NMR Determination of the Structure of Azolopyrimidines Produced from Reaction of Bidentate Electrophiles and Aminoazoles

Huwaida M. E. Hassaneen[a], Hamdi M. Hassaneen[a], Sherif F. M. Khiry[a], and Richard M. Pagni[b]

[a] Chemistry Department, Faculty of Science, Cairo University, Giza, A. R. Egypt
[b] Department of Chemistry, University of Tennessee, Knoxville, TN, USA

Reprint requests to Dr. H. M. E. Hassaneen. E-mail: huwaidah@hotmail.com

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A variety of aminoazoles were reacted with bidentate electrophiles producing azolopyrimidines. The regioselectivity of the nucleophilic attack could be defined from the ^{13}C chemical shift of the pyrimidine carbons and through NOE experiments.

Key words: Aminoazoles, NOE Experiment, Azolopyrimidines, Enaminonitrile

Introduction

Azolopyrimidines are biologically interesting molecules as indicated by the large number of recent papers dealing with synthesis, chemistry, and pharmacology of these molecules [1 – 9]. For example, zaleplon (**1**), a pyrazolopyrimidine, is a hypnotic agent licensed for treatment of insomnia [10], and allopurine (**2**), a 4-hydroxypyrazolopyrimidine used in the treatment of hyperuricemia and gout, inhibits *de novo* purine biosynthesis and xanthine oxidase [11] (Fig. 1). The triazolopyrimidine trapidil and its derivatives are coronary vasodilating and potential antiatherosclerotic drugs [12 – 14]. Also, pyrimidobenzimidazoles have been found to be of pharmacological interest; for example, pyrimido[1,2-*a*]benzimidazoles have been described as anti-hypertensive [15], anti-diabetic [16] and anti-inflammatory [17].

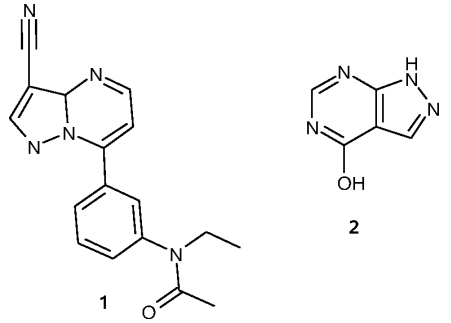


Fig. 1. Structures of zaleplon (**1**) and allopurine (**2**).

Results and Discussion

Azolopyrimidines with bridgehead nitrogen atoms are usually obtained from the reaction of bidentate electrophiles with cyclic amidines [18 – 20]. Because of the aromaticity of the reaction products in a variety of cases, acyclic intermediates for such reactions could not be isolated and structures assigned for reaction products were based mainly on ambiguous considerations. Recently, for example, Elnagdi *et al*. [21] could show through X-ray crystallography that, in the reaction of 3-aminopyrazole with benzylidenemalononitrile, the exocyclic amino group and not the ring nitrogen atom, as it was generally accepted [22], is the prime site of attack.

We now report on the reaction of 3(5)-aminopyrazoles **3a, b**, 2-aminobenzimidazole (**4**), and 3-amino-1,2,4-triazole (**5**) with arylidenemalononitrile **6**, enaminonitrile **7**, and β-ketoester **8** to show that the ^{13}C chemical shifts of pyrimidine carbons and NOE experiments can be utilized to ascertain the regioselectivity of addition or condensation reactions (Fig. 2).

