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An interesting recyclization in the course of reduction of 1-(2-nitro-4-R-phenyl)-1*H*-benzimidazoles with tin(II) chloride

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Reduction of 1-(2-nitro-4-R-phenyl)-1*H*-benzimidazoles with tin(II) chloride in an acidic water–alcohol medium is accompanied by unusual recyclization of 1-(2-amino-4-R-phenyl)-1*H*-benzimidazoles formed at the first stage into isomeric 1-(2-aminophenyl)-5-R-1*H*-benzimidazoles.

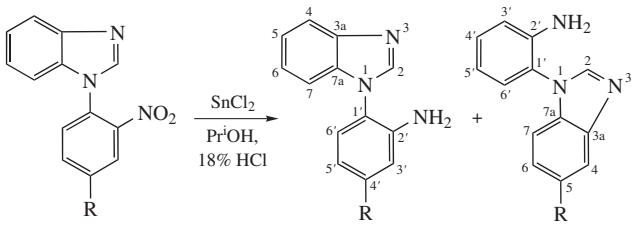
Reduction of nitroaromatic compounds is often accompanied by various alternative reactions, such as condensation to give azo and azoxy compounds,[1] different types of rearrangements,[2] reductive cyclization,[3] *etc*. These reactions give various products whose structures depend on the synthesis conditions.

Herein, we report that reduction of 1-(2-nitro-4-trifluoromethylphenyl)-1*H*-benzimidazole **1a** with $SnCl_2$ in an acidic water–alcohol medium affords two products which were separated by fractional extraction in hexane. The ^{1}H NMR spectra of these compounds contained proton signals shaped as narrow singlets of the imidazole ring and wide singlets of the amino group, at δ 5.58 (NH_2), 8.49 (H^2) for one of the compounds and at δ 5.58 (NH_2), 8.34 (H^2) for the other one.† Both products had the same *m*/*z* values, $[M]^+$ 277.

The ^{13}C NMR spectra of the compounds contain signals of 14 carbon atoms. Both spectra were found to manifest carbon atoms bound to three fluorine atoms, as suggested by the signal as a quartet at δ 124.53 (J_{CF} 271.64 Hz) and 125.01 (J_{CF} 271.64 Hz). The occurrence of a far spin–spin coupling constant of F atom with a carbon atom bound to the CF_3 group results in splitting of the signal from this atom, again to give a quartet. The low-intensity signals at δ 134.10, 143.78 for one compound and at δ 136.40, 142.82 for the other one belong to the node carbon atoms.

The observed spectral characteristics allowed us to assume that reduction of compound **1a** involves the formation of two isomeric 1-substituted benzimidazoles, namely, 1-(2-amino-4-trifluoromethylphenyl)-1*H*-benzimidazole **2a** and 1-(2-aminophenyl)-5-trifluoromethyl-1*H*-benzimidazole **3a** (Scheme 1).

To prove their structures, we performed full assignment of signals in the ^{13}C and ^{1}H NMR spectra using 2D spectroscopy: {^{1}H-^{1}H}NOESY, {^{1}H-^{13}C}HNBC and {^{1}H-^{13}C}HSQC. Correla-



1a–d **2a–d** **3a–d**

a R = CF_3 **c** R = CO_2Me
b R = CN **d** R = CO_2Et

Scheme 1

† *Compounds* **2a–d** *and* **3a–d** *(general procedure)*. A solution of $SnCl_2$ (0.0225 mol) in 18% HCl (25 ml) was added to a solution of compound **1a–d** (0.005 mol) in isopropanol (25 ml) at 60 °C. After 1 h the mixture was treated with 25% aqueous ammonia to pH 7–8 and extracted with chloroform (200 ml, several portions). The chloroform was distilled off to give a mixture of compounds **2** and **3**, which was separated by fractional extraction in hexane.

*1-(2-Amino-4-trifluoromethylphenyl)-1*H*-benzimidazole* **2a**: yield 64%, mp 204–207 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 5.58 (s, 2H, NH_2), 6.99 (dd, 1H, $H^{5'}$, *J* 1.6 Hz, *J* 8.2 Hz), 7.19 (dd, 1H, H^7, *J* 2.1 Hz, *J* 7.8 Hz), 7.28 (m, 3H, H^5, H^6, $H^{3'}$), 7.35 (d, 1H, $H^{6'}$, *J* 8.1 Hz), 7.79 (dd, 1 H, H^4, *J* 2.2 Hz, *J* 7.7 Hz), 8.34 (s, 1H, H^2). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 111.22 (C^7), 112.42, 112.45 ($C^{5'}$), 112.65, 112.69 ($C^{3'}$), 120.15 (C^4), 122.49 (C^5), 123.35 ($C^{1'}$), 123.47 (C^6), 124.53 (CF_3, J_{CF} 271.64 Hz), 129.54 ($C^{6'}$), 130.55 ($C^{4'}$, *J* 31.44 Hz), 134.10 (C^{7a}), 143.78 (C^{3a}), 144.23 (C^2), 145.67 ($C^{2'}$). MS, *m*/*z* (%): 277 $[M]^+$ (100), 256 (8), 249 (11), 207 (8), 186 (9), 113 (5), 100 (7), 90 (8), 77 (11), 63 (14), 50 (12), 44 (8), 39 (10), 42 (35). Found (%): C, 60.61; H, 3.58; N, 15.19. Calc. for $C_{14}H_{10}N_3F_3$ (%): C, 60.65; H, 3.61; N, 15.16.

