzyl), 8.05 (s, 1 H, H14).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 19.2 (Me9), 19.4 (Me10), 26.0 (2 Me5), 47.9 (CH_2 from *N*-benzyl), 70.7 (C3), 89.0 (C5), 123.6 (C11), 127.2 (C*p*, Ph from *N*-benzyl), 127.6 (C*o*, Ph from *N*-benzyl), 128.1 (C8), 128.3 (C*m*, Ph from *N*-benzyl), 130.4 (C9), 130.5 (C10), 136.0 (C12), 137.7 (C*i*, Ph from *N*-benzyl), 147.7 (C7), 163.7 (C14), 173.7 (C2), 177.3 (C4).

Anal. Calcd for $C_{22}H_{25}N_3O_2$ (363.46): C, 72.70; H, 6.93; N, 11.56. Found: C, 72.25; H, 6.74; N, 12.00.

(2-{[(4*E*)-2-Amino-1-oxaspiro[4.5]dec-2-en-4-ylidene]amino}-4,5-dimethylphenyl)benzylformamide (3d)

This was prepared analogously from 1-benzyl-5,6-dimethylbenzimidazole (**1b**; 0.236 g, 1 mmol), nitrile **2b** (0.149 g, 1 mmol), and H_2O (0.018 g, 1 mmol) as a flesh-colored powder; yield: 0.375 g (93%); mp 224–225 °C.

IR: 499, 507, 561, 610, 641, 695, 722, 745, 877, 886, 928, 950, 999, 1064, 1104, 1119, 1195, 1244, 1261, 1309, 1344, 1365, 1425, 1437, 1496, 1541, 1567, 1602, 1612, 1660, 2853, 2864, 2880, 2923, 2936, 2950, 3028, 3064, 3085, 3109, 3286, 3322 cm^{-1}.

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 1.50–2.00 (m, 10 H, cyclohexyl), 2.23 (s, 3 H, Me9), 2.27 (s, 3 H, Me10), 4.23 (s, 1 H, H3), 4.79 (s, 2 H, CH_2 from *N*-benzyl), 6.62 (s, 1 H, H11), 6.91 (s, 1 H, H8), 7.20 (s, 2 H, NH_2), 7.20–7.40 (m, 5 H, Ph from *N*-benzyl), 8.04 (s, 1 H, H14).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 19.1 (Me9), 19.4 (Me10), 22.2, 24.8, 34.4 (5 CH_2, cyclohexyl), 47.9 (CH_2 from *N*-benzyl), 70.7 (C3), 90.3 (C5), 123.6 (C11), 127.2 (C*p*, Ph from *N*-benzyl), 128.1 (C*o*, Ph from *N*-benzyl), 128.4 (C8), 128.8 (C*m*, Ph from *N*-benzyl), 129.9 (C9), 130.5 (C10), 136.0 (C12), 138.0 (C*i*, Ph from *N*-benzyl), 147.6 (C7), 163.7 (C14), 174.0 (C2), 177.2 (C4).

Anal. Calcd for $C_{25}H_{29}N_3O_2$ (403.52): C, 74.41; H, 7.24; N, 10.41. Found: C, 74.80; H, 7.35; N, 10.48.

(2-{[(3*E*)-5-Amino-2,2-dimethylfuran-3(2*H*)-ylidene]amino}-5-methoxyphenyl)methylformamide (3e)

This was prepared analogously from 6-methoxy-1-methyl-1*H*-benzimidazole (**1c**; 0.162 g, 1 mmol), nitrile **2a** (0.109 g, 1 mmol), and H_2O (0.018 g, 1 mmol) as a yellow powder; yield: 0.269 g (93%); mp 169–171 °C.

IR: 505, 530, 617, 642, 694, 708, 769, 797, 868, 956, 976, 1038, 1058, 1092, 1109, 1188, 1215, 1334, 1360, 1374, 1415, 1497, 1561, 1607, 1650, 1688, 2835, 2930, 2978, 3188, 3395 cm^{-1}.

