INTERACTION OF 1,2-DIAMINOBENZIMIDAZOLE WITH N-ARYLIMIDES

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Substituted 10-amino-2,3,4,10-tetrahydro-4-oxo-N-arylpyrimido[1,2-*a*]benzimidazole-2-carboxamides are formed by condensation of 1,2-diaminobenzimidazole with N-arylmaleimides in isopropyl alcohol in the presence of catalytic amount of acetic acid.

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Introduction

Aminobenzimidazole and its derivatives increasingly attract scientists' attention due to theirs multiscale biological activities such as antibacterial, antifungal, antihistaminic, cytostatic and hypotensive actions. Particular attention is paid to their use as medicines preparation to treat HIV infections.[1-2]

Benzimidazolepyrimidines[2] have special interest among the benzimidazole derivatives and a great number of works dedicated to prepare compounds consist this ring system starting from 2-aminobenzimidazole.[3] However, there is no data about synthesis of imidazopyrimidines from 1,2-diaminobenzimidazole as starting material.

In order to continue our studies on building of aza-heterocyclic compounds with imidazole moieties, the aim of present work is a study on the synthesis of substituted tetrahydrobenzimidazolepyrimidines in the reaction between 1,2-diaminobenzimidazole and N-maleimides as potential reactants to form various penta- and hexaatomic cycles in nucleophilic attacks.[4]

Experimental Part

General

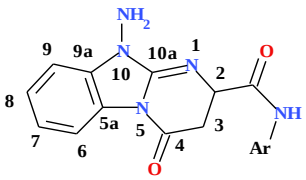
NMR Spectra of all new compounds were registered on Bruker DRX, 500 ^{1}H spectrometer at 500 MHz and ^{13}C at 125.76 MHz in DMSO-d_6, internal standard was TMS. Mass-spectra recorder on FINNIGAN MAT.INCOS 50 spectrometer (EI ionization, 70 eV). Elemental analyses was performed on Carlo Erba NA 1500.

Melting points was determined on Stuart SMP30. Identity of the reagents and synthesized compounds, quality of reaction mass were controlled out by TLC on Merck TLC Silica gel 60 F_{254} plate (eluents: methanol, chloroform and theirs mixture in the different ratios). Chromatograms were developed in the UV light and with iodine vapour.

1,2-Diaminobenzimidazole **1** was synthesized according to reported method[5]. The compounds **2a-e** were purchased from Acros Organics.

Preparation of 10-amino-2,3,4,10-tetrahydro-4-oxo-N-arylpyrimido[1,2-*a*]benzimidazole-2-carboxamides 5a-e.

A mixture of 0.74 g (5 mmol) of diaminobenzimidazole **1**, 5 mmol of N-arylmaleimide **2a-e**, 5 ml of isopropyl alcohol and 1-2 drops of acetic acid were heated under reflux for 1-2 h in a flax. The precipitate formed was filtered and recrystallized from the mixture of i-PrOH–DMFA 2:1 mixture. White powder compounds were obtained.



10-amino-2,3,4,10-tetrahydro-4-oxo-N-phenylpyrimido[1,2-*a*]benzimidazole-2-carboxamides, 5a.

Yield: 85 %. M.p. 214-215 ^{o}C. NMP ^{1}H (DMSO-d6): δ = 2.76 (dd, *J*=1.9, *J*=14.5 ,1H, H-3); 3.17 (dd, *J*=8.8, *J*=9.7, 1H, H-3); 5.34 (dd, *J*=1.8, *J*=6.9, 1H, H-2); 5.69 (s, 2H, NH_2); 7.03 (t, *J*=7.4, 1H, H-Ar); 7.18 (t, *J*=7.4, 1H, H-Bz); 7.23 (t, *J*=7.5, 1H, H-Bz); 7.31 (qu, *J*=7.8, 3H, H-Ar); 7.38 (d, *J*=7.7, 1H, H-Ar); 7.57 (d, *J*=7.8, 2H, H-Bz); 10.49 (s, 1H, CONH). NMR ^{13}C (DMSO-d6): δ = 33.5 (C-3); 53.5 (C-2); 108.7, 109.3 (C-7 and C-8); 119.5 (C Ph); 122.4,

123.7 (C-6 and C-9); 124.0, 127.4, 128.9, 131.7 (C Ph); 138.4 (C-5a and C-9a); 155.1 (C-10a); 167.1 (NHCO); 173.3 (C-4). Mass-spectra, *m/z* (I_{rel}, %): 201 $[M-120]^+$. $C_{17}H_{15}N_5O_2$ Found, %: C 63.16; H 4.70; N 21.73. Calculatēd, %: C 63.54; H 4.71; N 21.79.

