Monatsh Chem (2013) 144:677–680
DOI 10.1007/s00706-012-0847-9

ORIGINAL PAPER

7-Deazaadenines: synthesis of some new pyrrolo[2,3-*d*]-pyrimidin-4-amines

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Received: 4 October 2011 / Accepted: 22 August 2012 / Published online: 28 September 2012

Abstract New 2-aryl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amines (derivatives of 7-deazaadenine) were prepared through cyclocondensation of 2-amino-1*H*-pyrrole-3-carbonitriles with aryl nitriles in the presence of potassium *t*-butoxide in boiling *t*-butanol. All synthesized compounds were characterized on the basis of their spectral and microanalytical data.

Keywords 2-Amino-1*H*-pyrrole-3-carbonitriles · Aryl nitriles · 7-Deazaadenines · Pyrrolo[2,3-*d*]pyrimidin-4-amines

Introduction

In the last few decades, the chemistry of pyrrole and fused heterocyclic pyrroles has received considerable attention owing to their synthetic and effective biological importance [1–3]. Because of the presence of a pyrrolo[2,3-*d*]-pyrimidine moiety in some important antibiotics [4–6] and their structural resemblance to purines (**A**), interest has arisen in the construction of such compounds. Moreover, these compounds have been reported to possess significant anti-HIV [7], antitumor [8], antimicrobial [9], and antiangiogenic [10] activities. Pyrrolo[2,3-*d*]pyrimidin-4-amines (**C**) may be regarded as analogues of adenine (**B**) in which its *N*-7 (purine numbering) has been replaced by a CH group and therefore can be named as 7-deazaadenines. A number of these compounds are known to show anti-inflammatory [11], antifungal [12], and antibacterial [12] activities. Also, some 4-substituted aminopyrrolo[2,3-*d*]-pyrimidine derivatives are selective A_1-adenosine receptor antagonists [13] (Fig. 1).

These findings encouraged us to synthesize some new 7-deazaadenine derivatives. Therefore, in continuation of our previous works in the synthesis of new heterocyclic compounds with potential biological activities [14–30], in this paper we report a convenient synthesis of new 2-aryl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amines (derivatives of 7-deazaadenine) **3a–3f** by reaction of 2-amino-1*H*-pyrrole-3-carbonitriles **1a–1c** [31] with aryl nitriles **2a–2c** in the presence of potassium *t*-butoxide in boiling *t*-butanol (Scheme 1).

Results and discussion

Cyclocondensation of 2-amino-1*H*-pyrrole-3-carbonitriles **1a–1c** with aryl nitriles **2a–2c** in the presence of potassium *t*-butoxide in *t*-butanol under reflux gave products identified as 2-aryl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amines **3a–3f** (Table 1). The structures of new compounds **3a–3f** were deduced from their spectral and microanalytical data. For example, the ^{1}H NMR spectrum of **3d** in $CDCl_3$ did not show the NH_2 signal at $\delta = 4.06$ ppm belonging to the precursor **1b**, but instead showed a broad 2H signal at 5.05 ppm for an NH_2 group as well as a sharp 3H signal at 2.50 ppm for methyl protons indicating the formation of the bicyclic compound **3d**. The IR spectrum was devoid of the CN absorption band at 2,191 cm^{-1} of the precursor, which shows the inclusion of the nitrile moiety in the cyclocondensation process. Also this compound gave