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 1.40 (s, 6 H, 2 Me5), 2.96 (s, 3 H, *N*-Me), 3.73 (s, 3 H, *O*-Me10), 4.54 (s, 1 H, H3), 6.57 (d, $^3J_{H8,H9}$ = 8.8 Hz, 1 H, H8), 6.59 (d, 1 H, H9), 6.85 (s, 2 H, NH_2), 7.12 (s, 1 H, H11), 7.97 (s, 1 H, H14).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 25.4 (2 Me5), 32.9 (*N*-Me), 55.9 (*O*-Me10), 70.5 (C3), 92.5 (C5), 107.3 (C8), 108.6 (C9), 127.7 (C12), 128.6 (C11), 149.2 (C7), 159.4 (C10), 163.4 (C14), 176.6 (C2), 179.0 (C4).

Anal. Calcd for $C_{15}H_{19}N_3O_3$ (289.33): C, 62.27; H, 6.62; N, 14.52. Found: C 62.80; H 6.67; N 14.28.

(2-{[(4*E*)-2-Amino-1-oxaspiro[4.5]dec-2-en-4-ylidene]amino}-5-methoxyphenyl)methylformamide (3f)

This was prepared analogously from 6-methoxy-1-methyl-1*H*-benzimidazole (**1c**; 0.162 g, 1 mmol), nitrile **2b** (0.149 g, 1 mmol), and H_2O (0.018 g, 1 mmol) as a white powder; yield: 0.299 g (91%); mp 216–217 °C.

IR: 448, 499, 540, 584, 663, 702, 748, 783, 798, 836, 872, 918, 944, 993, 1037, 1057, 1096, 1193, 1209, 1222, 1278, 1346, 1436, 1496, 1548, 1616, 1665, 2710, 2764, 2866, 2940, 3007, 3111, 3322, 3373 cm^{-1}.

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 1.40–1.80 (m, 10 H, cyclohexyl), 2.94 (s, 3 H, *N*-Me), 3.71 (s, 3 H, *O*-Me10), 4.16 (s, 1 H, H3), 6.34 (d, $^3J_{H8,H9}$ = 8.8 Hz, 1 H, H8), 6.53 (d, 1 H, H9), 7.08 (s, 1 H, H11), 7.29 (s, 2 H, NH_2), 7.83 (s, 1 H, H14).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 22.2, 24.7 (3 CH_2, cyclohexyl), 32.8 (*N*-Me), 34.3 (2 CH_2, cyclohexyl), 55.7 (*O*-Me10), 70.5 (C3), 90.3 (C5), 107.7 (C8), 108.0 (C9), 127.8 (C12), 128.5 (C11), 151.1 (C7), 159.1 (C10), 163.3 (C14), 174.0 (C2), 177.6 (C4).

Anal. Calcd for $C_{18}H_{23}N_3O_3$ (329.40): C, 65.63; H, 7.04; N, 12.76. Found: C, 65.22; H, 7.04; N, 12.76.

(2-{[(3*E*)-5-Amino-2,2-dimethylfuran-3(2*H*)-ylidene]amino}-5-methoxyphenyl)benzylformamide (3g)

This was prepared analogously from 1-benzyl-6-methoxy-1*H*-benzimidazole (**1d**; 0.238 g, 1 mmol), nitrile **2a** (0.109 g, 1 mmol),

and H_2O (0.018 g, 1 mmol) as a yellow powder; yield: 0.358 g (98%); mp 211–212 °C.

IR: 455, 502, 564, 580, 608, 655, 696, 720, 752, 796, 830, 864, 876, 967, 1002, 1028, 1044, 1066, 1133, 1175, 1184, 1204, 1234, 1282, 1308, 1364, 1375, 1400, 1432, 1448, 1498, 1544, 1584, 1609, 1650, 1679, 2834, 2927, 2980, 3060, 3112, 3309, 3361 cm^{-1}.

