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A NEW SYNTHESIS OF AMINO SUBSTITUTED AZOLO[1,3,5]TRIAZINES *VIA* REACTION OF N^1,N^1-DIMETHYL-N^2-AZOLYLFORMAMIDINES WITH CYANAMIDE[1]

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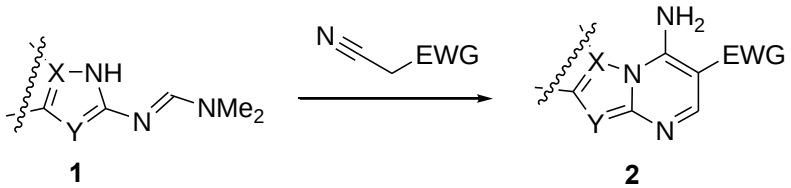
Abstract – The amino substituted triazine ring was annelated to aminoazoles using a new effective synthetic procedure. The method of preparation involved initial formation of azolylformamidines in the reaction of aminoazoles with *N*,*N*-dimethylformamide dimethyl acetal followed by the triazine ring closure with cyanamide affording therefore fused aminotriazines.

Hetarylformamidines prepared from *N*,*N*-dimethylformamide dimethyl acetal[2] have been well recognized as valuable building blocks for construction of various fused heterocyclic systems.[3] One of the most explored type of transformations of N^1,N^1-dimethyl-N^2-azolylformamidines (**1**) has been an annelation of a pyrimidine ring to the azoles (**1**) *via* reaction of the electrophilic amidine carbon atom with methylene active compounds followed by intramolecular ring closure upon reaction of the azole nitrogen atom with the reactive group introduced by the methylene compounds. In case of methylene active nitriles, amino substituted azolopyrimidines (**2**) were formed as products of the reaction (Scheme 1).[4]

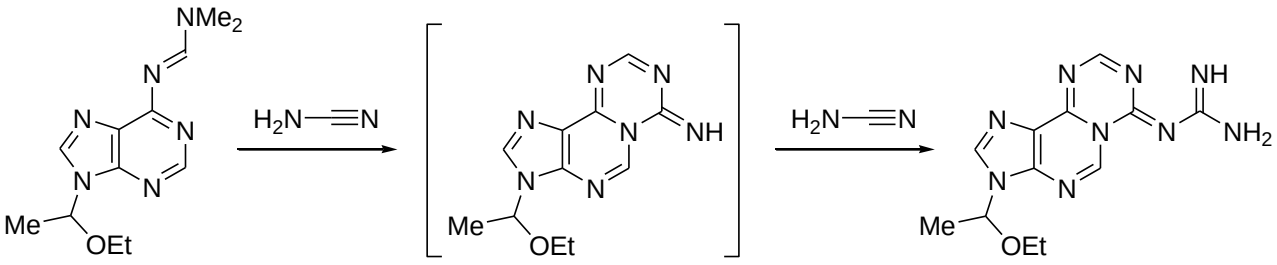


1 **2**

Scheme 1

A similar reaction of **1** utilizing *N*-nucleophiles with attached reactive electrophilic group (*e.g.* cyanamide or urethanes) has not been explored. These reactions are particularly interesting as they may lead to fused 1,3,5-triazines isosteric to biologically active purines, *e.g.* 1,2,4-triazolo[1,5-*a*][1,3,5]triazines (5-azapurines)[5] and pyrazolo[1,5-*a*][1,3,5]triazines (5-aza-9-deazapurines).[6]

Hosmane and Leonard reported[7] an example of the triazine ring closure observed when formamidine **3** was heated with cyanamide in isopropanol for 24 h (Scheme 2). The reaction was proposed to proceed *via* intermediate **4**, which was not isolated. Compound **5**, the product of subsequent addition of cyanamide to **4**, was obtained in 13% yield. No further investigations of this type of reactions have been carried out.