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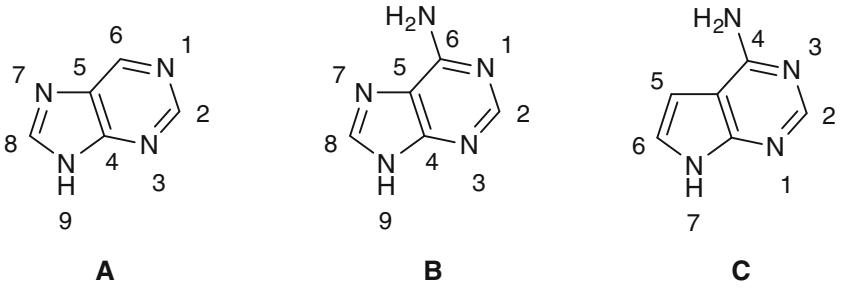
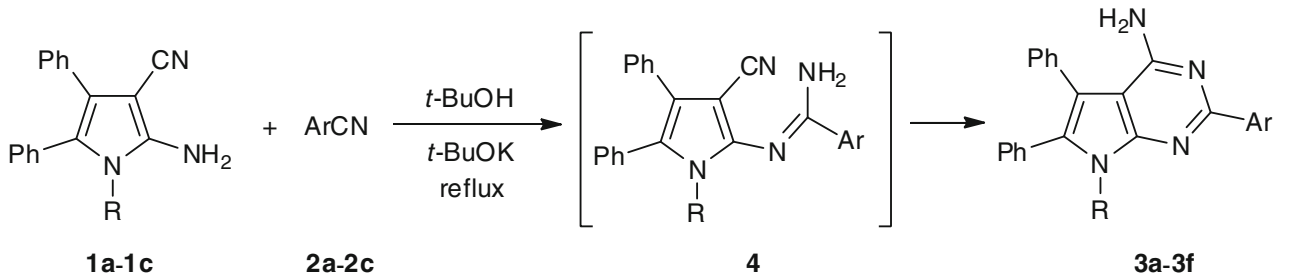


Fig. 1 Purine core (**A**), adenine (B), and its 7-deaza analogue (**C**)



1a: R = Me
1b: R = C_6H_{11}
1c: R = CH_2Ph
2a: Ar = Ph
2b: Ar = 4-ClC_6H_4
2c: Ar = 3-MeC_6H_4

3a: R = Me, Ar = Ph
3b: R = C_6H_{11}, Ar = Ph
3c: R = C_6H_{11}, Ar = 4-ClC_6H_4
3d: R = C_6H_{11}, Ar = 3-MeC_6H_4
3e: R = CH_2Ph, Ar = Ph
3f: R = CH_2Ph, Ar = 3-MeC_6H_4

Scheme 1

Table 1 Synthesis of 2-aryl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amines **3a**–**3f** (Scheme 1)

Entry	*R*	Ar	Product	Time/h	Yield/%[a]	M.p./°C
1	Methyl	C_6H_5	**3a**	6	71	232–233
2	Cyclohexyl	C_6H_5	**3b**	8	79	206–207
3	Cyclohexyl	4-ClC_6H_4	**3c**	8	67	207–209
4	Cyclohexyl	3-MeC_6H_4	**3d**	8	66	261–262
5	Benzyl	C_6H_5	**3e**	7	72	245–247
6	Benzyl	3-MeC_6H_4	**3f**	7	65	164–167

[a] Isolated yields

satisfactory elemental analysis data corresponding to the molecular formula $C_{31}H_{30}N_4$. The formation of the products **3a**–**3f** is assumed to proceed via the intermediates **4** prepared by initial nucleophilic attack of the amino group in the 2-position of pyrrole on the cyano group of aryl nitriles. However, under these conditions, attempts to isolate these intermediates failed after careful monitoring of the reactions.

In conclusion, we have reported a facile synthesis of some new pyrrolo[2,3-*d*]pyrimidin-4-amines (7-deazaadenines) in good yields by cyclocondensation of 2-amino-1*H*-pyrrole-3-carbonitriles with aryl nitriles in the presence of potassium *t*-butoxide in boiling *t*-butanol.

Experimental

Melting points were recorded on a Stuart SMP3 melting point apparatus. The IR spectra were obtained using a Bruker Tensor 27 spectrophotometer from KBr disks. ^{1}H NMR (500 MHz) spectra were recorded with a Bruker 500 MHz spectrometer. ^{13}C NMR (100 MHz) spectra were recorded with a Bruker 400 MHz spectrometer. Mass spectra were obtained using a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer.