Compounds **3a**, **b** reacted with arylidenemalononitrile **6** to yield aminopyrazolo-[1,5-*a*]pyrimidines that may be formulated as **10a**, **b** or isomeric **12a**, **b**. Thus, if the initial addition involves ring nitrogen atom N-2, as has been assumed earlier by Elnagdi *et al*. [22], Michael adduct **11** would be formed, which then on cyclization would yield **12**. On the other hand, if the exocyclic amino function reacts with the electrophilic carbon atom of **6**, **9** would be formed. The latter com-

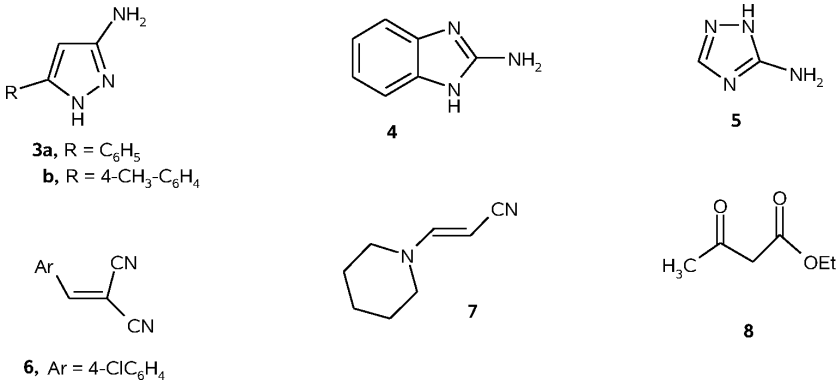
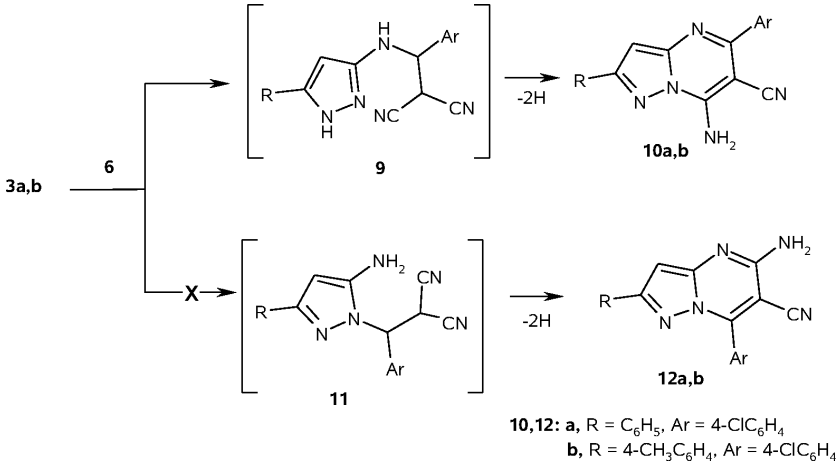


Fig. 2. Structures of compounds **3** – **8**.

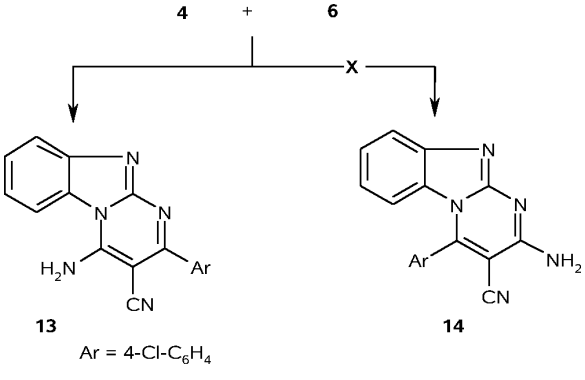


Scheme 1.

pounds would undergo cyclization and autoxidation to afford **10** (Scheme 1).

The ^{13}C NMR spectra of the reaction products revealed the pyrimidine carbon atom C-6 at $\delta \sim 71$ ppm. This can be assigned only to C-6 in compound **10**, as in **12** this carbon would be shielded only by the cyano group, while in **10** shielding by both the cyano group and the lone pair of electrons of the amino group leads to such high-field chemical shift. This conclusion is based on analogy to ^{13}C NMR data of **10** whose structure could be supported by X-ray crystallography [21].