10-amino-2,3,4,10-tetrahydro-N-(2-methylphenyl)-4-oxopyrimido[1,2-*a*]benzimidazole-2-carboxamides (5b).

Yield: 90 %. M.p. 240-241 °C. NMR ^{1}H (DMSO-d6): δ = 2.06 (s, 3H, CH_3); 2.80 (dd, *J*=1.8, *J*=14.9, 1H, H-3); 3.18 (dd, *J*=8.7, *J*=7.6, 1H, H-3) 5.45 (dd, *J*=1.8, *J*=7.3, 1H, H-2); 5.69 (s, 2H, NH_2); 7.00 – 7.17 (m, 2H, H-Bz); 7.19 – 7.26 (m, 3H, H-Ar); 7.28 – 7.40 (m, 3H, H-Bz + H-Ar); 9.90 (s, 1H, CONH). NMR ^{13}C (DMSO-d6): δ = 17.8 (CH_3); 33.6 (C-3); 53.0 (C-4); 108.7, 109.3 (C-7 and C-8); 114.8, 117.9, 120.2 (C Ar); 122.3, 122.8 (C-6 and C-9); 125.4, 126.0, 130.5 (C Ar); 135.0, 135.4 (C-5a and C-9a); 155.3 (C-10a); 167.4 (NHCO); 173.3 (C-4). Mass-spectra, *m/z* (I_{rel}, %): 201 $[M-134]^+$. $C_{18}H_{17}N_5O_2$ Found, %: C 64.09; H 5.09; N 20.88. Calcd, %: C 64.47; H 5.11; N 20.84.

10-amino-2,3,4,10-tetrahydro-N-(4-isopropylphenyl)-4-oxopyrimido[1,2-*a*]benzimidazole-2-carboxamide (5c).

Yeild 87 %. M.p. 245-246 °C. NMR ^{1}H (DMSO-d6): δ = 1.16 (d, *J*=6.9, 6H, 2CH_3-*i*Pr); 2.76 (dd, *J*=1.9, *J*=14.4, 1H, H-3); 2.83 (pent, *J*=6.8, 1H, CH-*i*Pr); 3.17 (dd, *J*=8.6, *J*=7.7, 1H, H-3); 5.34 (dd, *J*=2.2, *J*=6.6, 1H, H-2); 5.72 (s, 2H, NH_2); 7.15 – 7.20 (m, 2H, H-Bz); 7.23 (t, *J*=7.5, 2H, H-Ar); 7.29 (d, *J*=7.7, 1H, H-Ar); 7.39 (d, *J*=7.7, 1H, H-Ar); 7.48 (d, *J*=8.5, 2H, H-Bz); 10.45 (s, 1H, CONH). NMR ^{13}C (DMSO-d6): δ = 23.8, 23.9 (2CH_3-*i*Pr); 32.9 (CH-*i*Pr); 33.5 (C-3); 53.5 (C-2); 108.7, 109.3 (C-7 and C-8); 119.5 (C Ar); 122.3, 122.8 (C-6 and C-9); 126.6, 126.8, 127.4 (C Ar); 136.1 (C-5a and C-9a); 144.2 (C Ar); 155.1 (C-10a); 166.9 (NHCO); 173.3 (C-4). Mass-spectra, *m/z* (I_{rel}, %): 201 $[M-162]^+$. $C_{20}H_{21}N_5O_2$ Found, %: C 65.71; H 5.80; N 19.23. Calcd, %: C 66.10; H 5.82; N 19.27.

10-amino-2,3,4,10-tetrahydro-N-(2,4-dimethylphenyl)-4-oxopyrimido[1,2-*a*]benzimidazole-2-carboxamide (5d).

