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SHORT COMMUNICATIONS

Effective method for the synthesis of azolo[1,5-*a*]pyrimidin-7-amines

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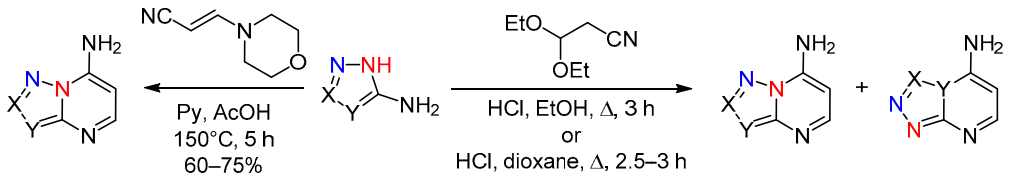


X = CH, CSMe, CCF_3, N, CHet; Y = N, CCO_2Et

Condensation of aminoazoles with (2*E*)-(3-morpholin-4-yl)acrylonitrile and 3,3-diethoxypropionitrile was used to synthesize a series of azolo[1,5-*a*]pyrimidin-7-amines. It was established that the reactions with certain aminotriazoles gave mixtures of regioisomers: azolo-[1,5-*a*]pyrimidin-7-amines and azolo[4,3-*a*]pyrimidin-5-amines.

Keywords: azolo[1,5-*a*]pyrimidin-7-amines, 3,3-diethoxypropionitrile, (2*E*)-(3-morpholin-4-yl)acrylonitrile, Dimroth rearrangement, heterocyclization.

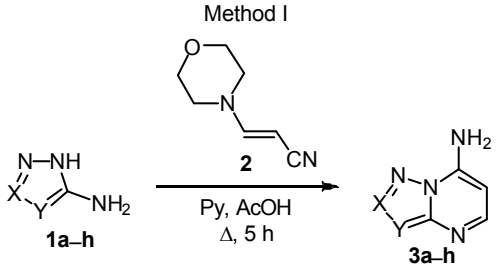
The class of azolo[1,5-*a*]pyrimidines contains compounds that are known as antiviral, antibacterial, antiparasitic, and antitumor agents.[1,2] The broad range of biological activity among such compounds can be explained by their structural analogy to natural purine bases involved in the control of key biological processes, as well as their ability to form chelates with metal ions.[3–5] The synthetic methods most commonly used for the construction of azolopyrimidine systems typically include heterocyclization reactions starting from the appropriate aminoazoles or functionalized pyrimidine derivatives. In the first case, the synthesis of pyrimidines according to [3+3] process relied on addition reactions between 3-aminoazoles and 1,3-dicarbonyl systems or their structural analogs.[2,6] Another route for the preparation of azolo[1,5-*a*]pyrimidines starting from pyrimidine derivatives is more versatile, but is complicated by the limited availability of these derivatives. Such approach, as a rule, employed heterocyclization reactions between 2-hydrazinopyrimidines or diaminopyrimidines and carbonyl compounds,[7–11] as well as oxidative cyclization of (pyrimidin-2-yl)amidines.[12,13] However, the synthesis of 7-amino-substituted azolopyrimidines has been described in the literature only twice – as preparation of unsubstituted [1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine and 2-methyl[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine by reactions of the respective aminotriazole with 3-(piperidino)-acrylonitrile or 3-(dimethylamino)acrylonitrile.[14–16] Many derivatives of [1,2,4]triazolo[1,5-*a*]pyrimidin-7-amines have been characterized with respect to various useful biological properties.[1] The synthesis of such amino derivatives most often involves a chlorodeoxygenation step that proceeds with mediocre yields, followed by *ipso*-substitution of halogen.[17] Thus, it is important to continue the search for new and convenient synthetic approaches to this class of compounds.

In the current work, we propose an alternative to the previously reported syntheses of azolo[1,5-*a*]pyrimidin-7-amines from aminoazoles **1a**–**h** and (2*E*)-(3-morpholin-4-yl)acrylonitrile (**2**), which can be obtained by a three-component condensation reaction of cyanoacetic acid with morpholine and triethylorthoformate[18] or from the commercially available 3,3-diethoxypropionitrile.

