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Unexpected domino reaction of 3-alkyl-1,2,4-triazolo[1,5-*a*]benzimidazoles with butylmagnesium bromide leading to benzimidazolyl guanidines

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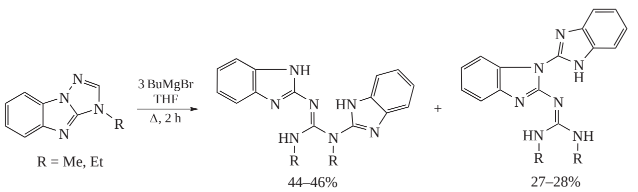
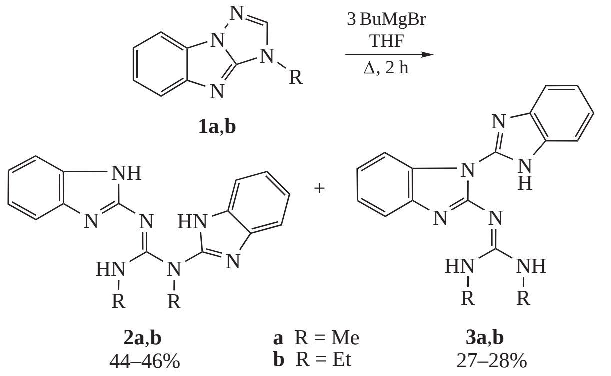
Reaction of 3-alkyl-1,2,4-triazolo[1,5-*a*]benzimidazoles with butylmagnesium bromide follows two hetarylotropic rearrangements to afford 1,2-bis(1*H*-benzimidazol-2-yl)-1,3-dialkylguanidines and 2-(1′*H*-1,2′-dibenzimidazol-2-yl)-1,3-dialkylguanidines.



The plethora of pharmacological properties of 1,2,4-triazolo[1,5-*a*]benzimidazole derivatives[1] has stimulated research that is focused on the development of functionalization of this tricyclic system. The electron-deficient atom C-2[2] and substitution at N-3 of the molecule are the prerequisites for the metallation reaction.

On treatment of 3-alkyl-1,2,4-triazolo[1,5-*a*]benzimidazoles[2] **1a**,**b** with butylmagnesium bromide in boiling THF in inert atmosphere, a fairly complicated anionic domino reaction occurs giving a mixture of isomeric benzimidazolyl guanidines **2a**,**b** and **3a**,**b** in 70% yield and a ratio of 1.6 : 1, respectively (Scheme 1).[†] The structures of compounds **2b** and **3a** were validated by the IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and X-ray structural analysis (Figures 1 and 2).[‡]

Apparently, the reaction starts with the formation of unstable organomagnesium compounds **4** which are in equilibrium with labile C-anions **5** (Scheme 2). These intermediates undergo



1a,**b**

2a,**b** 44–46%

a R = Me
b R = Et

3a,**b** 27–28%

Scheme 1

[†] IR spectra were recorded on a Varian Excalibur 3100 FT-IR spectrometer in solid phase. ^{1}H NMR spectra were recorded on a Varian Unity-300 spectrometer (300 MHz) in DMSO-d_6 (for compounds **2a**,**b**) and in $CDCl_3$ (for compounds **3a**,**b**). ^{13}C NMR spectra were recorded on a Bruker Avance-600 spectrometer (150 MHz) in $CDCl_3$. Chemical shifts are given with respect to remaining signal of deutero-solvent: 2.49 ppm (DMSO-d_6) and 7.24 ppm ($CDCl_3$) for ^{1}H, 77.0 ppm ($CDCl_3$) for ^{13}C. Mass spectra were measured on a Finnigan MATINCOS 50 spectrometer (for **2a**,**b**) and on a Shimadzu GCMS-QP2010SE apparatus (for **3a**,**b**) using direct sample introduction into ion source (EI, 80 eV). Melting points were determined on a Fisher-Johns Melting Point Apparatus.