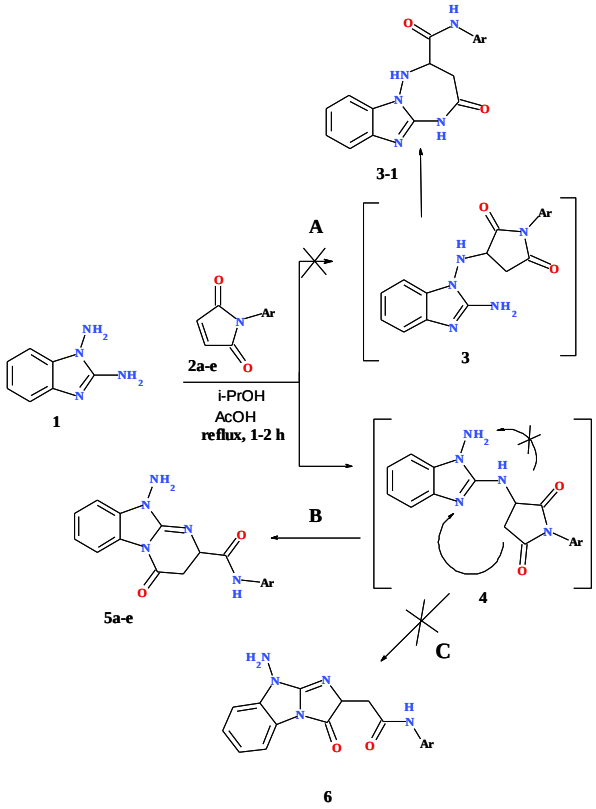
Yield 92 %. M.p. 238-239 °C. NMR ^{1}H (DMSO-d6): δ = 2.11 (s, 6H, 2CH_3); 2.77 (dd, *J*=1.9, *J*=14.4, 1H, H-3); 3.17 (dd, *J*=8.6, *J*=7.6, 1H, H-3); 5.41 (dd, *J*=2.0, *J*=6.8, 1H, H-2); 5.68 (s, 2H, NH_2); 6.95 (d, *J*=7.9, 1H, H-Ar); 7.02 (s, 1H, H-Ar); 7.14 (d, *J*=8.0, 1H, H-Ar); 7.19 – 7.25 (m, 2H, H-Bz); 7.32 (dd, *J*=1.7, *J*=5.0, 1H, H-Bz); 7.37 (dd, *J*=2.2, *J*=5.0, 1H, H-Bz); 9.80 (s, 1H, CONH). ЯМР ^{13}C (DMSO-d6): δ = 17.7, 20.6 (CH_3); 33.6 (C-3); 53.0 (C-2); 108.6, 109.3, 122.3, 122.6 (C-7, C-8, C-6, C-9); 125.4, 126.6, 127.4, 131.0, 131.7, 132.4 (C Ar); 135.2 (C-5a и C-9a); 155.1 (C-10a); 167.3 (NHCO); 173.3 (C-4). Mass-spectra, *m/z* (I_{rel}, %): 201 $[M-148]^+$. $C_{19}H_{19}N_5O_2$ Found, %: C 64.93; H 5.46; N 20.01. Calcd, %: C 65.32; H 5.48; N 20.04.

10-amino-2,3,4,10-tetrahydro-N-(5-chlorine-methylphenyl)-4-oxo-pyrimido[1,2-*a*]benzimidazole-2-carboxamide (5e).