^1H NMR (400.13 MHz, DMSO-d_6): δ = 1.49 (s, 6 H, 2 Me5), 3.73 (s, 3 H, *O*-Me10), 4.31 (s, 1 H, H3), 4.91 (s, 2 H, CH_2 from *N*-benzyl), 6.74 (s, 1 H, H11), 6.82–6.84 (m, 2 H, H8,9), 7.25 (s, 2 H, NH_2), 7.20–7.34 (m, 5 H, Ph from *N*-benzyl), 8.15 (s, 1 H, H14).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 25.2 (2 Me5), 47.7 (CH_2 from *N*-benzyl), 55.6 (*O*-Me10), 69.6 (C3), 88.9 (C5), 112.8 (C9), 113.4 (C11), 123.0 (C8), 126.2 (C*p*, Ph from *N*-benzyl), 128.0 (C*o*, Ph from *N*-benzyl), 128.2 (C*m*, Ph from *N*-benzyl), 133.6 (C12), 137.9 (C*i*, Ph from *N*-benzyl), 143.0 (C7), 154.6 (C10), 163.8 (C14), 173.7 (C2), 177.4 (C4).

Anal. Calcd for $C_{21}H_{23}N_3O_3$ (365.43): C, 69.02; H, 6.34; N, 11.50. Found: C, 68.72; H, 6.31; N, 11.30.

(2-{[(4*E*)-2-Amino-1-oxaspiro[4.5]dec-2-en-4-ylidene]amino}-5-methoxyphenyl)benzylformamide (3h)

This was prepared analogously from 1-benzyl-6-methoxy-1*H*-benzimidazole (**1d**; 0.238 g, 1 mmol), nitrile **2b** (0.149 g, 1 mmol), and H_2O (0.018 g, 1 mmol) as a brown powder; yield: 0.325 g (87%); mp 189–190 °C.

IR: 495, 520, 620, 696, 724, 749, 785, 813, 829, 839, 850, 910, 933, 949, 963, 1001, 1029, 1041, 1065, 1111, 1171, 1206, 1235, 1262, 1278, 1320, 1344, 1365, 1444, 1497, 1540, 1561, 1606, 1664, 2834, 2850, 2917, 2942, 3005, 3027, 3309 cm^{-1}.

^1H NMR (400.13 MHz, DMSO-d_6): δ = 1.50–1.80 (m, 10 H, cyclohexyl), 3.63 (s, 3 H, *O*-Me10), 4.26 (s, 1 H, H3), 4.85 (s, 2 H, CH_2 from *N*-benzyl), 6.66 (s, 1 H, H11), 6.76–6.78 (m, 2 H, H8,9), 7.20 (s, 2 H, NH_2), 7.20–7.40 (m, 5 H, Ph from *N*-benzyl), 8.10 (s, 1 H, H14).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 22.2, 24.9, 34.4 (5 CH_2, cyclohexyl), 47.9 (CH_2 from *N*-benzyl), 55.7 (*O*-Me10), 70.6 (C3), 90.4 (C5), 113.0 (C9), 113.6 (C11), 123.2 (C8), 127.3 (C*p*, Ph from *N*-benzyl), 127.8 (C*o*, Ph from *N*-benzyl), 128.1 (C*m*, Ph from *N*-benzyl), 133.6 (C12), 137.9 (C*i*, Ph from *N*-benzyl), 143.0 (C7), 154.6 (C10), 163.8 (C14), 174.1 (C2), 177.5 (C4).

Anal. Calcd for $C_{24}H_{27}N_3O_3$ (405.50): C, 70.09; H, 6.71; N, 10.36. Found: C, 69.81; H, 6.90; N, 10.15.

(2-{[(3*E*)-5-Amino-2,2-dimethylfuran-3(2*H*)-ylidene]amino}-4-nitrophenyl)methylformamide (3i)

This was prepeared analogously from 1-methyl-5-nitro-1*H*-benzimidazole (**1e**; 0.177 g, 1 mmol), nitrile **2a** (0.109 g, 1 mmol), and H_2O (0.018 g, 1 mmol) as an orange powder; yield: 0.301 g (99%); mp 199–200 °C.

IR: 499, 577, 603, 646, 706, 734, 747, 760, 822, 846, 897, 953, 991, 1004, 1073, 1120, 1132, 1185, 1201, 1212, 1247, 1290, 1335, 1362, 1376, 1429, 1457, 1485, 1508, 1537, 1621, 1674, 2877, 2931, 2983, 3106, 3292, 3352 cm^{-1}.