*General procedure for the reaction between butylmagnesium bromide and 3-alkyl-1,2,4-triazolo[1,5-*a*]benzimidazoles* **1a**,**b**. Solution of compounds **1a**,**b** (2 mmol) in 10 ml of absolute THF in argon atmosphere was added dropwise for 5 min to boiling THF (5 ml) solution of BuMgBr obtained from 146 mg (6 mmol) of magnesium and 822 mg (6 mmol) of butyl bromide. After the mixture was boiled for 2 h, it was cooled to 25 °C. Aqueous NH_4Cl saturated solution (10 ml) was added, and the organic layer was separated. It was treated with 10 ml of 15% HCl and 20 ml of Et_2O, the aqueous phase was separated and quenched with conc. NH_4OH. The precipitate formed was filtered, washed with water, and dried. The obtained mixture **2** + **3** was separated on chromatographic column with Al_2O_3 (eluent, $CHCl_3$) with collection of the corresponding fractions of compounds **2a**,**b** (R_f = 0.1) and **3a**,**b** (R_f = 0.6).

*1,2-Bis(1*H*-benzimidazol-2-yl)-1,3-dimethylguanidine* **2a**. Yield 294 mg (46%), colorless crystals, mp 212–213 °C (MeCN). IR (ν/cm^{-1}): 3396 (NH). ^{1}H NMR, δ: 2.97 (d, 3H, NH*Me*, *J* 4.8 Hz), 3.54 (s, 3H, NMe), 6.97–7.03 (m, 4H, H_{Ar}), 7.31 (br. s, 4H, H_{Ar}), 10.40 (q, 1H, N*H*Me, *J* 4.8 Hz), 11.66 (br. s, 2H, 2NH). ^{13}C NMR, δ: 31.4, 37.9, 108.0, 109.9, 117.8, 121.7, 121.8, 151.5, 155.4, 159.0. MS, *m/z* (%): 319 [M]$^+$ (15), 173 (100), 158 (13), 147 (34), 132 (7), 118 (23), 105 (9), 90 (12), 78 (4), 65 (5). Found (%): C, 63.87; H, 5.44; N, 30.75. Calc. for $C_{17}H_{17}N_7$ (%): C, 63.93; H, 5.37; N, 30.70.

*1,2-Bis(1*H*-benzimidazol-2-yl)-1,3-diethylguanidine* **2b**. Yield 306 mg (44%), colorless crystals, mp 199–200 °C (MeCN). IR (ν/cm^{-1}): 3265 (NH). ^{1}H NMR, δ: 1.15 (t, 3H, NHCH$_2$*Me*, *J* 7.2 Hz), 1.29 (t, 3H, NCH$_2$*Me*, *J* 6.9 Hz), 3.08–3.14 (m, 2H, NHC*H*$_2$Me), 4.01 (q, 2H, NC*H*$_2$Me, *J* 6.9 Hz), 7.01–7.06 (m, 4H, H_{Ar}), 7.34 (br. s, 4H, H_{Ar}), 10.39 (t, 1H, N*H*Et, *J* 5.0 Hz), 11.76 (br. s, 2H, 2NH). ^{13}C NMR, δ: 13.7, 15.7, 39.9, 45.2, 109.4, 117.5, 121.7, 121.8, 150.8, 155.7, 157.1. MS, *m/z* (%): 347 [M]$^+$ (12), 187 (100), 159 (59), 146 (22), 133 (19), 118 (23), 105 (20), 90 (18), 77 (6), 65 (10), 51 (4). Found (%): C, 65.59; H, 6.15; N, 28.31. Calc. for $C_{19}H_{21}N_7$ (%): C, 65.69; H, 6.09; N, 28.22.