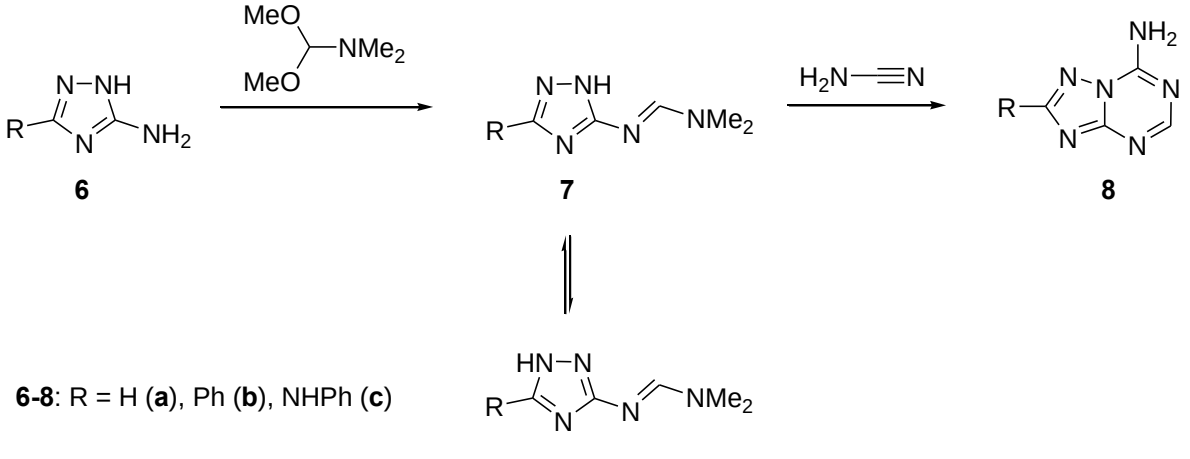


3 **4** **5**

Scheme 2

Herein we report new reactions of N^1,N^1-dimethyl-N^2-azolylformamidines with cyanamide affording formation of amino substituted azolo[1,3,5]triazines.

Initially we prepared N^1,N^1-dimethyl-N^2-1,2,4-triazolyl-3(5)-formamidine (**7a**) and attempted to involve it in the reaction with equimolar quantity of cyanamide (Scheme 3). Heating the reaction mixture in methanol for 24 h allowed preparation of 5-aza-adenine (**8a**) with 10% yield. Some improvement of the reaction yield up to 15% was achieved when two equivalents of cyanamide were used. Further increase of the yield to 32% was observed upon addition of sodium methoxide to the reaction.



6 **7** **8**

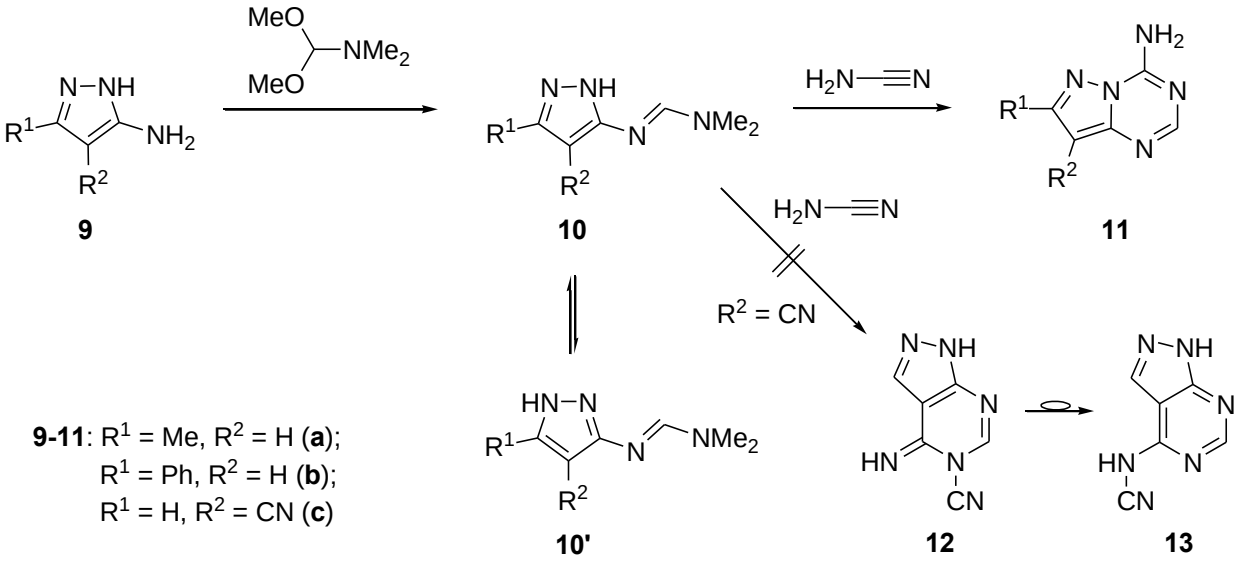
6-8: R = H (**a**), Ph (**b**), NHPh (**c**)