^1H NMR (400.13 MHz, DMSO-d_6): δ = 1.41 (s, 6 H, 2 Me5), 3.07 (s, 3 H, *N*-Me), 4.90 (s, 1 H, H3), 7.11 (d, $^3J_{H10,H11}$ = 8.8 Hz, 1 H, H11), 7.67 (d, 1 H, H10), 7.82 (s, 2 H, NH_2), 8.07 (s, 1 H, H14), 8.08 (s, 1 H, H8).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 25.7 (2 Me5), 32.7 (*N*-Me), 71.4 (C3), 90.3 (C5), 122.4 (C10), 123.0 (C11), 123.9 (C8), 135.2 (C12), 139.7 (C9), 157.3 (C7), 163.5 (C14), 175.4 (C2), 178.6 (C4).

Anal. Calcd for $C_{14}H_{16}N_4O_4$ (304.31): C, 55.26; H, 5.42; N, 18.41. Found: C, 55.20; H, 5.41; N, 18.32.

(2-{[(4*E*)-2-Amino-1-oxaspiro[4.5]dec-2-en-4-ylidene]amino}-4-nitrophenyl)methylformamide (3j)

This was prepared analogously from 1-methyl-5-nitro-1*H*-benzimidazole (**1e**; 0.177 g, 1 mmol), nitrile **2b** (0.149 g, 1 mmol), and H_2O (0.018 g, 1 mmol) to give a yellow powder; yield: 0.327 g (95%); mp 220–221 °C.

IR: 495, 564, 580, 634, 693, 747, 821, 838, 907, 919, 945, 978, 1001, 1049, 1116, 1137, 1201, 1233, 1255, 1277, 1306, 1335, 1351, 1436, 1490, 1516, 1540, 1575, 1593, 1612, 1654, 1668, 2851, 2931, 3097, 3157, 3212, 3265, 3307 cm^{-1}.

^1H NMR (400.13 MHz, DMSO-d_6): δ = 1.50–1.80 (m, 10 H, cyclohexyl), 3.10 (s, 3 H, *N*-Me), 4.66 (s, 1 H, H3), 7.47 (d, $^3J_{H10,H11}$ = 8.8 Hz, 1 H, H11), 7.67 (s, 2 H, NH_2), 7.78 (d, 1 H, H10), 8.06 (s, 1 H, H14), 8.08 (s, 1 H, H8).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 22.1, 24.6 (3 CH_2, cyclohexyl), 32.5 (*N*-Me), 34.1 (2 CH_2, cyclohexyl), 70.8 (C3), 91.2 (C5), 117.0 (C8,10), 126.5 (C11), 139.8 (C12), 146.2 (C9), 150.2 (C7), 162.8 (C14), 175.1 (C2), 178.7 (C4).

Anal. Calcd for $C_{17}H_{20}N_4O_4$ (344.37): C, 59.79; H, 5.85; N, 16.24. Found: C, 59.32; H, 5.64; N, 16.70.

(2-{[(3*E*)-5-Amino-2,2-dimethylfuran-3(2*H*)-ylidene]amino}-4-nitrophenyl)benzylformamide (3k)

This was prepared analogously from 1-benzyl-5-nitro-1*H*-benzimidazole (**1f**; 0.253 g, 1 mmol), nitrile **2a** (0.109 g, 1 mmol), and H_2O (0.018 g, 1 mmol) to give a yellow powder; yield: 0.376 g (99%); mp 197–198 °C.

IR: 513, 607, 665, 696, 726, 745, 760, 815, 836, 900, 961, 1007, 1086, 1184, 1223, 1270, 1286, 1301, 1310, 1344, 1429, 1456, 1485, 1522, 1541, 1563, 1615, 1657, 2913, 2929, 2987, 3169, 3326, 3345 cm^{-1}.