Yield: 83 %. M.p. 228-229 °C. NMR ^{1}H (DMSO-d6): δ = 2.18 (s, 3H, CH_3); 2.81 (dd, *J*=1.8, *J*=14.6, 1H, H-3); 3.19 (dd, *J*=8.8, *J*=7.5, 1H, H-3); 5.48 (dd, *J*=2.0, *J*=6.9, 1H, H-2); 5.54 (s, 2H, NH_2); 7.09 (dd, *J*=1.4, *J*=6.1, 1H, H-Ar); 7.15 – 7.26 (m, 3H, H-Bz + H-Ar); 7.33 (dd, *J*=1.4, *J*=7.3, 1H, H-Ar); 7.37 – 7.47 (m, 2H, H-Bz); 9.98 (s, 1H, CONH). NMR ^{13}C (DMSO-d6): δ = 17.3 (CH_3); 33.5 (C-3); 53.0 (C-2); 108.7, 109.4 (C-7 and C-8); 117.9, 120.2 (C Ar); 122.4, 122.7 (C-6 and C-9); 124.4, 125.5, 130.0 (C Ar); 134.9, 135.0 (C-5a and C-9a); 136.8 (C Ar); 155.1 (C-10a); 167.7 (NHCO); 173.3 (C-4). Mass-spectra, *m/z* (I_{rel}, %): 201 $[M-168.5]^+$. $C_{18}H_{16}ClN_5O_2$ Found, %: C 58.11; H 4.35; N 18.91. Calcd, %: C 58.46; H 4.36; N 18.94.

RESULTS AND DISCUSSIONS

Polynucleophilic character of 1,2-diaminobenzimidazole (1,3-N-C-N[6a-b] and 1,4-N-C-N-N[6c-d]) ensures various types of interactions with electrophilic reagents. There are two possible reaction ways with maleimides as it shown on the Scheme 1.



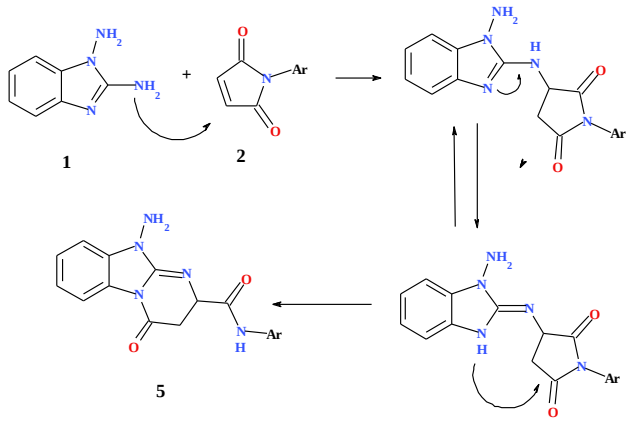
Scheme 1. Possible reaction routes in the interaction of 1,2-diaminobenzimidazole and N-arylmaleimides. **Ar:** Ph **(a);** 2-MePh **(b);** 4-*i*PrPh **(c);** 3, 4-diMePh **(d);** 2-Me-5-ClPh **(e)**

Heterocyclization of 1,2-diaminobenzimidazole **1** with N-arylmaleimides **2a-e** was performed in isopropyl alcohol under reflux for 1-2 h in the presence of catalytic amount of acetic acid. The reaction led to a white single product formation.

On the basis of NMR ^{1}H and ^{13}C spectra the products formed were assigned as 10-amino-2,3,4,10-tetrahydro-4-oxo-N-arylpirimido[1,2-*a*]benzimidazole-2-carboxamides (**5a-e**).

The all proton signals of aryl and CH_3 groups for the compounds **5** could be assigned in the NMR spectra of the isolated products. The proton signals of free NH_2 group linked to the imidazole ring was found at 5.69 ppm. The signals of methylene protons emerge as a doublet of doublet at 2.76-2.81 and 3.17-3.19 ppm (C-3) and the signals of amide protons are located in a stronger field (9.80-10.50 ppm). Based on the analysis of literature data[3] the methine proton of the hexaatomic cycle in structure **5** shows a doublet of doublet signal (C-2) at 5.34-5.48 ppm resonating with the protons of the methylene fragment (C-3)**.**

^{13}C NMR spectra of the compounds **5a-e** contain the characteristic signals of benzene moiety C-5a, C-6, C-7, C-8, C-9, C-9a and the signal of C10 at 108, 109, 122, 123, 135-138 ppm and at 155 ppm, respectively. Carbon atom signals of pyrimidine cycle are located at 33, 53 and 173 ppm, assigned to C-3, C-2 and C-4 atoms, respectively. Appearance of the singlet of NH_2 group (2H) in the 1H NMR spectra of reaction products unambiguously excludes the formation of heptaatomic rings **3-1** (reaction route A).

