2-Aminobenzimidazole in three-component cyclization reactions with formaldehyde and primary amines

Kh. S. Shikhaliev, A. Yu. Potapov, and D. V. Kryl´skii*

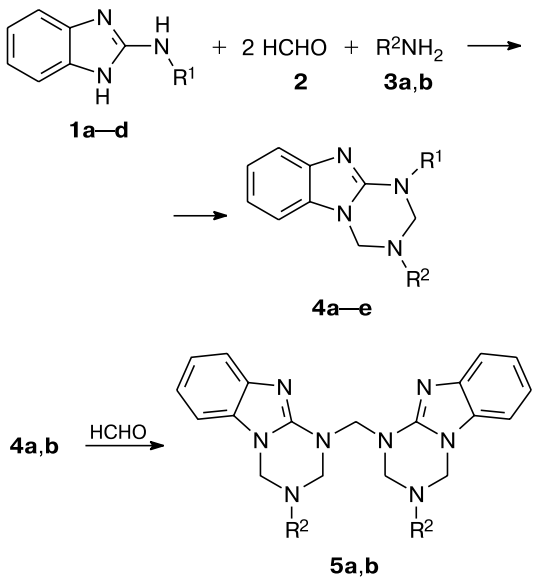
Voronezh State University,
1 Universitetskaya pl., 394006 Voronezh, Russian Federation.
E-mail: chocd261@chem.vsu.ru

Three-component condensation of 2-aminobenzimidazole and its *N*-substituted derivatives with formaldehyde and primary amines gave 1,2,3,4-tetrahydro[1,3,5]triazino[1,2-*a*]benzimidazoles.

Key words: 2-aminobenzimidazole, hetarylguanidines, 1,3,5-tetrahydrotriazines, formaldehyde, 1,2,3,4-tetrahydro[1,3,5]triazino[1,2-*a*]benzimidazoles, three-component condensation.

Three-component condensation involving 2-aminobenzimidazole (**1a**) and carbonyl compounds opens up broad prospects for the synthesis of various nitrogen-containing heterocycles. Earlier,[1] we have shown that reactions of hetarylguanidines with formaldehyde (**2**) and primary amines **3** yield 1,3,5-hexahydrotriazines. Here, this reaction was successfully applied to 2-aminobenzimidazole (**1a**) and its 2-arylamino (**1b**) and 2-alkylamino derivatives (**1c,d**).

Scheme 1



R^1 = H (**1a**, **4a**,**b**); Ph (**1b**, **4c**); $PhCH_2$ (**1c**, **4d**); $Ph(CH_2)_2$ (**1d**, **4e**); R^2 = $PhCH_2$ (**3a**, **4a**,**c**—**e**, **5a**); $Ph(CH_2)_2$ (**3b**—**5b**)

Under optimized reaction conditions (molar ratio 1 : 2.1 : 1, dioxane or propan-2-ol, reflux), R^1,R^2-1,2,3,4-tetrahydro[1,3,5]triazino[1,2-*a*]benzimidazoles **4a**—**e** were obtained in 60—80% yields (Scheme 1).

The reaction proceeded most smoothly for $R^1 = Ph(CH_2)_n$ (n = 1, 2). In the case of *N*-unsubstituted aminobenzimidazole (**1a**), two molecules of **4a,b** become linked by a methylene bridge (formaldehyde fragment) through the N(1) atoms of the tetrahydrotriazine ring to give by-products **5a,b**. In contrast to the ^{1}H NMR spectra of compounds **4a,b**, the spectra of compounds **5a,b** show a singlet for the methylene protons (δ 5.05—5.06), instead of a singlet due to the proton of the endocyclic amino group (δ 5.35). As expected, the use of an excess of formalin (molar ratio of the reagents was 1 : 3 : 1) increased the yields of products **5a,b** to 72—77%. The structures of the compounds obtained were confirmed by ^{1}H NMR spectroscopy, mass spectrometry, and elemental analysis.

Experimental

The course of the reactions was monitored and the purity of the compounds obtained was checked by TLC on Silufol UV-254 plates with $CHCl_3$—AcOEt (1 : 2) as an eluent. ^{1}H NMR spectra were recorded on a Bruker AC-300 instrument (300 MHz) in DMSO-d_6 with Me_4Si as the internal standard. Mass spectra were recorded on a LKB 9000 instrument (EI, 70 eV).

Starting 2-alkylaminobenzimidazoles **1a,c,d** were prepared according to a known procedure;[2] 2-phenylaminobenzimidazole (**1b**) was prepared as described in Ref. 3.

1,2,3,4-Tetrahydro[1,3,5]triazino[1,2-*a*]benzimidazoles 4a—e (general procedure). A mixture of 2-aminobenzimidazole **1a**—**d** (0.01 mol), 40% formalin **2** (0.021 mol), and amine **3a,b** (0.01 mol) was refluxed in dioxane or isopropyl alcohol (5 mL)

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for 30 min. The precipitate of compound **4a**—**e** that formed was filtered off and recrystallized from dioxane—DMF.

3-Benzyl-1,2,3,4-tetrahydro[1,3,5]triazino[1,2-*a*]benzimidazole (4a). The yield was 65%, m.p. 122—124 °C. Found (%): C, 72.83; H, 6.13; N, 21.12. $C_{16}H_{16}N_4$. Calculated (%): C, 72.70; H, 6.10; N, 21.20. ^{1}H NMR, δ: 2.85 (s, 2 H, CH_2Ph); 4.86 (s, 2 H, $C(2)H_2$); 4.95 (s, 2 H, $C(4)H_2$); 5.35 (s, 1 H, NH); 6.80—7.35 (m, 9 H, H arom.). MS, *m/z*: 264 $[M]^+$.