*General procedure for the preparation of 2-aryl-7H-pyrrolo[2,3-d]pyrimidin-4-amines **3a–3f***

To a solution of 5 mmol 2-amino-1*H*-pyrrole-3-carbonitriles **1a**–**1c** and 1 mmol potassium *t*-butoxide in 25 cm^3 *t*-butanol, 5.5 mmol aryl nitriles **2a**–**2c** was added. The reaction mixture was heated under reflux for 6–8 h. The reaction was monitored by TLC. Upon completion, the solvent was evaporated in vacuo, the residue was dissolved in 25 cm^3 water, and subsequently neutralized by 1 N HCl. The crude product was collected and recrystallized from

ethanol to give compounds **3a**–**3f** in 65–79 % yields (Table 1).

7-Methyl-2,5,6-triphenyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**3a**, $C_{25}H_{20}N_4$)
^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.84$ (s, 3H, CH_3), 5.15 (s, 2H, NH_2), 7.27–7.55 (m, 13H, H_{ar}), 8.50–8.55 (m, 2H, H_{ar}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 29.87$, 100.54, 113.56, 126.86, 127.90, 128.13, 128.29, 128.39, 128.58, 129.30, 130.54, 130.80, 130.87, 134.84, 135.44, 139.22, 152.24, 156.73, 158.16 ppm; IR (KBr): $\bar{\nu} = 3{,}286$, 3,162 (NH_2) cm^{-1}; MS: *m/z* (%) = 376 (M^+, 71), 257 (15), 256 (22), 214 (14), 189 (12), 118 (14), 104 (88), 91 (19), 77 (100), 69 (37), 57 (62), 55 (62).

7-Cyclohexyl-2,5,6-triphenyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**3b**, $C_{30}H_{28}N_4$)
^{1}H NMR ($CDCl_3$): $\delta = 1.20$–2.00 (m, 8H, cyclohexyl), 2.90–3.05 (m, 2H, cyclohexyl), 4.00–4.10 (m, 1H, CH–N), 5.09 (br s, 2H, NH_2), 7.25–7.70 (m, 13H, H_{ar}), 8.53 (d, 2H, $J = 8.2$ Hz, H_{ar}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.60$, 26.38, 31.44, 56.81, 101.12, 113.33, 126.67, 127.84, 128.15, 128.25, 128.30, 128.39, 129.18, 130.58, 131.11, 131.55, 135.09, 135.52, 139.41, 151.67, 156.82, 156.87 ppm; IR (KBr): $\bar{\nu} = 3{,}292$, 3,169 (NH_2) cm^{-1}; MS: *m/z* (%) = 444 (M^+, 92), 362 (100), 259 (16), 257 (16), 241 (21), 214 (12), 128 (10), 104 (36), 83 (12), 77 (18), 67 (14), 57 (9), 55 (31).

2-(4-Chlorophenyl)-7-cyclohexyl-5,6-diphenyl-7H-pyrrolo-[2,3-d]pyrimidin-4-amine (**3c**, $C_{30}H_{27}ClN_4$)
^{1}H NMR ($CDCl_3$): $\delta = 1.20$–2.00 (m, 8H, cyclohexyl), 2.85–3.00 (m, 2H, cyclohexyl), 4.00–4.10 (m, 1H, CH–N), 5.04 (br s, 2H, NH_2), 7.20–7.50 (m, 12H, H_{ar}), 8.46 (d, 2H, $J = 8.6$ Hz, H_{ar}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.61$, 26.34, 31.46, 56.80, 101.19, 113.35, 126.72, 128.20, 128.31, 128.37, 128.40, 129.13, 130.56, 131.07, 131.43, 134.97, 135.08, 135.68, 137.98, 151.52, 155.89, 156.79 ppm; IR (KBr): $\bar{\nu} = 3{,}306$, 3,145 (NH_2) cm^{-1}; MS: *m/z* (%) = 480 (M^++2, 28), 478 (M^+, 85), 396 (100), 259 (33), 257 (26), 241 (47), 214 (28), 189 (18), 155 (35), 138 (59), 128 (32), 104 (26), 83 (34), 77 (35), 57 (37), 55 (79).