7'

Scheme 3

Analogously, N^1,N^1-dimethyl-N^2-1,2,4-triazolyl-5(3)-formamidines (**7b,c**) were prepared from amines **6b,c** by treatment with *N*,*N*-dimethylformamide dimethyl acetal and then converted to corresponding 5-aza-adenines (**8b,c**) with the yields substantially higher than that for **8a**. Similarly to 5(3)-amino-1,2,4-triazoles,[8] annular tautomerism in the triazole ring of formamidines **7** resulted in the equilibrium between two tautomeric forms **7** and **7′** (Scheme 3). Tautomeric preferences and rate of tautomeric exchange were found to be highly dependent on the substutuents on the triazole ring, physical state, solvent, temperature *etc*.[9] Signals of two tautomeric forms **7** and **7′** were observed in the NMR spectra (DMSO-d_6 solution) of phenyl substituted **7b**. The tautomer **7′** was found to be minor in the equilibrium (ΔG_{298} = 7.8 kJ/mol).

The developed method was further extended to the annelation of amino-1,3,5-triazine to 5(3)-aminopyrazoles (**9**) and 2-aminobenzimidazole (**14**) using the same sequence of the reactions with *N*,*N*-dimethylformamide dimethyl acetal and then cyanamide (Schemes 4 and 5).

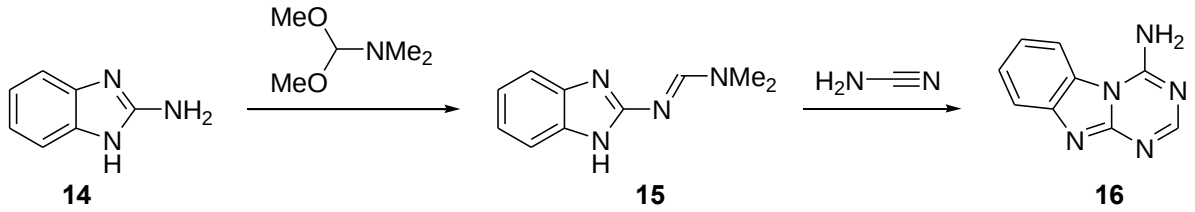


Scheme 4

4-Aminopyrazolo[1,5-*a*][1,3,5]triazines (**11**) were successfully synthesized from aminopyrazoles (**9**) *via* N^1,N^1-dimethyl-N^2-pyrazolyl-5(3)-formamidines (**10**) (Scheme 4). The NMR spectroscopy data for **10a** in DMSO-d_6 solution revealed that two tautomers **10** and **10′** were almost equistable (ΔG_{298} = 0.35 kJ/mol). Changing methyl group in the pyrazole ring to phenyl moiety (compound **10b**) shifted the tautomeric equilibrium towards tautomeric form **10**, which was substantially preferred over **10′** (ΔG_{298} = 3.2 kJ/mol). A reaction of amines with N^1,N^1-dimethyl-N^2-pyrazolyl-5(3)-formamidines bearing a cyano group in position 4 of the pyrazole ring has been established to proceed *via* a pyrimidine ring closure with subsequent Dimroth rearrangement.[10] This methodology has been successfully utilized for the preparation of bioactive pyrazolo[3,4-*d*]pyrimidines.[11] Therefore treatment of **10c** with cyanamide might theoretically

result in the formation of pyrazolo[3,4-*d*]pyrimidines (**12** or/and **13**) alternative to 4-amino-8-cyanopyrazolo[1,5-*a*][1,3,5]triazine (**11c**). We found that heating **10c** with cyanamide in methanol in the presence of sodium methoxide regioselectively provided **11c**.