3-Phenethyl-1,2,3,4-tetrahydro[1,3,5]triazino[1,2-*a*]benzimidazole (4b). The yield was 60%, m.p. 128—130 °C. Found (%): C, 73.14; H, 6.50; N, 20.22. $C_{17}H_{18}N_4$. Calculated (%): C, 73.35; H, 6.52; N, 20.13. ^{1}H NMR, δ: 2.65 (t, 2 H, $CH_2C\underline{H}_2Ph$, J = 7.0 Hz); 2.78 (t, 2 H, $C\underline{H}_2CH_2Ph$, J = 7.0 Hz); 4.86 (s, 2 H, $C(2)H_2$); 4.95 (s, 2 H, $C(4)H_2$); 5.35 (s, 1 H, NH); 6.76—7.34 (m, 9 H, H arom.). MS, *m/z*: 278 $[M]^+$.

3-Benzyl-1-phenyl-1,2,3,4-tetrahydro[1,3,5]triazino[1,2-*a*]benzimidazole (4c). The yield was 71%, m.p. 131—133 °C. Found (%): C, 77.73; H, 5.88; N, 16.32. $C_{22}H_{20}N_4$. Calculated (%): C, 77.62; H, 5.92; N, 16.46. ^{1}H NMR, δ: 3.75 (s, 2 H, CH_2Ph); 4.88 (s, 2 H, $C(2)H_2$); 5.15 (s, 2 H, $C(4)H_2$); 6.85—7.38 (m, 14 H, H arom.). MS, *m/z*: 340 $[M]^+$.

1,3-Dibenzyl-1,2,3,4-tetrahydro[1,3,5]triazino[1,2-*a*]benzimidazole (4d). The yield was 75%, m.p. 104—106 °C. Found (%): C, 78.14; H, 6.16; N, 15.95. $C_{23}H_{22}N_4$. Calculated (%): C, 77.94; H, 6.26; N, 15.81. ^{1}H NMR, δ: 3.70, 4.25 (both s, 2 H each, CH_2Ph); 4.75 (s, 2 H, $C(2)H_2$); 5.10 (s, 2 H, $C(4)H_2$); 6.90—7.39 (m, 14 H, H arom.). MS, *m/z*: 354 $[M]^+$.

3-Benzyl-1-phenethyl-1,2,3,4-tetrahydro[1,3,5]triazino[1,2-*a*]benzimidazole (4e). The yield was 80%, m.p. 119—121 °C. Found (%): C, 78.39; H, 6.43; N, 15.12. $C_{24}H_{24}N_4$. Calculated (%): C, 78.23; H, 6.57; N, 15.20. ^{1}H NMR, δ: 2.91 (t, 2 H, $CH_2C\underline{H}_2Ph$, J = 7.0 Hz); 3.67 (s, 2 H, CH_2Ph); 4.12 (t, 2 H, $C\underline{H}_2CH_2Ph$, J = 7.0 Hz); 4.83 (s, 2 H, $C(2)H_2$); 4.94 (s, 2 H, $C(4)H_2$); 6.85—7.35 (m, 14 H, H arom.). MS, *m/z*: 368 $[M]^+$.

1-(1,2,3,4-Tetrahydro[1,3,5]triazino[1,2-*a*]benzimidazol-3-ylmethyl)-1,2,3,4-tetrahydro[1,3,5]triazino[1,2-*a*]benzimidazoles 5a,b (general procedure). A mixture of 2-aminobenzimidazole (**1a**) (0.01 mol), 40% formalin **2** (0.03 mol), and amine **3a,b** (0.01 mol) was refluxed in dioxane (5 mL) for 30 min. The precipitate of compound **5a,b** that formed was filtered off and recrystallized from DMF.

3-Benzyl-1-(3-benzyl-1,2,3,4-tetrahydro[1,3,5]triazino[1,2-*a*]benzimidazol-1-ylmethyl)-1,2,3,4-tetrahydro[1,3,5]triazino[1,2-*a*]benzimidazole (5a). The yield was 77%, m.p. >300 °C. Found (%): C, 73.39; H, 6.11; N, 20.83. $C_{34}H_{32}N_8$. Calculated (%): C, 73.31; H, 5.97; N, 20.72. ^{1}H NMR, δ: 3.72 (s, 4 H, 2 CH_2Ph); 5.06 (s, 2 H, NCH_2N); 4.90 (s, 4 H, 2 $C(2)H_2$); 4.98 (s, 4 H, 2 $C(4)H_2$); 6.85—7.38 (m, 18 H, H arom.). MS, *m/z*: 540 $[M]^+$.

3-Phenethyl-1-(3-phenethyl-1,2,3,4-tetrahydro[1,3,5]triazino[1,2-*a*]benzimidazol-1-ylmethyl)-1,2,3,4-tetrahydro-[1,3,5]triazino[1,2-*a*]benzimidazole (5b). The yield was 72%, m.p. >300 °C. Found (%): C, 73.87; H, 6.35; N, 19.63. $C_{34}H_{32}N_8$. Calculated (%): C, 73.92; H, 6.38; N, 19.70. ^{1}H NMR, δ: 2.92 (t, 4 H, 2 $CH_2C\underline{H}_2Ph$, J = 7.0 Hz); 3.70 (t, 4 H, 2 $C\underline{H}_2CH_2Ph$, J = 7.0 Hz); 5.05 (s, 2 H, NCH_2N); 4.87 (s, 4 H, 2 $C(2)H_2$); 4.93 (s, 4 H, 2 $C(4)H_2$); 6.83—7.38 (m, 18 H, H arom.). MS, *m/z*: 568 $[M]^+$.

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