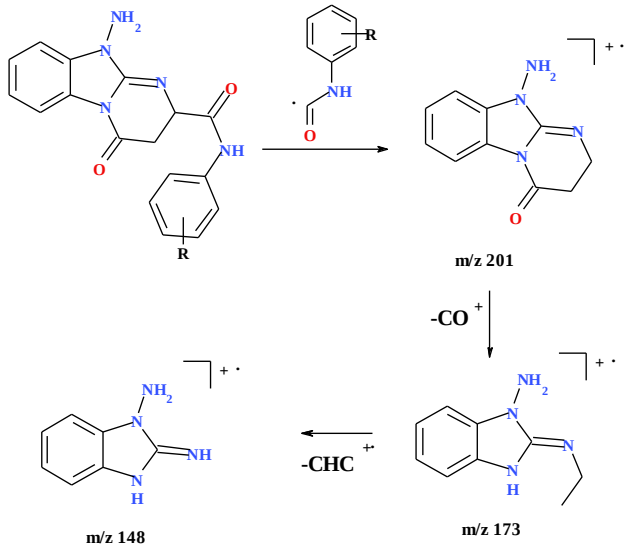


Scheme 2. A possible reaction mechanism leads to formation of compounds **5**

A possible reaction mechanism leads to formation of compounds **5** is assumed on the basis of work dedicated to interaction of N-arylmaleimides[3a] and maleic anhydride[3b] with aminoazoles (Scheme 2) when both five and six-membered ring systems can be formed depending on the cyclization conditions. Based on the polynucleophilic nature of 1,2-diaminobenzimidazole **(1),** the interaction with maleimides **(2a-e)** might be started with addition of the first or the second NH_2 group of diaminoimidazole to the double bound of aryl maleimide moiety with formation of intermediate products **3** or **4**, respectively. Since intermediate **3** would be cyclized to seven or six-membered rings without free NH_2 group based on the presence of NH_2 signals in NMR spectra of the products **5**, the exclusive formation of intrermediate **4** can be assumed.

Among the two possible route of intramolecular cyclization of the intermediate **4** the direction "B" leads the found tetrahydropyrimido[1,2-*a*]benzimidazoles **5**, whereas the path “C” would result dihydroimidazoles **6**.

In the mass spectra analysis of reaction products the molecular ion could not be fixed. For similar structures, it was noted forming fragments with m/z 201.[3,4] The probable fragmentation route is represented on the Scheme 3. It is assumed that on the first step there is a bond splitting with following elimination of arylamide’s moiety leading to relatively stable tetrahydrobenzimidazopyrimidine ion (m/z 201) and 1-amino-2-imino-benzimidazole-ion (m/z 148). This last one is subjected to further fragmentation.



Scheme 3. Fragmentation pathway of the compounds **5**.

Conclusions

Thus, determined new heterocyclization of 1,2-diaminobenzimidazole with N-arylmaliemides have completely proceeded regionselectively with formation of 10-amino-2,3,4,10-tetrahydro-4-oxo-N-arylpyrimido[1,2-a]-benzimidazole-4-oxo-2-carboxoamides.

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References

[1](a) Betti, L., Botta, M., Corelli, F., Floridi, M., Giannaccini, G., Maccari, L., ... & Corsano, S., *J. Med. Chem.*, **2002**, *45(17)*, 3603. (b) Lopez-Rodriguez, M. L., Benhamu, B., Morcillo,

M. J., Tejada, I., Avila, D., Marco, I., ... & Del Río, J., *Bioorg. Med. Chem*., **2004**, *12(19)*, 5181. (c) Borza, K. S., Gere, A., Kolok, S., Nagy, J., Fodor, L., Galgóczy, K., ... & Domány, G., *Bioorg. Med. Chem. Lett.*, **2006**, *16(17)*, 4638. (d) Beaulieu, C., Wang, Z., Denis, D., Greig, G., Lamontagne, S., O'Neill, G., ... & Wang, J., *Bioorg. Med. Chem. Lett.*, **2004**, *14(12)*, 3195. (e) Ayhan-Kilcigil, G., Kuş, C. T., Cobanb, T., Can-Ekeb, B., Iscanb, M., *J. Enzym. Inhib. Med. Chem*., **2004**, *19*; 129. (f) Kamal, A., Subba Rao, A. V., Lakshma Nayak, V., Subba Reddy, N. V., Konderu S., Ramakrishna, G., Mallika, A., *Org. Biomol. Chem.*, **2014,** *12*, 9864. (g) Romero, D. H., Torres Heredia, V. E., García-Barradas, O., López, M. E. M., Pavón, E. S., *J. Chem. Biochem.*, **2014**, *2(2)*, 45.

