Asian Journal of Chemistry Vol. 22, No. 6 (2010), 4625-4628

Synthesis of Pyrrolo[2,3-d]pyrimidin-4-ones(7-deazapurines) Under Solvent- and Catalyst-Free Conditions

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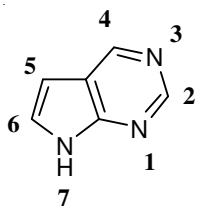
A facile one-pot synthesis of some new 3,7-dihydro-4*H*-pyrrolo[2,3-d]pyrimidin-4-ones in good yields has been developed through cyclo-condensation of 2-amino-1*H*-pyrrole-3-carboxamides with triethyl orthoesters in solvent- and catalyst-free conditions.

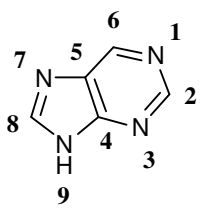
Key Words: Pyrrolo[2,3-d]pyrimidin-4-ones, 7-Deazapurines, Triethyl orthoesters, Solvent-free conditions, Catalyst-free conditions.

INTRODUCTION

Pyrrolo[2,3-d]pyrimidine (**I**) may be regarded as an analogue of purine (**II**) in which its N-7 has been replaced by a CH group and therefore can be named as 7-deazapurine. Literature reports had already established pyrrolo[2,3-d]pyrimidins as antitumor[1], antimicrobial[2], antiangiogenic[3] agents with potential application as enzyme inhibitors[4]. 7-Deazapurine moiety is also found in some important antibiotics[5-7]. Moreover, these compounds have been shown to induce neurogenesis in murine embryonic stem cells[8]. On the other hand, 7-deazapurines have been synthesized as analogues of potent A_1- and A_2-adenosine receptor antagonists[9]. Some of 4-substituted aminopyrrolo[2,3-d]pyrimidins have been identified as selective A_1-adenosine receptor antagonists[10]. The later compounds are generally prepared from pyrrolo[2,3-d]-pyrimidin-4-ones as precursors[10].



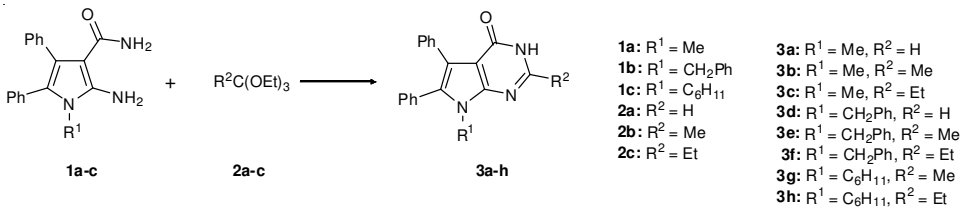
(I)



(II)

Prompted by these findings and our interest in the synthesis of new heterocyclic compounds with potential biological activities[11-14], in this paper we wish to report an efficient approach to the synthesis of new 3,7-dihydro-4*H*-pyrrolo[2,3-

d]pyrimidin-4-ones (**3a-h**) (7-deazapurines) through cyclocondensation of 2-amino-1*H*-pyrrole-3-carboxamides (**1a-c**) with triethyl orthoesters (**2a-c**) without any solvent and catalyst (**Scheme-I**).



Scheme-I: Synthesis of new pyrrolo[2,3-d]pyrimidin-4-ones (7-deazapurines)

EXPERIMENTAL

Melting points were recorded on an electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrophotometer as KBr disks. The ^{1}H NMR (100 and 500 MHz) spectra were recorded on Bruker AC100 and Bruker DRX500 spectrometers. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV.

General procedure for the synthesis of 3,7-dihydro-4*H*-pyrrolo[2,3-d]-pyrimidin-4-ones (3a-h): A mixture of 2-amino-1*H*-pyrrole-3-carboxamides (**1a-c**)[15] (1 mmol) and triethyl orthoesters (**2a-c**) (1.5 mmol) was heated under reflux for 6-8 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature. The precipitate was filtered off, washed with *n*-hexane and recrystallized from ethanol to give new compounds **3a-h** in good yields.

Spectral data for new compounds 3a-h

7-Methyl-5,6-diphenyl-3,7-dihydro-4*H*-pyrrolo[2,3-d]pyrimidin-4-one (3a): Yield 70 %; m.p. 287-289 ºC; ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 3.57 (s, 3H, NCH_3), 7.07-7.42 (m, 10H, phenyl groups), 7.97 (s, 1H, CH of pyrimidine ring), 11.92 (s, 1H, NH); IR (KBr, ν_{max}, cm^{-1}): 1655 (C=O), 3449 (NH); MS, m/z: 301 (M^+).

2,7-Dimethyl-5,6-diphenyl-3,7-dihydro-4*H*-pyrrolo[2,3-d]pyrimidin-4-one (3b): Yield 66 %; m.p. 350-352 ºC; ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 2.38 (s, 3H, CH_3), 3.52 (s, 3H, NCH_3), 7.08-7.42 (m, 10H, phenyl groups), 11.81 (s, 1H, NH); IR (KBr, ν_{max}, cm^{-1}): 1652 (C=O), 3423 (NH); MS, m/z: 315 (M^+).