7-Cyclohexyl-2-(3-methylphenyl)-5,6-diphenyl-7H-pyrrolo-[2,3-d]pyrimidin-4-amine (**3d**, $C_{31}H_{30}N_4$)
^{1}H NMR ($CDCl_3$): $\delta = 0.85$–1.95 (m, 8H, cyclohexyl), 2.50 (s, 3H, CH_3), 2.90–3.05 (m, 2H, cyclohexyl), 4.00–4.10 (m, 1H, CH–N), 5.05 (br s, 2H, NH_2), 7.20–7.45 (m, 12H, H_{ar}), 8.32 (d, 2H, $J = 8.0$ Hz, H_{ar}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.71$, 25.63, 26.39, 31.43, 56.76, 101.08, 113.29, 125.01, 126.64, 128.13, 128.18, 128.29, 128.38, 128.49, 129.96, 130.59, 131.12, 131.58, 135.13, 135.43, 137.68, 139.40, 151.69, 156.83, 157.08 ppm; IR (KBr): $\bar{\nu} = 3{,}304$, 3,161 (NH_2) cm^{-1}; MS: *m/z* (%) = 458 (M^+, 15), 376 (100), 259 (11), 241 (10), 125 (14), 111 (21), 97 (30), 83 (32), 71 (35), 69 (30), 57 (57), 55 (54).

7-Benzyl-2,5,6-triphenyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**3e**, $C_{31}H_{24}N_4$)
^{1}H NMR ($CDCl_3$): $\delta = 5.16$ (s, 2H, NH_2), 5.52 (s, 2H, CH_2), 6.95–7.65 (m, 18H, H_{ar}), 8.60-8.65 (m, 2H, H_{ar}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 46.14$, 100.53, 114.21, 126.86, 127.24, 127.65, 128.01, 128.25, 128.28, 128.38, 128.53, 129.16, 129.35, 130.53, 130.87, 131.22, 134.69, 135.34, 138.35, 139.22, 152.32, 156.91, 158.24 ppm; IR (KBr): $\bar{\nu} = 3{,}285$, 3,158 (NH_2) cm^{-1}; MS: *m/z* (%) = 452 (M^+, 100), 375 (10), 361 (49), 257 (16), 241 (8), 214 (9), 187 (12), 128 (15), 104 (55), 91 (81), 77 (36), 59 (91), 57 (40).

7-Benzyl-2-(3-methylphenyl)-5,6-diphenyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**3f**, $C_{32}H_{26}N_4$)
^{1}H NMR ($CDCl_3$): $\delta = 2.49$ (s, 3H, CH_3), 5.18 (br s, 2H, NH_2), 5.52 (s, 2H, CH_2), 7.05–7.45 (m, 17H, H_{ar}), 8.33 (d, 2H, $J = 7.0$ Hz, H_{ar}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.65$, 46.13, 100.48, 114.18, 125.18, 126.82, 126.83, 127.21, 127.68, 128.22, 128.34, 128.51, 128.56, 128.57, 130.15, 130.51, 130.88, 131.21, 134.69, 135.30, 137.77, 138.36, 139.12, 152.33, 156.81, 158.38 ppm; IR (KBr): $\bar{\nu} = 3{,}305$, 3,134 (NH_2) cm^{-1}; MS: *m/z* (%) = 466 (M^+, 100), 389 (11), 375 (61), 257 (18), 241 (9), 214 (8), 194 (11), 128 (14), 118 (41), 104 (9), 91 (91), 77 (16), 57 (28), 55 (24).

Acknowledgments The authors express their gratitude to the Islamic Azad University, Mashhad Branch for its financial support.

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