The amino-1,3,5-triazine ring was also successfully annelated to 2-aminobenzimidazole (**14**) using condensation with *N*,*N*-dimethylformamide dimethyl acetal and subsequent treatment of the resulted **15** with cyanamide affording therefore 4-amino-1,3,5-triazino[1,2-*a*]benzimidazole (**16**) (Scheme 5).



14 **15** **16**

Scheme 5

It should be noted that despite using excess of cyanamide, no products of cyanamide addition to the amino group at the annelated triazine ring were isolated for any of the explored substrates (*cf*. Scheme 2).

Our attempts to prepare oxo-analogues of the synthesized fused aminotriazines (**8**, **11**, and **16**) using urethane instead of cyanamide in a similar reaction with the N^1,N^1-dimethyl-N^2-azolylformamidines (**7**, **10**, and **15**) were unsuccessful and furnished isolation of the starting formamidines.

In summary, new practical and general method of the amino-1,3,5-triazine annelation to aminoazoles was successfully developed and exemplified by preparation of 7-amino-1,2,4-triazolo[1,5-*a*][1,3,5]triazines (**8**), 4-aminopyrazolo[1,5-*a*][1,3,5]triazines (**11**) and 4-amino-1,3,5-triazino[1,2-*a*]benzimidazole (**16**).

EXPERIMENTAL

General Methods. Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III spectrometer (400 MHz), using DMSO-d_6 as a solvent and TMS as an internal reference. 5(3)-Amino-1,2,4-triazoles (**1b,c**) were prepared according to previously reported methods;[8] 5(3)-amino-3(5)-phenylpyrazole (**5**) was synthesized using known method.[12] Other reagents were purchased from Alfa Aesar.

General method for preparation of N^1,N^1-dimethyl-N^2-azolylformamidines (7, 10, and 15).

A mixture of aminoazoles (**6**, **9** or **14**, 10 mmol) with *N*,*N*-dimethylformamide dimethyl acetal (2.0 mL, 15 mmol) in toluene (10 mL) was heated under reflux. Upon completion of the reaction, the mixture was cooled and precipitated formamidines (**7**, **10** or **15**) were filtered and washed with hexane. The compounds were sufficiently pure and were used for the next step without further purification; analytical samples were recrystallized from toluene.

N^1,N^1-Dimethyl-N^2-1,2,4-triazolyl-3(5)-formamidine (7a)

Reaction time: 3 h. Yield 71%; mp 159-161 °C (toluene). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.95 (3H, s, NMe), 3.07 (3H, s, NMe), 7.57 (1H, br. s, H-5/3), 8.40 (1H, s, N=C*H*-NMe$_2$), 12.86 (1H, br. s, N(1)H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 34.0 (NMe), 40.0 (NMe), 148.9 (C-5/3), 157.2 (N=*C*H-NMe$_2$), 160.7 (C-3/5). Anal. Calcd for $C_5H_9N_5$: C, 43.15; H, 6.52; N, 50.33. Found: C, 43.12; H, 6.57; N, 50.28.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-[3(5)-phenyl-1,2,4-triazol-5(3)-yl]formamidine (7b)**

Reaction time: 1.5 h. Yield 93%; mp 199-201 °C (toluene). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.99 (3H, s, NMe), 3.12 (3H, s, NMe), 7.35 (1H, t, J = 7.3 Hz, H-4′), 7.42 (2H, t, J = 7.5 Hz, H-3′ and H-5′), 7.99 (2H, d, J = 7.5 Hz, H-2′ and H-6′), 8.41* and 8.52 (1H, s, N=C*H*-NMe$_2$), 12.97 and 13.67* (1H, s, N(1)H); *- signals of minor tautomeric form (K_T = 23.4). ^{13}C NMR (100 MHz, DMSO-d_6): δ 34.1 (NMe), 40.1 (NMe), 125.3 (C-3′ and C-5′), 128.2 (C-4′), 128.9 (C-2′ and C-6′), 132.3 (C-1′), 157.3 (N=*C*H-NMe$_2$), 158.7 (C-5), 160.9 (C-3). Anal. Calcd for $C_{11}H_{13}N_5$: C, 61.38; H, 6.09; N, 32.54. Found: C, 61.41; H, 6.12; N, 32.46.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-[3(5)-phenylamino-1,2,4-triazol-5(3)-yl]formamidine (7c)**