2-Ethyl-7-methyl-5,6-diphenyl-3,7-dihydro-4*H*-pyrrolo[2,3-d]pyrimidin-4-one (3c): Yield 65 %; m.p. 307-308 ºC; ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 1.26 (t, 3H, J = 7.5 Hz, CH_3), 2.65 (q, 2H, *J* = 7.5 Hz, CH_2), 3.54 (s, 3H, NCH_3), 7.08-7.41 (m, 10H, phenyl groups), 11.78 (s, 1H, NH); IR (KBr, ν_{max}, cm^{-1}): 1655 (C=O), 3449 (NH); MS, m/z: 329 (M^+).

7-Benzyl-5,6-diphenyl-3,7-dihydro-4*H*-pyrrolo[2,3-d]pyrimidin-4-one (3d): Yield 60 %; m.p. 220-222 ºC; ^{1}H NMR (100 MHz, $CDCl_3$, δ ppm): 5.34 (s, 2H, CH_2), 6.70-7.50 (m, 15H, phenyl groups), 7.80 (s, 1H, CH of pyrimidine ring), 12.32 (s, 1H, NH); IR (KBr, ν_{max}, cm^{-1}): 1654 (C=O), 3422 (NH); MS, m/z: 377 (M^+).

7-Benzyl-2-methyl-5,6-diphenyl-3,7-dihydro-4*H*-pyrrolo[2,3-d]pyrimidin-4-one (3e): Yield 67 %; m.p. 290-292 ºC; ^{1}H NMR (100 MHz, $CDCl_3$, δ ppm): 2.50 (s, 3H, CH_3), 5.33 (s, 2H, CH_2), 6.65-7.50 (m, 15H, phenyl groups), 12.56 (s, 1H, NH); IR (KBr, ν_{max}, cm^{-1}): 1652 (C=O), 3424 (NH); MS, m/z: 391 (M^+).

7-Benzyl-2-ethyl-5,6-diphenyl-3,7-dihydro-4*H*-pyrrolo[2,3-d]pyrimidin-4-one (3f): Yield 64 %; m.p. 277-279 ºC; ^{1}H NMR (100 MHz, $CDCl_3$, δ ppm): 1.36 (t, 3H, J = 7.5 Hz, CH_3), 2.77 (q, 2H, J = 7.5 Hz, CH_2), 5.32 (s, 2H, CH_2), 6.70-7.50 (m, 15H, phenyl groups), 12.06 (s, 1H, NH); IR (KBr, ν_{max}, cm^{-1}): 1656 (C=O), 3424 (NH); MS, m/z : 405 (M^+).

7-Cyclohexyl-2-methyl-5,6-diphenyl-3,7-dihydro-4*H*-pyrrolo[2,3-d]pyrimidin-4-one (3g): Yield 67 %; m.p. 261-262 ºC; ^{1}H NMR (100 MHz, $CDCl_3$, δ ppm): 0.95-2.00 (m, 8H, cyclohexyl), 2.30-2.80 (m, 5H, cyclohexyl and CH_3), 3.70-4.10 (m, 1H, CH-N), 6.90-7.45 (m, 10H, phenyl groups), 12.32 (s, 1H, NH); IR (KBr, ν_{max}, cm^{-1}): 1655 (C=O), 3429 (NH); MS, m/z: 383 (M^+).

7-Cyclohexyl-2-ethyl-5,6-diphenyl-3,7-dihydro-4*H*-pyrrolo[2,3-d]pyrimidin-4-one (3h): Yield 62 %; m.p. 338-340 ºC; ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 1.00-1.20 (m, 3H, cyclohexyl), 1.26 (t, 3H, J = 7.5 Hz, CH_3), 1.58 (d, 1H, J = 12 Hz, cyclohexyl), 1.77 (d, 4H, J = 10.4 Hz, cyclohexyl), 2.56 (m, 2H, cyclohexyl), 2.65 (q, 2H, J = 7.5 Hz, CH_2), 3.79 (t, 1H, J = 12 Hz, CH-N), 7.02-7.42 (m, 10H, phenyl groups), 11.70 (br, 1H, NH); IR (KBr, ν_{max}, cm^{-1}): 1655 (C=O), 3424 (NH); MS, m/z: 397 (M^+).

RESULTS AND DISCUSSION

Treatment of 2-amino-1*H*-pyrrole-3-carboxamides (**1a-c**) with triethyl orthoesters (**2a-c**) under reflux without any solvent and catalyst gave products which were identified as 3,7-dihydro-4*H*-pyrrolo[2,3-d]pyrimidin-4-ones (**3a-h**) (**Scheme-I**). The structural assignments of new compounds **3a-h** were based upon the spectral data.

The ^{1}H NMR spectrum of **3e** did not show the two NH_2 signals at δ 5.08 and 5.30 ppm, but instead showed a 1H signal at δ 12.56 ppm for NH group as well as a sharp 3H signal at δ 2.50 for methyl protons indicating the formation of the bicyclic compound **3e**. Also, the signal of methylene group shifted of δ 4.98 ppm for **1b** to δ 5.33 ppm. The IR spectrum showed a band at 3424 cm^{-1} for NH absorption and a band at 1652 cm^{-1} for C=O group. The MS of **3e** showed a molecular ion peak at m/z: 391 (M^+) corresponding to the m.f. $C_{26}H_{21}N_3O$.

Conclusion

In conclusion, we have reported the synthesis of some new 3,7-dihydro-4*H*-pyrrolo[2,3-d]pyrimidin-4-ones (**3a-h**) (7-deazapurines) through cyclocondensation of 2-amino-1*H*-pyrrole-3-carboxamides (**1a-c**) with triethyl orthoesters (**2a-c**) without any solvent and catalyst.

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(*Received*: 17 September 2009; *Accepted*: 17 February 2010) AJC-8452