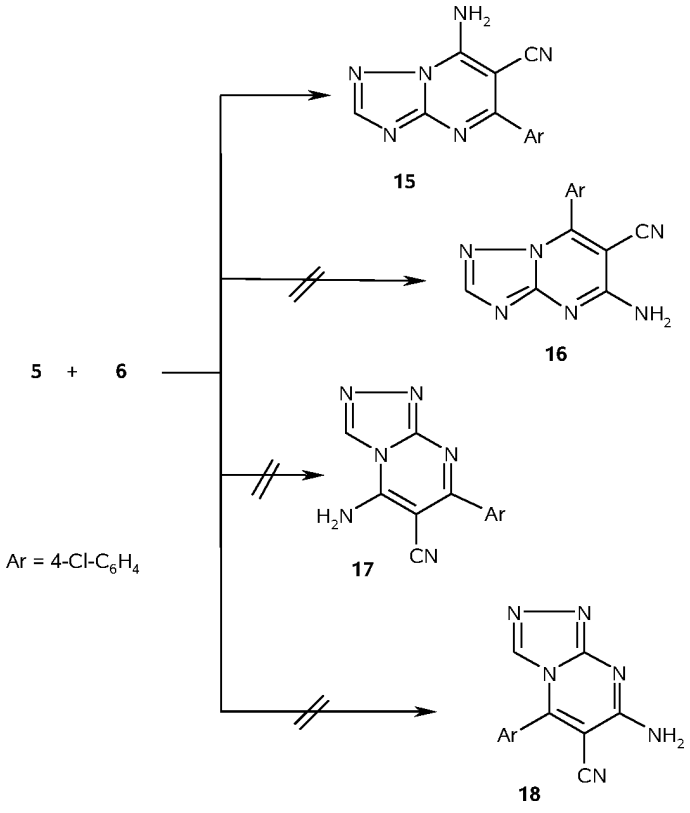
Similarly, 2-aminobenzimidazole **4** reacted with **6** to yield a pyrimido[1,2-*a*]benzimidazole that may be formulated as **13** or isomeric **14** (Scheme 2). Structure **13** could be readily established for this product based on its ^{13}C NMR spectrum, as well as on results of NOE difference experiments. Thus, the ^{13}C NMR signal of the pyrimidine carbon atom C-3 appeared at δ = 72 ppm, which is consistent with structure **13** in which both amino and cyano groups are shielding.



Scheme 2.

Moreover, irradiation at the amino group resonance has enhanced the 6-H signal in the pyrimido[1,2-*a*]benzimidazole ring.

The reaction of 3-amino-1,2,4-triazole **5** with **6** could afford the isomeric products **15** – **18** (Scheme 3). The ^{13}C chemical shift indentified the pyrimidine car-



Scheme 3.

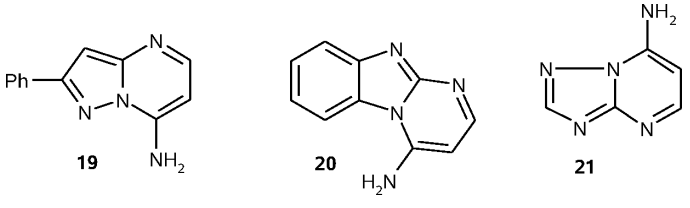


Fig. 3. Structures of compounds **19** – **21**.

bon atom C-6 at δ = 75 ppm, which clearly excludes possible formation of **16** or **18**, and we are left with **15** and **17**. NOE difference experiments indicated that the triazole proton and the amino protons do not show mutual signal enhancement, thus establishing structure **15** as the reaction product. Thus, it is believed that 3-aminotriazole **5** behaves analogously to **3** and **4**; the exocyclic amino function is also the prime site of attack by the electrophilic α,β-unsaturated moiety.