*1-(2-Amino-4-cyanophenyl)-1*H*-benzimidazole* **2b**: yield 61%, mp 186–190 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 5.58 (s, 2H, NH_2), 7.08 (dd, 1H, $H^{5'}$, *J* 1.9 Hz), 7.18 (dd, 1H, H^7, *J* 2.2 Hz, *J* 8.0 Hz), 7.28 (m, 3H, H^5, H^6, $H^{3'}$), 7.34 (d, 1H, $H^{6'}$, *J* 8.0 Hz), 7.77 (dd, 1H, H^4, *J* 2.3 Hz, *J* 7.9 Hz), 8.32 (s, 1H, H^2). MS, *m*/*z* (%): 234 $[M]^+$ (100), 219 (6), 206 (17), 194 (5), 179 (8), 152 (5), 143 (8), 126 (5), 117 (6), 103 (8), 90 (16), 76 (13), 63 (22), 50 (13), 39 (15). Found (%): C, 71.73; H, 4.21; N, 23.99. Calc. for $C_{14}H_{10}N_4$ (%): C, 71.79; H, 4.27; N, 23.93.

*1-(2-Amino-4-methoxycarbonylphenyl)-1*H*-benzimidazole* **2c**: yield 48%, mp 230–234 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.87 (s, 3H, Me), 5.39 (s, 2H, NH_2), 7.17 (dd, 1H, H^7, *J* 2.1 Hz, *J* 8.0 Hz), 7.25–7.29 (m, 4H, H^5, H^6, $H^{5'}$, $H^{6'}$), 7.59 (t, 1H, $H^{3'}$, *J* 7.0 Hz), 7.77 (dd, 1H, H^4, *J* 2.1 Hz, *J* 7.8 Hz), 8.32 (s, 1H, H^2). MS, *m*/*z* (%): 267 $[M]^+$ (100), 236 (18), 208 (29), 191 (6), 181 (16), 154 (8), 145 (8), 127 (7), 117 (27), 103 (21), 90 (30), 77 (33), 63 (28), 52 (28), 39 (18). Found (%): C, 67.39; H, 4.82; N, 15.77. Calc. for $C_{15}H_{13}N_3O_2$ (%): C, 67.42; H, 4.87; N, 15.73.

*1-(2-Amino-4-ethoxycarbonylphenyl)-1*H*-benzimidazole* **2d**: yield 45%, mp 173–174 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.34 (t, 3H, Me, *J* 7.4 Hz), 4.33 (m, 2H, OCH_2), 5.36 (s, 2H, NH_2), 7.18 (dd, 1H, H^7, *J* 1.6 Hz, *J* 8.1 Hz), 7.25–7.29 (m, 4H, H^5, H^6, $H^{5'}$, $H^{6'}$), 7.59 (d, 1H, $H^{3'}$, *J* 1.6 Hz), 7.76 (dd, 1H, H^4, *J* 2.4 Hz, *J* 7.5 Hz), 8.31 (s, 1H, H^2). MS, *m*/*z* (%): 281 $[M]^+$ (100), 267 (5), 253 (30), 236 (24), 208 (21), 191 (5), 181 (13), 154 (6), 145 (5), 127 (5), 118 (10), 103 (7), 90 (11), 77 (14), 63 (10), 52 (10), 39 (6). Found (%): C, 68.31; H, 5.29; N, 15.01. Calc. for $C_{16}H_{15}N_3O_2$ (%): C, 68.33; H, 5.34; N, 14.95.