Reaction time: 10 min. Yield 96%; mp 207-209 °C (toluene). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.96 (3H, s, NMe), 3.07 (3H, s, NMe), 6.73 (1H, t, J = 7.3 Hz, H-4′), 7.17 (2H, t, J = 7.9 Hz, H-3′ and H-5′), 7.53 (2H, d, J = 8.6 Hz, H-2′ and H-6′), 8.34 (1H, s, N=C*H*-NMe$_2$), 8.76 (1H, s, N*H*Ph), 12.13 (1H, s, N(1)H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 34.1 (NMe), 40.1 (NMe), 115.4 (C-2′ and C-6′), 118.3 (C-4′), 128.4 (C-3′ and C-5′), 142.5 (C-1′), 157.0 (N=*C*H-NMe$_2$), 158.1 and 158.3 (C-3 and C-5). Anal. Calcd for $C_{11}H_{14}N_6$: C, 57.38; H, 6.13; N, 36.50. Found: C, 57.40; H, 6.22; N, 36.33.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-[3(5)-methylpyrazol-5(3)-yl]formamidine (10a)**

Reaction time: 1 h. Yield 70%; mp 127-128 °C (toluene), lit.:[13] 120-122 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.08 (3H, br. s, Me), 2.86 (3H, br. s, NMe), 2.96 (3H, br. s, NMe), 5.56 (1H, br. s, H-4), 7.89 (1H, s, N=C*H*-NMe$_2$), 11.62 (1H, br. s, N(1)H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.9* and 14.0 (br. s, Me), 33.8 (NMe), 39.5 (NMe), 88.8 and 94.2* (br. s, C-4), 138.3* (C-5), 146.7 (C-3), 152.6 (C-5), 154.2* and 154.8 (br. s, N=*C*H-NMe$_2$), 159.3* (C-3); *- signals of minor tautomeric form (K_T = 1.15). Anal. Calcd for $C_7H_{12}N_4$: C, 55.24; H, 7.95; N, 36.81. Found: C, 55.27; H, 8.12; N, 36.60.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-[3(5)-phenylpyrazol-5(3)-yl]formamidine (10b)**

Reaction time: 1 h. Yield 96%; mp 177-179 °C (toluene). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.92 (3H, s, NMe), 3.02 (3H, s, NMe), 6.24 and 6.29* (1H, br. s, H-4), 7.25 (1H, br. t, J = 7.4 Hz, H-4′), 7.37 (2H, br. t, J = 7.5 Hz, H-3′ and H-5′), 7.72 (2H, br. d, J = 7.6 Hz, H-2′ and H-6′), 8.04 (1H, s, N=C*H*-NMe$_2$), 12.20 and 12.43* (1H, br. s, N(1)H); *- signals of minor tautomeric form (K_T = 3.6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 33.8 (NMe), 39.6 (NMe), 86.1 (C-4), 134.5 (C-3′ and C-5′), 126.8 (C-4′), 128.3 (C-2′ and C-6′), 134.6 (C-1′), 149.6 (C-3), 153.4 (C-5), 155.5 (N=*C*H-NMe$_2$). Anal. Calcd for $C_{12}H_{14}N_4$: C, 67.27; H, 6.59; N,

26.15. Found: C, 67.18; H, 6.70; N, 26.02.

N^1,N^1-Dimethyl-N^2-[4-cyanopyrazol-5(3)-yl]formamidine (10c)

Reaction time: 7 h. Yield 84%; mp 162-164 °C (toluene), lit.:[14] 155-157 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.96 (3H, s, NMe), 3.06 (3H, s, NMe), 7.81 (1H, br. s, H-3/5), 8.01 (1H, s, N=C*H*-NMe$_2$), 12.77 (1H, br. s, N(1)H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 33.9 (NMe), 40.0 (NMe), 82.9 (C-4), 115.9 (CN), 136.4 (CH-5/3), 155.0 (N=*C*H-NMe$_2$), 156.2 (C-3/5). Anal. Calcd for $C_7H_9N_5$: C, 51.52; H, 5.56; N, 42.92. Found: C, 51.45; H, 5.66; N, 42.84.