Similar to the behavior of **6** toward **3a**, **4**, and **5**, 3-(piperidin-1-yl)acrylonitrile **7** reacted with **3a**, **4**, and **5** to yield aminoazolopyrimidines **19**, **20** and **21**, respectively (Fig. 3). The structure of the latter products was established by ^{13}C NMR spectroscopy which revealed chemical shift values of $\delta \sim 90$ ppm for the pyrimidine carbons of compounds **19**, **20** and **21**, respectively. 7-Amino-1,2,4-triazolo[1,5-*a*]pyrimidine **21** was further established based on NOE difference experiments which indicated that the triazole proton and the amino protons do not show significant mutual signal enhancement.

Forty years ago Hori reported that 3-amino-5-methyl-pyrazole (**22**) reacts with ethyl acetoacetate to yield 2,5-dimethylpyrazolo[1,5-*a*]pyrimidin-7-one (**23**) but not the isomeric 2,7-dimethyl-pyrazolo[1,5-*a*] pyrimidin-5-one (**24**) (Fig. 4) [23].

In the course of our investigations, we found that the reaction of **3a** and ethyl acetoacetate **8** in acetic acid solution afforded **25** as indicated from NOE experiments showing that the methyl and the 6-H protons are proximal. Similarly, reaction of **4** and **5** with ethyl acetoacetate led to formation of 4-methyl-pyrimido[1,2-*a*]

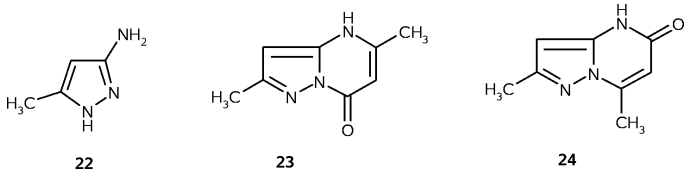


Fig. 4. Structures of compounds **22** – **24**.

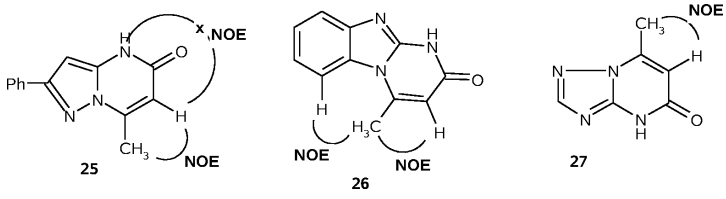


Fig. 5. Structures of compounds **25** – **27** and selected NOE correlations.

benzimidazol-2-one (**26**) and 7-methyl-1,2,4-triazolo [1,5-*a*]pyrimidin-5-one (**27**), respectively. The structures of products **26** and **27** were also derived on the basis of NOE experiments (Fig. 5). Thus, the presence or absence of an NOE between specific protons allowed the structures for these compounds to be established.

Experimental Section

General procedures

All melting points were determined on a GallenKamp electrothermal apparatus and are uncorrected. IR spectra were recorded as KBr pellets with a Pye Unicam SP 3000 infrared spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in deuterated dimethylsulfoxide [D_6]-DMSO solution at 300 MHz on a Varian Gemini NMR spectrometer using tetramethylsilane (TMS) as internal reference, and the results are expressed as δ values. Mass spectra were performed on a Shimadzu GCMS-QP 1000 Ex mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University.

*General procedure for the preparation of compounds **10a,b, 13** and **15***

A mixture of aminoazoles **3a**, **b**, **4** or **5** (0.01 mol) in pyridine (10 mL), and arylidenemalononitrile **6** (0.01 mol) was refluxed for 6 h. The solid product was filtered off and crystallized from dimethylformamide to give compounds **10a**,**b**, **13** and **15**, respectively.