[2](a) Alper, S., Temiz-Arpaci, O., Aki-Sener, E., I. Yalcin, *Il Farmaco*, **2003**, *58(7)*, 497-507. (b) Gata, L., Perna, F., Figura, N., Ricci, C., Holton, J., D′Anna, L., Miglioli, M., D. Vaira, *J. Antimicrob. Chemother*. **2003**, *51*, 439. (c) Kucukbay, H., Durmaz, R., Orhan, E., S. Gunal, *Il Farmaco.* **2003**, 58, 431. (d) Kazimierczuk, Z., J.A. Upcroft, J.A., Upcroft, P., Gorska, A., Starosciak, B., A. Laudy, *Acta Biochim. Polon*., **2002**, *49*, I, 185. (e) Garuti, L., Roberti, M., C. Cermelli, *Bioorg. Medicinal Chem. Letter*, **1999**, *9*, 2525. (f) Akbay, A., Oren, I., Temiz-Arpaci, O., Aki-Sener, E., I. Yalcin, *Arzneim.-Forcsh./Drug Res.* **2003**, *53*, 266. (g) Casse, C., Giannoni, f., Nguyen, V.T., Dubois, M.F., O. Bensaude, *J. Biol. Chem.*, **1999**, *274*, 16097.

[3](a) Shikhaliev, Kh. S., Potapov, A. Yu., Kryl'skii, D. V., *Russ. Chem. Bull., Int. Ed*., **2007**, *56*, 367. (b) Romano, C., Cuesta, E., Avendaño, C., *Heterocycles*, **1990**, *31*, 267. (c) Shikhaliyev, H. S., Kryl'skii, D. V., Potapov, A. Yu., Krysin, M. Yu., Trefilova, J. H., *Math. Univ. Chem. Chem. Eng. Technol.*, **2004**, *47(*3), 149 [in Rus.]. (d) Kovigin, Y. A., Shikhaliyev, H. S., Potapov, A., Krylsky, D. V., *Math. Univs. Chem. Chem. Eng. Technol.*, **2005**, *48(1)*, 59 [in Rus.].

[4](a) Rudenko, R. V., Komykhov, S. A., Desenko, S. M., Musatov, V. I., Shishkin, O. V., Konovalova, I. A., Vashchenko, E. V., Chebanov, V. A., *Synthesis*, **2011**, *5*, 783. (b) Filimonov, S. I., Korsakov, M. K., Chirkova, Zh. V., Abramov, I. G., Stashina, G. A., Firgang, S. I., Kovygin, Yu. A., Shikhaliev, Kh. S., *Chem. Heterocycl. Compd.*, **2013**, *49*, 993.

[5]Pozharsky, A. F., Anisimov, V. A., Tsupak, E. B., *Practical works on heterocyclic chemistry*, Publishing house of Rostov University, **1988**, 106.

[6](a) Morkovnik, A. S., Divaeva, L: N., Kuz'Menko, T. A., Borodkin, G. S., *Russ. J. Org. Chem.*, **2013**, *49(6)*, 895. (b) Kuz'menko, T. A., Kuz'menko, V. V., Pozharskii, A. F., Anisimova, V.A., *Chem. Heterocycl. Compd.*, **1990**, *26(11)*, 1264. (c) Povstyanoi, M. V., Kruglenko, V. P., Gnidets, V. P., *Chem. Heterocycl. Compd*., **1984**, *20(5)*, 568. (d) Gnidets, V. P., Kruglenko, V. P., Povstyanoi, M. V., Klyuev, N. A., *Chem. Heterocycl. Compd.*, **2002**, *38(5)*, 598.

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