N^1,N^1-Dimethyl-N^2-benzimidazolyl-2-formamidine (15)

Reaction time: 10 min. Yield 94%; mp 242-244 °C (toluene). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.01 (3H, s, NMe), 3.12 (3H, s, NMe), 6.87-7.03 (2H, m, H-5 and H-6), 7.12-7.34 (2H, m, H-4 and H-7), 8.67 (1H, s, N=C*H*-NMe$_2$), 11.62 (1H, br. s, N(1)H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 34.2 (NMe), 40.1 (NMe), 109.2 (br. s, C-7), 116.0 (br. s, C-4), 119.3 (br. s, C-5), 120.1 (br. s, C-6), 133.7 (br. s, C-7a), 143.0 (br. s, C-3a), 157.5 (N=*C*H-NMe$_2$), 158.5 (C-2). Anal. Calcd for $C_{10}H_{12}N_4$: C, 63.81; H, 6.43; N, 29.77. Found: C, 63.77; H, 6.50; N, 29.62.

General method of preparation of 7-amino-1,2,4-triazolo[1,5-a][1,3,5]triazines (8), 4-aminopyrazolo[1,5-a][1,3,5]triazines (11), and 4-amino-1,3,5-triazino[1,2-a]benzimidazole (16).

Metallic sodium (0.138 g, 6 mmol) was dissolved in MeOH (10 mL) and mixed with N^1,N^1-dimethyl-N^2-azolylformamidines (**7**, **10**, or **15**, 3 mmol) and cyanamide (0.25 g, 6 mmol); the mixture was heated under reflux for 24 h. The solvent was evaporated under reduce pressure, the residue was dissolved in water (20 mL) and acidified with $HCl_{conc.}$ to pH 3. After stirring at 0 °C for 30 min, the precipitate formed was filtered, washed with cold water and recrystallized from suitable solvent.

7-Amino-1,2,4-triazolo[1,5-a][1,3,5]triazine (8a)

Yield 32%; mp 328-330 °C (water), lit.:[15] 320 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 (1H, s, H-5), 8.50 (1H, s, H-2), 8.75 (1H, br. s, NH), 9.06 (1H, br. s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 151.8 (C-7), 154.8 (C-2), 156.9 (C-3a), 159.0 (C-5). Anal. Calcd for $C_6H_7N_5$: C, 35.30; H, 2.96; N, 61.74. Found: C, 35.19; H, 3.08; N, 61.55.

7-Amino-2-phenyl-1,2,4-triazolo[1,5-a][1,3,5]triazine (8b)

Yield 72%; mp 358-360 °C (DMF), lit.:[16] 290-293 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.53-7.58 (3H, m, H-3′, H-4′ and H-5′), 8.18-8.24 (2H, m, H-2′ and H-6′), 8.34 (1H, s, H-5), 8.72 (1H, br. s, NH), 9.09 (1H, br. s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 127.0 (C-3′ and C-5′), 128.9 (C-2′ and C-6′), 130.1 (C-1′), 130.7 (C-4′), 151.6 (C-7), 157.6 (C-3a), 159.2 (C-5), 163.5 (C-2). Anal. Calcd for $C_6H_7N_5$: C, 56.60; H, 3.80; N, 39.60. Found: C, 56.51; H, 3.94; N, 39.44.