*7-Amino-6-cyano-5-(4-chlorophenyl)-2-phenyl-pyrazolo [1,5-a]pyrimidine (**10a**)*

This compound was obtained as yellow crystals, (2.9 g, 84 %), m. p. 330 °C. – IR: ν = 3304, 3161 (NH_2), 2212 (CN) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]-DMSO): δ = 7.09 (s, 1H, 3-H), 7.45 – 7.59 (m, 5H, Ar-H), 7.83 (d, J = 8.2 Hz, 2H, Ar-H), 8.09 (d, J = 8.2 Hz, 2H, Ar-H), 8.83 (br., 2H, NH_2). – ^{13}C NMR (75 MHz, [D_6]-DMSO): δ = 72.13 (C-6), 94.77, 116.34 (CN), 126.38, 128.31, 128.73, 129.41, 130.37, 131.84, 134.86, 136.21, 148.71, 150.63, 156.29, 157.43. – MS (EI, 70 eV): *m/z* (%) = 345 (100) $[M]^+$. – $C_{19}H_{12}ClN_5$ (345.79): calcd. C 66.00, H 3.50, Cl 10.25, N 20.25; found C 66.20, H 3.75, Cl 10.10, N 20.12.

*7-Amino-6-cyano-5-(4-chlorophenyl)-2-(4-methylphenyl)-pyrazolo[1,5-a]pyrimidine (**10b**)*

This compound was obtained as yellow crystals, (2.88 g, 80 %), m. p. 310 °C. – IR: ν = 3304, 3233 (NH_2), 2211 (CN) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]-DMSO): δ = 2.32 (s, 3H, CH_3), 7.02 (s, 1H, 3-H), 7.25 (d, J = 8.2 Hz, 2H, Ar-H), 7.56 (d, J = 8.2 Hz, 2H, Ar-H), 7.82 (d, J = 8.2 Hz, 2H, Ar-H), 7.95 (d, J = 8.2 Hz, 2H, Ar-H), 8.83 (br., 2H, NH_2). – ^{13}C NMR (75 MHz, [D_6]-DMSO): δ = 20.94 (CH_3), 71.98 (C-6), 94.51, 116.39 (CN), 126.27, 128.27, 129.06, 129.25, 130.35, 134.83, 136.22, 138.98, 148.65, 150.55, 156.35, 157.27. – MS (EI, 70 eV): *m/z* (%) = 359 (100) $[M]^+$. – $C_{20}H_{14}ClN_5$ (359.82): calcd. C 66.76, H 3.92, Cl 9.85, N 19.46; found C 66.60, H 3.99, Cl 9.66, N 19.53.

*4-Amino-3-cyano-2-(4-chlorophenyl)-pyrimido[1,2-a] benzimidazole (**13**)*

This compound was obtained as yellow crystals, (2.46 g, 77 %), m. p. 330 °C. – IR: ν = 3421, 3326 (NH_2), 2186 (CN) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]-DMSO): δ = 7.02 (m, 1H, 7-H), 7.34 (m, 1H, 8-H), 7.53 (d, J = 9 Hz, 1H, 9-H), 7.66 (d, J = 8.2 Hz, 2H, Ar-H), 7.82 (d, J = 8.2 Hz, 2H, Ar-H), 8.22 (d, J = 9 Hz, 1H, 6-H), 8.62 (br., 2H, NH_2). – ^{13}C NMR (75 MHz, [D_6]-DMSO): δ = 72.26, 112.68, 12.14, 121.28, 121.78, 125.05, 126.28, 130.85, 131.45, 136.72, 136.24, 143.38, 152.58, 153.15, 163.07. – MS (EI, 70 eV): *m/z* (%) = 319 (38.2) $[M]^+$. – $C_{17}H_{10}ClN_5$ (319.76): calcd. C 63.86, H 3.15, Cl 11.09, N 21.90; found C 63.66, H 3.02, Cl 11.00, N 21.87.