*2-(1′*H*-1,2′-Dibenzimidazol-2-yl)-1,3-dimethylguanidine* **3a**. Yield 179 mg (28%), colorless crystals, mp 220–221 °C (MeCN). IR (ν/cm^{-1}): 3445 (NH). ^{1}H NMR, δ: 2.91 (s, 3H, Me), 3.05 (s, 3H, Me), 4.40 (br. s, 1H, N*H*Me), 7.18–7.24 (m, 2H, H_{Ar}), 7.26–7.36 (m, 2H, H_{Ar}), 7.42–7.46 (m, 2H, H_{Ar}), 7.79 (d, 1H, H_{Ar}, *J* 7.8 Hz), 8.73–8.76 (m, 1H, H_{Ar}), 10.20 (br. s, 1H, N*H*Me), 12.81 (s, 1H, NH). ^{13}C NMR, δ: 27.4, 28.4, 110.0, 114.4, 116.1, 118.5, 121.61, 121.67, 121.72, 123.1, 130.0, 131.4, 141.3,

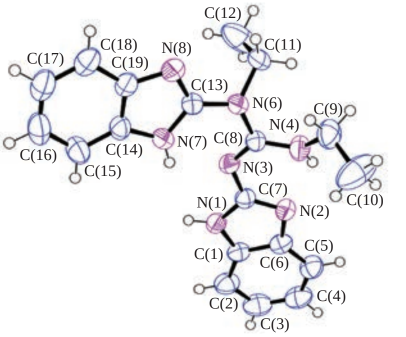


Figure 1 Molecular structure of **2b** in the representation of atoms as ellipsoids of thermal vibrations with 50% probability.

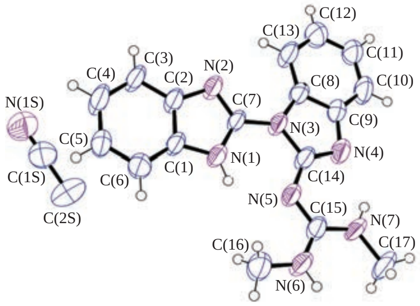
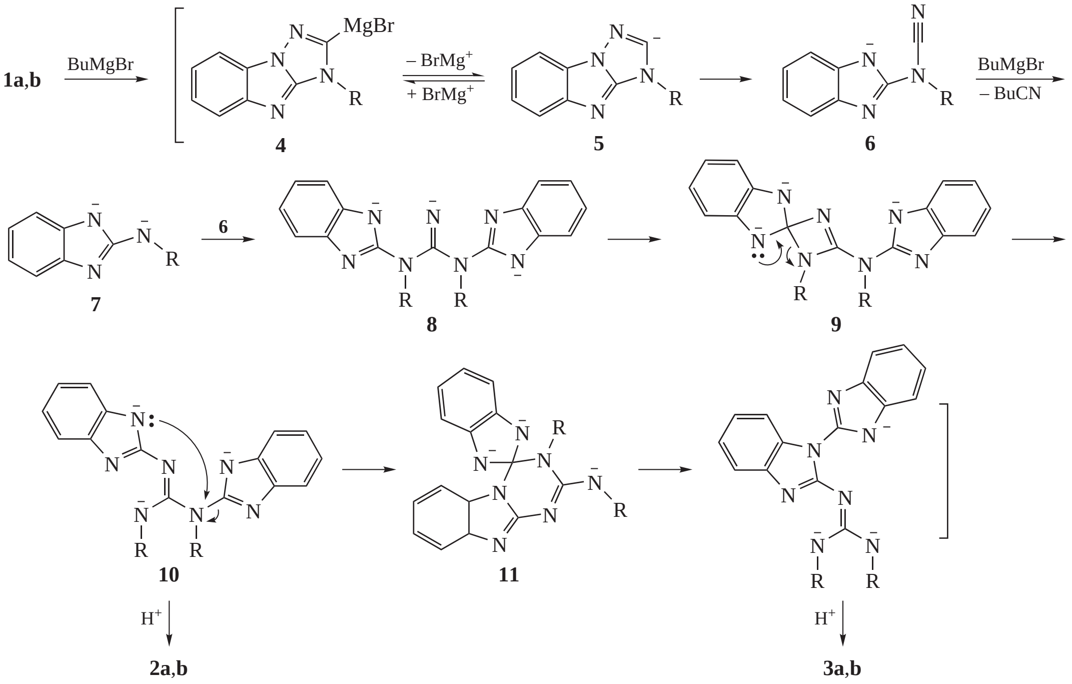


Figure 2 Molecular structure of **3a**·MeCN in the representation of atoms as ellipsoids of thermal vibrations with 50% probability.