It was established that refluxing solutions containing azoles **1a**–**h** with (2*E*)-(3-morpholin-4-yl)acrylonitrile (**2**)

provided the target compounds – azolo[1,5-*a*]pyrimidin-7-amines **3a**–**h** (Scheme 1). In such solvents as MeCN, DMF, and AcOH, products **3a**–**h** were obtained in 30–40% yields. However, using a mixture of Py and AcOH in equimolar ratio allowed to increase the yields of these products to 60–75%.

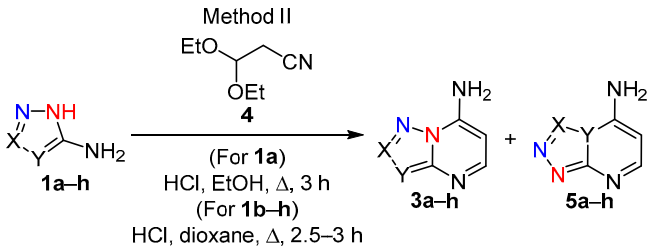
Scheme 1



3 a X = CH, Y = N (75%), **b** X = CSMe, Y = N (60%), **c** X = CCF_3, Y = N (63%), **d** X = Y = N (72%), **e** X = CH, Y = CCO_2Et (67%), **f** X = C(2-thienyl), Y = N (69%), **g** X = C(2-Fur),Y = N (65%), **h** X = CMe, Y = N (62%)

Another synthetic approach, based on the interaction of 3-aminoazoles **1a**–**h** with 3,3-diethoxypropionitrile (**4**) (Scheme 2), proceeded nonselectively with compounds **1a**,**b**,**h** – the reaction in three examples was accompanied by the formation of isomeric azolo[4,3-*a*]pyrimidines **5**.

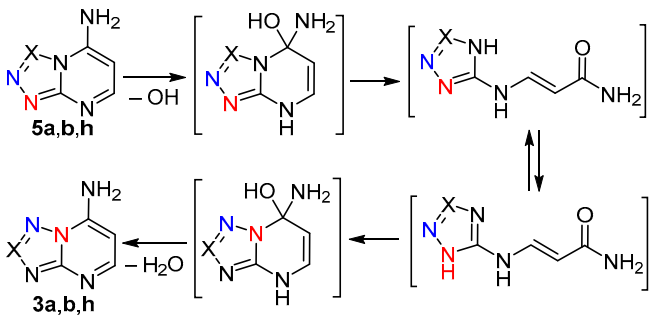
Scheme 2



In the case of aminoazoles **1a**,**h**, the regioisomeric products **5a**,**h** were predominant in the reaction mixture (their content was 95 and 60%, respectively), while in the case of compound **1b** the fraction of isomer **5b** was around 5% (the product ratio was determined from ^{1}H NMR spectra). However, the subsequent treatment of mixtures containing compounds **3a** + **5a** and **3h** + **5h** with 2% KOH solution in water and treatment of a mixture of compounds **3b** + **5b** with 1% KOH solution in aqueous alcohol solution was accompanied by Dimroth rearrangement of the less stable isomers **5a**,**b**,**h** into products **3a**,**b**,**h** with good yields. The proposed mechanism of this rearrangement process is given in Scheme 3.

As described in the literature, azaindolizines have a general tendency to undergo Dimroth rearrangement, involving the migration of two heteroatoms in the ring system, which occurs either under basic or acidic conditions.[19,20] The initial step of the base-catalyzed reaction includes a nucleophilic attack by hydroxide ion at position 5, followed by opening of the pyrimidine ring, tautomerization of the formed intermediate, and its recyclization.

Scheme 3



In order to select optimal conditions for the synthesis, the reaction of acetal **4** with aminoazoles **1a**–**h** was studied in various solvents. It was established that the reaction in AcOH was accompanied by acetylation of the starting aminoazoles **1a**–**h**, substantially degrading the target product yields. The system of Py and AcOH was also unsuitable. Better results were obtained by performing the synthesis in DMF, EtOH, and dioxane, with similar yields of the products.