7-Amino-2-phenylamino-1,2,4-triazolo[1,5-a][1,3,5]triazine (8c)

Yield 70%; mp 319-320 °C (DMF/water). ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.92 (1H, t, J = 7.3 Hz, H-4′), 7.29 (2H, dd, J = 7.4 Hz, J = 8.5 Hz, H-3′ and H-5′), 7.79 (2H, d, J = 8.6 Hz, H-2′ and H-6′), 8.21 (1H, s, H-5), 8.28 (1H, br. s, NH), 8.81 (1H, br. s, NH), 9.78 (1H, s, N*H*Ar). ^{13}C NMR (100 MHz, DMSO-d_6): δ 117.0 (C-2′ and C-6′), 120.4 (C-4′), 128.6 (C-3′ and C-5′), 140.6 (C-1′), 150.3 (C-7), 155.8 (C-3a), 158.6 (C-5), 161.8 (C-2). Anal. Calcd for $C_{10}H_9N_7$: C, 52.86; H, 3.99; N, 43.15. Found: C, 52.80; H, 4.07; N, 43.08.

4-Amino-7-methylpyrazolo[1,5-a][1,3,5]triazine (11a)

Yield 42%; mp 207-209 °C (EtOH), lit.:[17] 188 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.41 (3H, s, Me), 6.24 (1H, s, H-8), 8.02 (1H, s, H-2), 8.22 (1H, br. s, NH), 8.54 (1H, br. s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.2 (Me), 94.8 (C-8), 149.4 and 150.4 (C-7 and C-8a), 153.6 (C-2), 154.6 (C-4). Anal. Calcd for $C_6H_7N_5$: C, 48.32; H, 4.73; N, 46.95. Found: C, 48.34; H, 4.77; N, 46.78.

4-Amino-7-phenylpyrazolo[1,5-a][1,3,5]triazine (11b)

Yield 85%; mp 307-309 °C (DMF), lit.:[18] 283-286 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.97 (1H, s, H-8), 7.46 (1H, t, J = 7.3 Hz, H-4′), 7.52 (2H, t, J = 7.3 Hz, H-3′ and H-5′), 8.09 (2H, d, J = 7.3 Hz, H-2′ and H-6′), 8.10 (1H, s, H-2), 8.33 (1H, br. s, NH), 8.76 (1H, br. s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 92.3 (C-8), 126.3 (C-3′ and C-5′), 128.7 (C-2′ and C-6′), 129.2 (C-4′), 132.1 (C-1′), 149.8 and 150.6 (C-7 and C-8a), 153.8 (C-2), 155.2 (C-4). Anal. Calcd for $C_{11}H_9N_5$: C, 62.55; H, 4.29; N, 33.16. Found: C, 62.48; H, 4.35; N, 33.10.

4-Amino-8-cyanopyrazolo[1,5-a][1,3,5]triazine (11c)

Yield 37%; mp 293-295 °C, decomp. (DMF/water). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (1H, s, H-2), 8.69 (1H, s, H-7), 8.91 (1H, br. s, NH), 9.21 (1H, br. s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 80.1 (C-8), 113.2 (CN), 146.9 (C-7), 151.1 (C-8a), 152.4 (C-4), 157.3 (C-2). Anal. Calcd for $C_6H_4N_6$: C, 45.00; H, 2.52; N, 52.48. Found: C, 44.92; H, 2.65; N, 52.32.

4-Amino-1,3,5-triazino[1,2-a]benzimidazole (16)

Yield 53%; mp 313-315 °C (DMF), lit.:[16] 296-298 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.39 (1H, t, J = 7.8 Hz, H-7), 7.53 (1H, t, J = 7.7 Hz, H-8), 7.76 (1H, d, J = 7.9 Hz, C-9), 8.28 (1H, s, H-2), 8.43 (1H, d, J = 8.2 Hz, C-6), 8.60 (2H, br. s, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 114.1 (C-6), 118.4 (C-9), 121.3 (C-7), 125.0 (C-5a), 125.8 (C-8), 143.2 (C-9a), 152.0 (C-10a), 153.4 (C-4), 159.1 (C-2). Anal. Calcd for $C_9H_7N_5$: C, 58.37; H, 3.81; N, 37.82. Found: C, 58.25; H, 3.92; N, 37.63.

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