Scheme 2

spontaneous ring-chain isomerization with the cleavage of the N–N bond into N-anion of cyanamide **6**, which can be considered similar to the ring-opening of 1,2,4-triazoles under the action of a nucleophile.[3,4] According to the data of quantum chemical studies by DFT method (B3LYP/6-31G**, gas-phase conditions), N–N bond in magnesium derivative **4** (R = Me) and especially in

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141.7, 147.2, 155.7, 157.8. MS, *m/z* (%): 319 [M]$^+$ (42), 288 (7), 249 (40), 233 (4), 208 (35), 173 (100), 147 (21), 118 (11), 90 (9), 71 (30), 57 (9). Found (%): C, 63.84; H, 5.48; N, 30.64. Calc. for $C_{17}H_{17}N_7$ (%): C, 63.93; C, 5.37; N, 30.70.

*2-(1'*H*-1,2'-Dibenzimidazol-2-yl)-1,3-diethylguanidine* **3b**. Yield 188 mg (27%), colorless crystals, mp 204–205 °C (MeCN). IR (ν/cm^{-1}): 3451 (NH). ^{1}H NMR, δ: 1.41 (t, 6H, 2CH$_2$*Me*, *J* 7.3 Hz), 3.27 (br. s, 2H, NHC*H*$_2$Me), 3.52 (br. s, 2H, C*H*$_2$Me), 4.36 (br. s, 1H, N*H*Et), 7.19–7.24 (m, 2H, H$_{\text{Ar}}$), 7.27–7.48 (m, 4H, H$_{\text{Ar}}$), 7.79 (d, 1H, H$_{\text{Ar}}$, *J* 7.5 Hz), 8.71–8.75 (m, 1H, H$_{\text{Ar}}$), 10.30 (br. s, 1H, N*H*Et), 12.84 (s, 1H, NH). ^{13}C NMR, δ: 14.6, 36.6, 109.9, 114.5, 116.1, 118.7, 121.66, 121.75, 121.77, 123.1, 130.5, 131.4, 141.3, 141.8, 147.2, 155.8, 156.3. MS, *m/z* (%): 347 [M]$^+$ (76), 302 (12), 275 (11), 260 (7), 249 (81), 233 (16), 214 (6), 208 (52), 187 (100), 161 (20), 144 (12), 133 (12), 118 (19), 103 (10), 99 (12), 90 (18), 77 (8), 71 (35), 69 (12), 55 (11). Found (%): C, 65.61; H, 6.17; N, 28.29. Calc. for $C_{19}H_{21}N_7$ (%): C, 65.69; H, 6.09; N, 28.22.

‡ *Crystal data for compounds* **2b** *and* **3a**. X-ray diffraction analysis was performed on a Bruker Apex II diffractometer equipped with CCD-detector (MoKα irradiation, graphite monochromator, ω-scanning). Monocrystals of **2b** and **3a**·MeCN were obtained by crystallization from MeCN.