The structure of the synthesized compounds was confirmed by NMR and IR spectra, as well as the results of elemental analysis. IR spectra of compounds **3a**–**h** contained the characteristic absorption bands of primary amino group in the region of 3210–3430 cm^{-1}. ^{1}H NMR spectra of all compounds featured a broadened singlet at 7.84–8.51 ppm, with its integral value corresponding to two protons, which was assigned to the amino group, as well as two doublets of pyrimidine protons H-5 and H-6 in the ranges of 8.17–8.98 ppm and 6.30–6.58 ppm, respectively, and other signals that were assigned to the azole part of the molecule.

The structure of the regioisomeric products and the occurrence of Dimroth rearrangement were proved by using two-dimensional ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC NMR experiments for compounds **3a** and **5a** that were isolated as individual samples (Fig. 1). The following signals were clearly identified in ^{1}H–^{13}C HSQC spectrum of [1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (**3a**): the C-2 carbon atom (154.4 ppm), which showed a cross peak with the only singlet of H-2 proton (8.44 ppm), the C-6 carbon atom (90.8 ppm), which was shifted upfield due to the electron-donating effect of the amino group, and the C-5 carbon atom (153.5 ppm), which was identified by method of exclusion. On the basis of ^{1}H–^{13}C HMBC spectrum it was possible to identify the signal of the C-7 atom (149.3 ppm), which gave cross peaks with the signals of H-5 (8.26 ppm) and H-6 (6.30 ppm) protons, as well as the signal of bridgehead C-3a atom was recognized by its cross peak with the signals of triazole proton H-2 (8.44 ppm) and pyrimidine proton H-5 (8.26 ppm), in agreement with the structure presented in Figure 1.

^{1}H–^{13}C HSQC spectrum of [1,2,4]triazolo[4,3-*a*]-pyrimidin-5-amine (**5a**), by analogy to the spectrum of compound **3a**, allowed to unequivocally assign the signals of C-3 carbon atom (131.5 ppm), C-6 carbon atom (88.1 ppm), and C-7 carbon atom (155.1 ppm). The signals of

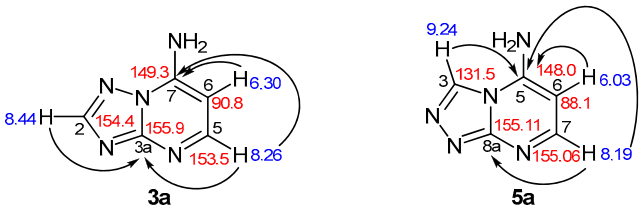


Figure 1. The key interactions in $^{1}H–^{13}C$ HSQC and $^{1}H–^{13}C$ HMBC spectra of compounds **3a**, **5a** (δ, ppm).

pyrimidine protons H-6 (6.03 ppm) and H-7 (8.19 ppm) showed cross peaks with the signal of C-5 carbon atom (147.9 ppm), enabling unequivocal determination of its position. The signal of the only triazole ring proton H-3 (9.24 ppm) in this case did not show a cross peak with the signal of the bridgehead carbon atom C-8a (155.1 ppm), the position of which, in turn, was established from the spin-spin coupling to the H-7 proton (8.19 ppm). At the same time, a cross peak was observed between the signal of H-3 proton (9.24 ppm) and the C-5 carbon atom (147.9 ppm), which was in agreement with the structure presented in Figure 1.

Thus, we have developed a convenient and simple method for the synthesis of azolo[1,5-*a*]pyrimidin-7-amines by using (2*E*)-(3-morpholin-4-yl)acrylonitrile and 3,3-diethoxypropionitrile.

Experimental

IR spectra were recorded on a Bruker Alpha spectrometer equipped with a ZnSe ATR accessory. One-dimensional ^{1}H and ^{13}C NMR spectra, as well as two-dimensional $^{1}H–^{13}C$ HSQC and $^{1}H–^{13}C$ HMBC experiments were acquired on a Bruker DRX-400 instrument (400 and 101 MHz, respectively) or a Bruker Avance NEO 600 instrument (600 and 151 MHz, respectively), equipped with a Prodigy broadband gradient cryoprobe, using DMSO-d_6 as solvent and TMS as internal standard. Elemental analysis was performed on a PerkinElmer PE 2400 elemental analyzer. Melting points were determined in open capillaries on a Stuart SMP3 apparatus. Column chromatography was performed with Silica gel 60 (40–63 μm).