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tions were performed using one pair of compounds as an example. In this way, the location of the amino group in structures **2a** and **3a** was confirmed unambiguously. For compound **2a**, cross-peaks were observed corresponding to coupling of amino group protons with the H^2 proton of the imidazole ring (δ 8.34, s) and the $H^{3'}$ proton of the benzene ring being a doublet (δ 7.28, J 1.6 Hz). This suggests that the NH_2 group is located at the *ortho*-position with respect to the benzimidazole moiety and at the *meta*-position with respect to the CF_3 group. The two-dimensional {^{1}H-^{1}H} NOESY spectrum of isomer **3a** contains correlation peaks between the protons of the primary aromatic amine and the H^2 (δ 8.49, s) and $H^{3'}$ protons (δ 6.96, dd, J 1.2 Hz, J 8.1 Hz). Such correlations are only possible if the amino group is present in the *o*-phenylene moiety of compound **3**. The expected correlations were observed for the other spatially proximate protons.

{^{1}H-^{13}C}HNBC and {^{1}H-^{13}C}HSQC data also confirmed that the compounds obtained had isomeric *N*-(2-aminophenyl)benzimidazole structures.

Similar results were obtained in the reduction of other 1-(2-nitro-4-R-phenyl)-1*H*-benzimidazoles **1b–d**. In all the cases, the reaction mixture contained both amino products **2b–d** and **3b–d**, where compound **2** predominated. Formation of products **3** was probably due to attack on 2-position of the benzimidazole system by the amino group formed upon the reduction, to produce a new C–N bond. Subsequent opening of the already existing imidazole ring resulted in compound **3**.

In order to check this assumption, we heated the target compound **2a** under the reaction conditions (60 °C and an acidic aqueous–organic medium, namely a mixture of 25 ml of 18% HCl and 25 ml of Pr^{i}OH) in the absence of the reducing agent, and obtained both isomers **2a** and **3a** in approximately the same ratio as that observed in the main experiment. This fact suggests that isomerization recyclization involves the amino group of compound **2**.

To conclude, reduction of 1-(2-nitro-4-R-phenyl)-1*H*-benzimidazoles with tin(II) chloride in an acidic water–alcohol medium results not only in the formation of 1-(2-amino-4-R-phenyl)-1*H*-benzimidazoles but also in the isomerization of the latter to 1-(2-aminophenyl)-5-R-1*H*-benzimidazoles.

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*1-(2-Aminophenyl)-5-trifluoromethyl-1*H*-benzimidazole* **3a**: yield 28%, mp 142–144 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 5.14 (s, 2H, NH_2), 6.71 (t, 1H, $H^{5'}$, J 8.1 Hz), 6.96 (dd, 1H, $H^{3'}$, J 1.2 Hz, J 8.1 Hz), 7.15 (dd, 1H, $H^{6'}$, J 1.2 Hz, J 8.1 Hz), 7.26 (t, 1H, $H^{4'}$, J 8.4 Hz), 7.34 (d, 1H, H^7, J 8.5 Hz), 7.59 (dd, 1H, H^6, J 1.4 Hz, J 8.5 Hz), 8.11 (d, 1H, H^4, J 1.2 Hz), 8.49 (s, 1H, H^2). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 111.95 (C^7), 116.19 ($C^{5'}$), 116.21 ($C^{3'}$), 116.95, 116.98 (C^4), 119.30 ($C^{2'}$), 119.47, 119.50 (C^6), 122.83 (C^5, J 31.44 Hz), 125.01 (CF_3, J 271.64 Hz), 128.02 ($C^{6'}$), 130.02 ($C^{4'}$), 136.40 (C^{7a}), 142.82 (C^{3a}), 144.60 ($C^{1'}$), 146.58 (C^2). MS, *m*/*z* (%): 277 $[M]^+$ (100), 258 (8), 249 (13), 237 (7), 207 (9), 181 (6), 154 (5), 138 (6), 125 (6), 118 (11), 107 (8), 102 (5), 90 (6), 80 (18), 75 (12), 65 (26), 52 (15), 44 (5), 39 (20), 32 (22). Found (%): C, 60.59; H, 3.57; N, 15.20. Calc. for $C_{14}H_{10}N_3F_3$ (%): C, 60.65; H, 3.61; N, 15.16.

*1-(2-Aminophenyl)-1*H*-benzimidazole-5-carbonitrile* **3b**: yield 26%, mp 207–209 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 5.12 (s, 2H, NH_2), 6.70 (t, 1H, $H^{5'}$, J 7.8 Hz), 6.94 (dd, 1H, $H^{3'}$, J 8.2 Hz, J 1.1 Hz), 7.14 (dd, 1H, $H^{6'}$, J 1.1 Hz, J 7.8 Hz), 7.25 (t, 1H, $H^{4'}$, J 8.1 Hz), 7.29 (d, 1H, H^7, J 8.5 Hz), 7.64 (dd, 1H, H^6, J 1.4 Hz, J 8.4 Hz), 8.31 (d, 1H, H^4, J 1.2 Hz), 8.52 (s, 1H, H^2). MS, *m*/*z* (%): 234 $[M]^+$ (100), 219 (5), 206 (16), 194 (5), 179 (6), 152 (5), 143 (4), 118 (5), 103 (5), 90 (8), 80 (12), 76 (6), 65 (19), 52 (13), 39 (18). Found (%): C, 71.75; H, 4.20; N, 23.97. Calc. for $C_{14}H_{10}N_4$ (%): C, 71.79; H, 4.27; N, 23.93.