*7-Amino-6-cyano-5-(4-chlorophenyl)-triazolo[1,5-a] pyrimidine (**15**)*

This compound was obtained as colorless crystals, (2.08 g, 77 %), m. p. 310 °C. – IR: ν = 3304, 3233 (NH_2), 2211 (CN) cm^{-1}. – ^1H NMR (300 MHz, [D_6]-DMSO): δ = 7.56 (d, J = 8.2 Hz, 2H, Ar-H), 7.83 (d, J = 8.2 Hz, 2H, Ar-H), 8.54 (s, 1H, 2-H), 9.20 (br., 2H, NH_2). – ^{13}C NMR (75 MHz, [D_6]-DMSO): δ = 75.54 (C-6), 115.43 (CN), 120.71, 128.37, 130.53, 135.47, 151.47, 154.94, 155.93, 163.06. – MS (EI, 70 eV): *m/z* (%) = 270 (100) $[M]^+$. – $C_{12}H_7ClN_6$ (270.68): calcd. C 53.25, H 2.61, Cl 13.10, N 31.05; found C 53.08, H 2.44, Cl 13.25, N 31.02.

*General procedure for the preparation of compounds **19**, **20** and **21***

A solution of **3a**, **4** and **5** (0.01 mol) and **7** (1.36 g, 0.01 mol) in pyridine (10 mL) was refluxed for 5 h, then left to cool at r. t. The solid product, formed was collected by filtration and crystallized from dimethylformamide to give compounds **19**, **20** and **21**, respectively.

*7-Amino-2-phenyl-pyrazolo[1,5-a]pyrimidine (**19**)*

This compound was obtained as yellow crystals, (1.62 g, 77 %), m. p. 200 °C. – IR: ν = 3374, 3297 (NH_2) cm^{-1}. – ^1H NMR (300 MHz, [D_6]-DMSO): δ = 6.14 (d, J = 8 Hz, 1H, 6-H), 6.85 (s, 1H, 3-H), 7.35 – 7.58 (m, 5H, Ar-H), 7.81 (br., 2H, NH_2), 8.05 (d, J = 8 Hz, 1H, 5-H). – ^{13}C NMR (75 MHz, [D_6]-DMSO): δ = 87.95, 91.08, 126.14, 128.62, 128.99, 133.0, 147.85, 149.49, 150.46, 153.85. – MS (EI, 70 eV): *m/z* (%) = 210 (100) $[M]^+$. – $C_{12}H_{10}N_4$ (210.24): calcd. C 68.56, H 4.79, N 26.65; found C 68.60, H 4.55, N 26.46.

*4-Amino-pyrimido[1,2-a]benzimidazole (**20**)*

This compound was obtained as yellow crystals, (1.23 g, 67 %), m. p. 272 °C. – IR: ν = 3262, 3069 (NH_2) cm^{-1}. – ^1H NMR (300 MHz, [D_6]-DMSO): δ = 6.21 (d, J = 8 Hz, 1H, 3-H), 7.20 (m, 1H, 7-H), 7.44 (m, 1H, 8-H), 7.69 (d, J = 9 Hz, 1H, 9-H), 8.22 (d, J = 8 Hz, 1H, 2-H), 8.39 (d, J = 9 Hz, 1H, 6-H), 12.54 (br., 2H, NH_2). – ^{13}C NMR (75 MHz, [D_6]-DMSO): δ = 89.16, 114.42, 117.59, 119.20, 121.17, 125.10, 125.91, 144.06, 152.30, 153.99. – MS (EI, 70 eV): *m/z* (%) = 184 (100) $[M]^+$. – $C_{10}H_8N_4$ (184.20): calcd. C 65.21, H 4.38, N 30.42; found C 65.35, H 4.33, N 30.32.

*7-Amino-triazolo[1,5-a]pyrimidine (**21**)*

This compound was obtained as colorless crystals, (0.93 g, 69 %), m. p. 280 °C. – IR: ν = 3334, 3264 (NH_2) cm^{-1}. – ^1H NMR (300 MHz, [D_6]-DMSO): δ = 6.31 (d, J = 8 Hz, 1H, 6-H), 8.12 (br., 2H, NH_2), 8.25 (d, J = 8 Hz, 1H, 5-H), 8.42 (s, 1H, 2-H). – ^{13}C NMR (75 MHz, [D_6]-DMSO): δ = 90.79, 149.23, 153.47, 154.36, 155.86. – MS (EI, 70 eV): *m/z* (%) = 135 (100) $[M]^+$. – $C_5H_5N_5$ (135.13): calcd. C 44.44, H 3.73, N 51.83; found C 44.40, H 3.55, N 51.79.