Preparation of compounds 3a–h (General method). Method I. A mixture of Py (4.4 ml) and AcOH (3.0 ml) was stirred and treated by the addition of 5-aminoazole **1a–h** (0.01 mol) and (2*E*)-(3-morpholin-4-yl)-acrylonitrile (**2**) (1.38 g, 0.01 mol). The obtained mixture was refluxed at 150°C for 5 h. After refluxing, the mixture was cooled. The precipitate that formed was filtered off, washed with a small amount of EtOH, and dried.

Method II. A solution (or suspension) of the appropriate aminoazole **1a–h** (0.01 mol) in solvent (15 ml) (EtOH in the case of compound **3a**, dioxane in the case of compounds **3b–h**) was stirred at 50°C and treated by adding 3,3-diethoxypropionitrile (**4**) (1.5 ml, 0.01 mol), then 36% HCl solution (0.86 ml, 0.01 mol). The reaction mixture was refluxed for 2.5–3 h, the suspension (or solution) was cooled to room temperature, and the target product was isolated by the method indicated for each particular compound.

[1,2,4]Triazolo[1,5-*a*]pyrimidin-7-amine (3a). Yield 1.01 g (75%, method I), beige powder, mp 276–279°C (MeCN). Method II. The obtained suspension was neutralized with Et_3N, the precipitate was filtered off, washed with EtOH, $CHCl_3$, and air-dried. The dry product was dissolved in H_2O (20 ml) and treated by adding a solution of KOH (0.561 g) in H_2O (10 ml), then stirred overnight at room temperature. The obtained suspension was neutralized with AcOH to pH ~7 and evaporated to dryness at reduced pressure, the dry residue was triturated with EtOH, filtered, and washed with EtOH. Yield 0.96 g (71%, method II), white powder, mp 276–278°C. IR spectrum, ν, cm^{-1}: 3244, 3298 (NH_2). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 6.30 (1H, d, *J* = 5.5, H-6); 8.14 (2H, br. s, NH_2); 8.26 (1H, d, *J* = 5.5, H-5); 8.43 (1H, s, H-2). ^{13}C NMR spectrum (101 MHz), δ, ppm 90.8 (C-6); 149.3 (C-7); 153.5 (C-5); 154.4 (C-2); 155.9 (C-3a). Found, %: C 44.29; H 3.88; N 52.10. $C_5H_5N_5$. Calculated, %: C 44.44; H 3.73; N 51.83.

[1,2,4]Triazolo[4,3-*a*]pyrimidin-5-amine (5a). The suspension of compound **3a** obtained according to method II was neutralized with Et_3N, the precipitate was filtered off, washed with EtOH, $CHCl_3$, and air-dried. The product was adsorbed on silica gel (0.04–0.063 mm), isomer **3a** was eluted ($CHCl_3$–MeOH, 5:1), then product **5a** was eluted with MeOH. Yield 0.97 g (72%), beige powder, mp 287–289°C. ^{1}H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 6.03 (1H, d, *J* = 5.1, H-6); 8.18 (2H, br. s, NH_2); 8.20 (1H, d, *J* = 5.1, H-7); 9.24 (1H, s, H-3). ^{13}C NMR spectrum (151 MHz), δ, ppm 88.1 (C-6); 131.5 (C-3); 148.0 (C-5); 155.1 (C-7); 155.1 (C-8a). Found, %: C 44.36; H 3.56; N 52.08. $C_5H_5N_5$. Calculated, %: C 44.44; H 3.73; N 51.83.

2-(Methylsulfanyl)[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (3b). Yield 1.08 g (60%, method I), beige powder, mp 230–233°C (MeCN). Method II. The precipitate was filtered off and air-dried. The dry precipitate was dissolved in 1:1 H_2O–EtOH mixture (50 ml) and treated with a solution of KOH (1.122 g) in H_2O (10 ml), stirred overnight at 40°C, then cooled to room temperature, and neutralized with AcOH to pH ~7. EtOH was evaporated at reduced pressure, the precipitate was filtered off and dried under reduced pressure at 110°C over P_2O_5. Yield 1.56 g (86%, method II), white powder, mp 231–233°C. IR spectrum, ν, cm^{-1}: 3274, 3308 (NH_2). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 2.64 (3H, s, CH_3); 6.24 (1H, d, *J* = 5.7, H-6); 8.05 (2H, br. s, NH_2); 8.17 (1H, d, *J* = 5.7, H-5). ^{13}C NMR spectrum (101 MHz), δ, ppm 13.3 (CH_3); 91.1 (C-6); 148.2 (C-7); 152.9 (C-5); 156.4 (C-3a); 165.6 (C-2). Found, %: C 39.96; H 3.93; N 38.68; S 17.54. $C_6H_7N_5S$. Calculated, %: C 39.77; H 3.89; N 38.65; S 17.69.