A colorless prismatic crystal with the size of 0.10 × 0.05 × 0.05 mm was used for compound **2b** ($C_{19}H_{21}N_8$, M = 347.43). The crystal is rhombic at 296(2) K; space group is *Pbca*; unit cell parameters: a = 10.796(11), b = 16.203(16) and c = 20.51(2) Å, Z = 8, d_{calc} = 1.286 g cm^{-3}, μ = 0.082. 27038 reflections were collected in the interval of 1.99 < θ < 26.73° angles, 3810 of them were independent (R_{int} = 0.107), including 1900 reflections with $I > 2\sigma(I)$. The correction for absorption ($T_{\text{min}}/T_{\text{max}}$ = = 0.992/0.996) was performed.[9] Final refinement parameters: R_1 = 0.058, wR_2 = 0.143 [according to reflections with $I > 2\sigma(I)$], R_1 = 0.133, wR_2 = = 0.187 with the Q-factor S of 1.01. Maximum/minimum peaks of remaining electron density are 0.269/–0.261 eÅ^{-3}.

The colorless crystal with the size 0.32 × 0.14 × 0.12 mm was used for compound **3a**·MeCN ($C_{19}H_{20}N_8$, M = 360.43). The crystal is triclinic at 120(2) K; space group is $P\bar{1}$; unit cell parameters: a = 6.9782(7), b = = 10.8303(11) and c = 12.2571(12) Å, α = 87.6230(10)°, β = 76.8790(10)°, γ = 88.2620(10)°, Z = 2, d_{calc} = 1.328 g cm^{-3}, μ = 0.086. 8239 reflections were collected in the interval of 3.00 < θ < 26.86° angles, 3788 of them were independent (R_{int} = 0.038), including 2842 reflections with $I > 2\sigma(I)$. The correction for absorption was not performed. Final refinement parameters: R_1 = 0.069, wR_2 = 0.195 [according to reflections with $I > 2\sigma(I)$], R_1 = 0.089, wR_2 = 0.208 with the Q-factor S of 1.00. Maximum/minimum peaks of remaining electron density are 0.401/–0.311 eÅ^{-3}.

Structures **2b** and **3a**·MeCN were determined by the direct method and refined by the full matrix least-square method in anisotropic approximation for non-hydrogen atoms by F^2_{hkl}. Hydrogen atoms were placed into geometrically calculated locations and refined by the riding model. All calculations were performed using SHELX program complex.[10]

CCDC 1405703 and 1405704 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

its free C-anion is greatly weakened. At the same time, as it follows from the character of localized transition states, the isomerization of these structures represents the monomolecular process with activation barrier $\Delta G^{\neq}$ of 2.1 kcal mol^{-1} for C-anion **5** and 25 kcal mol^{-1} for magnesium bromide **4**.

In the next reaction step N-anion **6** and its *N*-magnesium bromide are decyanized by the excessive BuMgBr and are transformed into highly nucleophilic N-anions of 2-alkylaminobenzimidazoles **7**, analogously to other cyanamidohetarenes.[4] The addition of N-anions **7** to the $C\equiv N$ bond of the unreacted cyanamides **6** gives tri-N-anions of symmetrical 1,3-dibenzimidazolyl guanidines **8**.

The most interesting stages of the domino process are two tandem hetarylotropic rearrangements which occur in the end. The first one represents a 1,3-sigmatropic migration of the benzimidazol-2-yl substituent of compound **8** between sp^3 and sp^2 guanidine nitrogen atoms, which leads to the unsymmetrical structures **10**, precursors of dibenzimidazolyl guanidines **2**. This transformation is similar to the 1,3-arylotropic rearrangement of 2-arylamino-1,3-diazepines[5] and apparently also proceeds through the diazetic transition state of type **9**.

The second rearrangement of intermediate **10** affords guanidines **3** and refers to the 1,5-sigmatropic type. In this case the deprotonated benzimidazole group binded to the guanidine nitrogen sp^3-atom migrates to the nitrogen atom in the ring of the second benzimidazole fragment. This process is initiated by the intramolecular N-nucleophilic attack with the formation of hexatomic cyclic transition state **11**, which allows the simultaneous cleavage and formation of C–N σ-bonds to occur.

In conclusion, the described transformation makes it possible to access fairly complicated unusual guanidines bearing two benzimidazole substituents. The compound obtained can be of interest due to the potent pharmacological activity[6,7] and hetarylguanidines complexation abilities.[8]

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