^1H NMR (400.13 MHz, DMSO-d_6): δ = 1.44 (s, 6 H, 2 Me5), 4.52 (s, 1 H, H3), 4.95 (s, 2 H, CH_2 from *N*-benzyl), 7.20–7.40 (m, 5 H, Ph from *N*-benzyl), 7.41 (d, $^3J_{H10,H11}$ = 8.8 Hz, 1 H, H11), 7.66 (d, 1 H, H10), 7.60 (s, 2 H, NH_2), 7.73 (s, 1 H, H8), 8.19 (s, 1 H, H14).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 26.9 (2 Me5), 47.6 (CH_2 from *N*-benzyl), 70.6 (C3), 90.3 (C5), 116.7 (C10), 116.7 (C8), 127.3 (C*p*, Ph from *N*-benzyl), 127.9 (C*o*, Ph from *N*-benzyl), 128.8 (C*m*, Ph from *N*-benzyl), 129.0 (C11), 136.3 (C*i*, Ph from *N*-benzyl), 139.7 (C12), 146.5 (C9), 150.1 (C7), 163.9 (C14), 175.3 (C2), 178.8 (C4).

Anal. Calcd for $C_{20}H_{20}N_4O_4$ (380.40): C, 63.15; H, 5.30; N, 14.73. Found: C, 62.60; H, 5.19; N, 14.65.

(2-{[(4*E*)-2-Amino-1-oxaspiro[4.5]dec-2-en-4-ylidene]amino}-4-nitrophenyl)benzylformamide (3l)

This was prepared analogously from 1-benzyl-5-nitro-1*H*-benzimidazole (**1f**; 0.253 g, 1 mmol), nitrile **2b** (0.149 g, 1 mmol), and H_2O (0.018 g, 1 mmol) as a yellow powder; yield: 0.416 g (99%); mp 177–179 °C.

IR: 501, 522, 547, 635, 661, 696, 728, 740, 754, 795, 811, 823, 837, 901, 915, 945, 1001, 1063, 1079, 1139, 1191, 1219, 1237, 1263, 1313, 1345, 1372, 1404, 1444, 1481, 1520, 1551, 1611, 1650, 1660, 2861, 2932, 3180, 3390 cm^{-1}.

^1H NMR (400.13 MHz, DMSO-d_6): δ = 1.50–2.00 (m, 10 H, cyclohexyl), 4.62 (s, 1 H, H3), 5.00 (s, 2 H, CH_2 from *N*-benzyl), 6.93 (s, 2 H, NH_2), 7.20–7.40 (m, 5 H, Ph from *N*-benzyl), 7.62–7.65 (m, 2 H, H10,11), 7.98 (s, 1 H, H8), 8.23 (s, 1 H, H14).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 21.9, 24.5, 33.9 (5 CH_2, cyclohexyl), 47.3 (CH_2 from *N*-benzyl), 70.8 (C3), 91.6 (C5), 116.1 (C10), 116.6 (C8), 126.9 (C11), 127.2 (C*p*, Ph from *N*-benzyl), 127.9 (C*o*, Ph from *N*-benzyl), 128.1 (C*m*, Ph from *N*-benzyl),

137.3 (C*i*, Ph from *N*-benzyl), 139.4 (C12), 146.6 (C9), 150.3 (C7), 162.7 (C14), 175.1 (C2), 179.0 (C4).

Anal. Calcd for $C_{23}H_{24}N_4O_4$ (420.47): C, 65.70; H, 5.75; N, 13.32. Found: C, 65.41; H, 5.72; N, 13.50.

(2-{[(3*E*)-5-Amino-2,2-dimethylfuran-3(2*H*)-ylidene]amino}-4-phenyl)methylformamide (3m)

This was prepared analogously from 1-methyl-1*H*-benzimidazole (**1g**; 0.132 g, 1 mmol), nitrile **2a** (0.109 g, 1 mmol), and H_2O (0.018 g, 1 mmol) as a flesh-colored powder; yield: 0.235 g (91%); mp 179–180 °C. The IR and NMR spectral characteristics of formamide **3m** were in agreement with the published data.[11]

Acknowledgment

This work was supported by the Russian Fund for Basic Research (Grant No. 08-03-00156), the Presidium of RAS (Program 15), and the Presidium of the Department of Chemical Sciences and Materials RAS (Grant No. 5.1).

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