2-(Trifluoromethyl)[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (3c). Yield 1.28 g (63%, method I), white powder, mp 233–235°C (*i*-PrOH). Method II. The obtained solution was neutralized with Et_3N, then the reaction mixture was evaporated at reduced pressure, the dry residue was triturated with $CHCl_3$, the precipitate was filtered off. The obtained product was crystallized from *i*-PrOH. Yield 1.31 g (65%, method II), white powder, mp 233–235°C. IR spect-

rum ν, cm^{-1}: 1180 (CF), 3312, 3331 (NH_2). ^1H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 6.45 (1H, d, *J* = 5.7, H-6); 8.37 (1H, d, *J* = 5.7, H-5); 8.51 (2H, br. s, NH_2). ^{13}C NMR spectrum (151 MHz), δ, ppm (*J*, Hz): 92.8 (C-6); 119.6 (q, J_{CF} = 271.0, CF_3); 150.3 (C-7); 154.4 (q, J_{CF} = 38.0, C-2); 155.1 (C-5); 156.2 (C-3a). Found, %: C 35.26; H 1.81; N 34.28. $C_6H_4F_3N_5$. Calculated, %: C 35.48; H 1.98; N 34.48.

Tetrazolo[1,5-*a*]pyrimidin-7-amine (3d). Yield 0.98 g (72%, method I), beige powder, mp 270–275°C (DMF). Method II. The precipitate was filtered off and air-dried. The dry residue was dissolved in H_2O (15 ml); the solution was stirred and adjusted with aqueous ammonia to pH ~8, the precipitate was filtered off, and dried in a vacuum desiccator over P_2O_5. Yield 0.91 g (67%, method II), pale-yellow powder, mp 274–276°C. IR spectrum, ν, cm^{-1}: 3274, 3296 (NH_2). ^1H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 6.58 (1H, d, *J* = 7.5, H-6); 7.84 (2H, br. s, NH_2); 8.98 (1H, d, *J* = 7.5, H-5). ^{13}C NMR spectrum (151 MHz), δ, ppm 104.4 (C-6); 132.9 (C-5); 155.5 (C-3a); 162.3 (C-7). Found, %: C 35.16; H 2.92; N 61.92. $C_4H_4N_6$. Calculated, %: C 35.30; H 2.96; N 61.74.

Ethyl 7-aminopyrazolo[1,5-*a*]pyrimidine-3-carboxylate (3e). Yield 1.38 g (67%, method I), white powder, mp 164–167°C (*i*-PrOH). Method II. Isolation and purification were performed analogously to the procedure for compound **3c**. Yield 1.82 g (88%, method II), white powder, mp 165–167°C. IR spectrum, ν, cm^{-1}: 1666 (C=O), 3320, 3430 (NH_2). ^1H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 1.28 (3H, t, *J* = 7.1, CH_3); 4.25 (2H, q, *J* = 7.1, CH_2); 6.31 (1H, d, *J* = 5.4, H-6); 8.08 (2H, br. s, NH_2); 8.25 (1H, d, *J* = 5.4, H-5); 8.47 (1H, s, H-2). ^{13}C NMR spectrum (101 MHz), δ, ppm 14.5 ($CH_2\underline{C}H_3$); 59.0 ($\underline{C}H_2CH_3$); 90.8 (C-6); 99.8 (C-3); 146.3 (C-2); 148.5 (C-3a); 148.7 (C-7); 151.9 (C-5); 162.2 ($\underline{C}OOCH_2$). Found, %: C 52.41; H 4.88; N 27.16. $C_9H_{10}N_4O_2$. Calculated, %: C 52.42; H 4.89; N 27.17.