*Methyl 1-(2-aminophenyl)-1*H*-benzimidazole-5-carboxylate* **3c**: yield 38%, mp 192–195 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.88 (s, 3H, Me), 5.10 (s, 2H, NH_2), 6.71 (t, 1H, $H^{5'}$, J 8.1 Hz), 6.94 (dd, 1H, $H^{3'}$, J 1.2 Hz, J 8.2 Hz), 7.14 (dd, 1H, $H^{6'}$, J 1.5 Hz, J 7.8 Hz), 7.23–7.27 (m, 1H, H^7, $H^{4'}$), 7.90 (dd, 1H, H^6, J 1.6 Hz, J 8.5 Hz), 8.34 (d, 1H, H^4, J 1.4 Hz), 8.43 (s, 1H, H^2). MS, *m*/*z* (%): 267 $[M]^+$ (100), 236 (78), 207 (18), 181 (21), 154 (6), 133 (4), 127 (5), 118 (33), 103 (9), 90 (18), 77 (20), 65 (18), 52 (9), 45 (5), 40 (20). Found (%): C, 67.37; H, 4.81; N, 15.78. Calc. for $C_{15}H_{13}N_3O_2$ (%): C, 67.42; H, 4.87; N, 15.73.

*Ethyl 1-(2-aminophenyl)-1*H*-benzimidazole-5-carboxylate* **3d**: yield 36%, mp 127–130 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.36 (t, 3H, H^3, J 7.4 Hz), 4.34 (m, 2H, OCH_2), 5.08 (s, 2H, NH_2), 6.70 (t, 1H, $H^{5'}$, J 7.5 Hz), 6.94 (dd, 1H, $H^{3'}$, J 1.4 Hz, J 8.0 Hz), 7.13 (dd, 1H, $H^{6'}$, J 7.8 Hz), 7.22–7.27 (m, 2H, H^7, $H^{4'}$), 7.90 (dd, 1H, H^6, J 1.3 Hz, J 8.5 Hz), 8.35 (d, 1H, H^4, J 1.6 Hz), 8.44 (s, 1H, H^2). MS, *m*/*z* (%): 281 $[M]^+$ (100), 266 (8), 253 (23), 236 (100), 208 (18), 181 (26), 154 (6), 126 (7), 118 (27), 103 (8), 90 (18), 77 (22), 65 (22), 52 (9), 45 (4), 40 (16). Found (%): C, 68.29; H, 5.31; N, 14.99. Calc. for $C_{16}H_{15}N_3O_2$ (%): C, 68.33; H, 5.34; N, 14.95.

References

1 (*a*) S. R. Sandler and W. Karo, *Organic Functional Group Preparation*, Academic Press, New York, 1986, vol. 11, p. 442; (*b*) F. A. Khan, J. Dash, Ch. Sudheer and R. K. Gupta, *Tetrahedron Lett.*, 2003, **44**, 7783.

2 (*a*) A. V. Vlaskina and V. P. Perevalov, *Chem. Heterocycl. Compd.*, 2004, **40**, 523 (*Khim. Geterotsikl. Soedin*., 2004, 620); (*b*) K. Polat, *Turk. J. Chem.*, 2003, **27**, 501; (*c*) D. S. Kopchuk, A. F. Khasanov, I. S. Kovalev, G. V. Zyryanov, V. L. Rusinov and O. N. Chupakhin, *Mendeleev Commun*., 2013, **23**, 209.

3 (*a*) R. S. Begunov, A. A. Sokolov and T. V. Shebunina, *Russ. J. Org. Chem*., 2013, **49**, 773 (*Zh. Org. Khim.*, 2013, **49**, 789); (*b*) D. Sawant, R. Kumar, P. R. Maulik and B. Kundu, *Org. Lett*., 2006, **8**, 1525; (*c*) M. J. Sandelier and P. DeShong, *Org. Lett*., 2007, **9**, 3209; (*d*) R.-G. Xing, Y.-N. Li, Q. Liu, Y.-F. Han, X. Wei, J. Li and B. Zhou, *Synthesis*, 2011, 2066; (*e*) A. A. Sokolov, M. A. Syroeshkin, R. S. Begunov, N. N. Rusakova and V. P. Gultyai, *Mendeleev Commun*., 2012, **22**, 312.

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