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]benzimidazol-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.

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

Benzimidazolepyrimidines2 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 imidazoypyrimidines 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 1H spectrometer at 500 MHz and 13C at 125.76 MHz in DMSO-d6, 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 F254 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 method5. The compounds 2a-e were purchased from Acros Organics.

Preparation of 10-amino-2,3,4,10-tetrahydro-4-oxo-N-arylpymrimido[1,2-a]benzimidazol-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 flask. 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]benzimidazol-2-carboxamides, 5a.

Yield: 85 %. M.p. 214-215 °C. NMP 1H (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, NH2); 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 13C (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,
10-amino-2,3,4,10-tetrahydro-N-(2-methylphenyl)-4-oxopyrimido[1,2-a]benzimidazole-2-carboxamide (5b).

Yield: 90 %, M.p. 240–241 °C. NMR 1H (DMSO-d6): δ = 2.06 (s, 3H, CH3); 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, NH2); 7.17 – 7.23 (m, 2H, H-Bz); 7.21 – 7.32 (m, 2H, H-Br + H-Ar); 8.0 (s, 1H, CONH). NMR 13C (DMSO-d6): δ = 17.8 (CH3); 33.6 (C-3); 50.3 (C=4); 108.7, 109.3 (C-7 and C-8); 114.8, 117.9, 120.2 (C Ar); 122.3, 122.9 (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 (Irel, %): 201 [M+134]⁺, C_{19}H_{22}N_{2}O_{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).

Yield 87 %. M.p. 245–246 °C. NMR 1H (DMSO-d6): δ = 1.16 (d, J=6.9, 6H, 2CH3-iPr); 2.76 (dd, J=1.9, J=14.4, 1H, H-3); 2.83 (pent, J=6.8, 1H, CH-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, NH2); 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 13C (DMSO-d6): δ = 23.8, 23.9 (2CH3-iPr); 32.9 (CH-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 (Irel, %): 201 [M+162]⁺, C_{20}H_{24}N_{2}O_{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 1H (DMSO-d6): δ = 2.11 (s, 6H, 2CH3); 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, NH2); 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). IIMP 13C (DMSO-d6): δ = 17.7, 20.6 (CH3); 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, 130.1, 131.7, 132.4 (C Ar); 135.2 (C-5a and C-9a); 155.1 (C-10a); 167.3 (NHCO); 173.3 (C=4). Mass-spectra, m/z (Irel, %): 201 [M+148]⁺, C_{19}H_{20}N_{2}O_{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-chloro-methylphenyl)-4-oxopyrimido[1,2-a]benzimidazole-2-carboxamide (5e).

Yield: 83 %, M.p. 228–229 °C. NMR 1H (DMSO-d6): δ = 2.18 (s, 3H, CH3); 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, NH2); 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); 9.89 (s, 1H, CONH). NMR 13C (DMSO-d6): δ = 17.3 (CH3); 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 (Irel, %): 201 [M-165]⁺, C_{19}H_{18}ClN_{2}O_{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=H-b and 1,4-N-C-N=H-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-PrPh (c); 3, 4-diMePh (d); 2-Me-5-CiPh (e)

Heterocyclization of 1,2-diaminobenzimidazole 5a-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-arylpirimidino[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$^a$ 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 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).

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-benzimidazolino-ion (m/z 148). This last one is subjected to further fragmentation.

A possible reaction mechanism leads to formation of compounds 5

![Scheme 2. A possible reaction mechanism leads to formation of compounds 5](image)

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![Scheme 3. Fragmentation pathway of the compounds 5](image)

Scheme 3. Fragmentation pathway of the compounds 5

Conclusions

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

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References

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