2-(Thiophen-2-yl)[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (3f). Yield 1.49 g (69%, method I), beige powder, mp >300°C (MeCN). Method II. The precipitate was filtered off and air-dried. The dry residue was dissolved in EtOH (40 ml) and treated by adding Et_3N to pH 8–9, the precipitate was filtered off, washed with $CHCl_3$, and air-dried. Yield 1.80 g (83%, method II), white powder, mp >300°C. IR spectrum ν, cm^{-1}: 3288, 3427 (NH_2). ^1H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 6.31 (1H, d, *J* = 5.5, H-6); 7.22 (1H, dd, *J* = 5.0, *J* = 3.6, H-4'); 7.72 (1H, d, *J* = 5.0, H-3'); 7.83 (1H, d, *J* = 3.6, H-5'); 8.17 (2H, br. s, NH_2); 8.25 (1H, d, *J* = 5.5, H-5). ^{13}C NMR spectrum (151 MHz), δ, ppm 91.4 (C-6); 127.9 (C-3'); 128.2 (C-4'); 128.9 (C-5'); 133.8 (C-2'); 149.0 (C-7); 153.6 (C-5); 156.5 (C-3a); 159.5 (C-2). Found, %: C 49.62; H 3.17; N 32.24. $C_9H_7N_5S$. Calculated, %: C 49.76; H 3.25; N 32.24.

2-(Furan-2-yl)[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (3g). Yield 1.31 g (65%, method I), brown powder, mp 275–277°C (decomp., MeCN). Method II. The precipitate was filtered off and air-dried. The dry residue was dissolved in H_2O (15 ml) and treated with a solution of KOH (0.561 g) in H_2O (5 ml), the precipitate was filtered off, dried under reduced pressure at 110°C over P_2O_5. Yield 1.37 g (68%, method II), light-beige powder, mp 276–278°C. IR spectrum ν, cm^{-1}: 3368, 3426 (NH_2). ^1H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 6.33 (1H, d, *J* = 5.5, H-6); 6.66 (1H, dd, *J* = 3.5, *J* = 1.8, H-4'); 7.17 (1H, d, *J* = 3.5, H-3'); 7.89 (1H, d, *J* = 1.8, H-5'); 8.25 (2H, br. s, NH_2); 8.26 (1H, d, *J* = 5.5, H-5). ^{13}C NMR spectrum (151 MHz), δ, ppm 91.5 (C-6); 111.9 (C-3'); 112.1 (C-4'); 144.9 (C-5'); 146.3 (C-2'); 149.3 (C-7); 153.7 (C-5); 156.4 (C-2); 156.5 (C-3a). Found, %: C 53.75; H 3.58; N 34.75. $C_9H_7N_5O$. Calculated, %: C 53.73; H 3.51; N 34.81.

2-Methyl[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (3h). Yield 0.92 g (62%, method I), beige powder, mp 208–210°C (MeCN). Method II. The precipitate was filtered off and air-dried. The dry residue was dissolved in H_2O (20 ml) and treated with a solution of KOH (1.122 g) in H_2O (10 ml), then maintained overnight at room temperature. The obtained solution was neutralized with AcOH to pH ~7 and cooled on ice bath. The cold suspension was filtered, the precipitate was dried under reduced pressure at 110°C over P_2O_5. Yield 0.90 g (60%, method II), beige powder, mp 209–211°C. IR spectrum, ν, cm^{-1}: 3210, 3342 (NH_2). ^1H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 2.42 (3H, s, CH_3); 6.23 (1H, d, *J* = 5.5, H-6); 8.05 (2H, br. s, NH_2); 8.17 (1H, d, *J* = 5.5, H-5). ^{13}C NMR spectrum (151 MHz), δ, ppm 14.8 (CH_3); 90.6 (C-6); 148.7 (C-7); 153.0 (C-5); 156.4 (C-3a); 163.5 (C-2). Found, %: C 48.37; H 4.70; N 46.88. $C_6H_7N_5$. Calculated, %: C 48.32; H 4.73; N 46.95.

Supplementary information file containing ^1H, ^{13}C NMR and ^1H–^{13}C HSQC, ^1H–^{13}C HMBC spectra of compounds **3a**–**h**, **5a** is available at the journal website at http://link.springer.com/journal/10593.

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