*General procedure for the preparation of compounds **25**, **26** and **27***

A mixture of aminoazoles **3a**, **4** or **5** (0.01 mol) and ethyl acetoacetate **8** (1.3 g, 0.01 mol) was refluxed in acetic acid solution (10 mL) for 3 h. The solid product formed was collected by filtration and crystallized from dimethylformamide to give compounds **25**, **26** and **27**, respectively.

*7-Methyl-2-phenyl-pyrazolo[1,5-a]pyrimidin-5-one (**25**)*

This compound was obtained as yellow crystals, (1.4 g, 62 %), m. p. 320 °C. – IR: ν = 3319 (NH), 1676 (CO) cm^{-1}. – ^1H NMR (300 MHz, [D_6]-DMSO): δ = 2.27 (s, 3H, CH_3), 5.57 (s, 1H, 6-H), 6.54 (s, 1H, 3-H), 7.35 – 7.45 (m, 3H, Ar-H), 7.94 – 7.97 (m, 2H, Ar-H), 12.43 (br., 1H, NH). – ^{13}C NMR (75 MHz, [D_6]-DMSO): δ = 18.59 (CH_3), 85.47, 95.24, 120.76, 126.10, 128.62, 132.48, 142.73, 150.12, 152.90, 156.17 (CO). – MS (EI, 70 eV): *m/z* (%) = 225 (100) $[M]^+$. – $C_{13}H_{11}N_3O$ (225.25): calcd. C 69.32, H 4.92, N 18.65; found C 69.19, H 4.55, N 18.42.

*4-Methyl-pyrimido[1,2-a]benzimidazol-2-one (**26**)*

This compound was obtained as yellow crystals, (1.27 g, 64 %), m. p. 200 °C. – IR: ν = 3031 (NH), 1690 (CO) cm^{-1}. – ^1H NMR (300 MHz, [D_6]-DMSO): δ = 2.27 (s, 3H, CH_3), 5.79 (s, 1H, 3-H), 7.23 (m, 1H, 7-H), 7.37 (m, 1H, 8-H), 7.46 (d, J = 9 Hz, 1H, 9-H), 8.39 (d, J = 9 Hz, 1H, 6-H), 12.17 (br., 1H, NH). – ^{13}C NMR (75 MHz, [D_6]-DMSO): δ = 21.71 (CH_3), 98.42, 111.43, 113.55, 119.61, 120.74, 125.37, 126.81, 135.17, 148.33, 159.13 (CO). – MS (EI, 70 eV): *m/z* (%) = 199 (100) $[M]^+$. – $C_{11}H_9N_3O$ (199.21): calcd. C 66.32, H 4.55, N 21.09; found C 66.30, H 4.55, N 21.22.

*7-Methyl-triazolo[1,5-a]pyrimidin-5-one (**27**)*

This compound was obtained as colorless crystals, (0.98 g, 65 %), m. p. 280 °C. – IR: ν = 3106 (NH), 1666 (CO) cm^{-1}. – ^1H NMR (300 MHz, [D_6]-DMSO): δ = 2.24 (s, 3H, CH_3), 5.67 (s, 1H, 6-H), 8.07 (s, 1H, 2-H), 12.52 (br., 1H, NH). – ^{13}C NMR (75 MHz, [D_6]-DMSO): δ = 18.50 (CH_3), 98.0, 121.20, 150.46, 151.46, 155.68 (CO). – MS (EI, 70 eV): *m/z* (%) = 150 (100) $[M]^+$. – $C_6H_6N_4O$ (150.14): calcd. C 48.00, H 4.03, N 37.32; found C 47.19, H 3.29, N 37.05.

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