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Pyrazolo[3,4-*d*]pyrimidine Analogues of Isoguanine

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Key Words: 4-amino-1-phenyl-5*H*-pyrazolo[3,4-*d*]pyrimidin-6-one; isoguanine analogue; nucleosides; isocyanate; ring annulation

Abstract: *4-Amino-1-phenyl-5H-pyrazolo[3,4-d]pyrimidin-6-one (5a) was synthesized in 68% yield in a one pot reaction involving the condensation of 5-amino-1-phenylpyrazole-4-carbonitrile with benzoyl isocyanate followed by an annulation with ammonia.*

The synthesis of 1-substituted isoguanosines is readily achieved via isocyanate addition to 5-aminoimidazole-4-carbonitrile derivatives, followed by ring closure of the resultant 5-(carbamoylamino)imidazole-4-carbonitriles.[1] The synthesis of isoguanosine, the parent compound having no additional substitutents in the 6-membered pyrimidine ring, as well as the isomeric guanosine[2], in reasonable yield has proven more elusive. Recent syntheses of isoguanosine recognised the facile ring closure of 5-(carbamoylamino)imidazole-4-carbonitriles achieving these intermediates via desulphurisation with dicyclohexylcarbodiimide (DCC)[3] or mercury salts[4]. Isoguanosine was synthesized in 68% overall yield from 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide via DCC desulphurisation.[3]

A similar synthetic challenge arose in the synthesis of the analogous unsubstituted 6-membered pyrimidine ring of 4-amino-1-phenyl-5*H*-pyrazolo[3,4-*d*]pyrimidin-6-one (**5a**). The substituted pyrimidine ring analogues were readily synthesized and have receptor affinity at A_1 and A_2 adenosine receptors.[5] Following the desulphurisation strategy[3] we accomplished the synthesis of **5a** in 28% yield from 5-amino-1-phenylpyrazole-4-carbonitrile (**1a**) via **2a, 3a** and **4a**.[6] As this pathway involved nitrile to amide to nitrile conversion we now report a synthesis that avoids this iteration. **1a** and benzoyl isocyanate (1.5 equiv) in DMF were stirred at 60°C for 12 hrs. The solvent was evaporated under reduced pressure to produce a white solid which was recrystallised from a mixture of ethyl acetate and hexane to yield 5-(N^1-benzoylcarbamoyl)amino-1-phenylpyrazole-4-carbonitrile (**4a**).[7] **4a** was dissolved in a mixture of DMF and ammonium hydroxide (28%) and stirred at room temperature for 48 hrs. The solvent was evaporated under reduced pressure and the crude product recrystallised from DMSO and water to afford pure **5a** in 50% overall yield from **1a**.[8] 5-Amino-1-(3-chlorophenyl)pyrazole-4-carbonitrile (**1b**) was used to prepare 4-amino-1-(3-chlorophenyl)-5*H*-pyrazolo[3,4-*d*]pyrimidin-6-one (**5b**) in 65% overall yield.[9,10]

The synthesis of **5a** from **1a** in a one pot reaction could be achieved, even though the base required to effect ring closure could not be added to the initial reaction mixture as it resulted in formation of a complex mixture. **1a** and benzoyl isocyanate (1.5 equiv) in DMF were stirred at 60°C for 12 hrs, ammonium hydroxide (28 %) added, the reaction mixture stirred at 60°C for a further 24 hrs, and workup as above gave pure **5a** in 68% overall yield.

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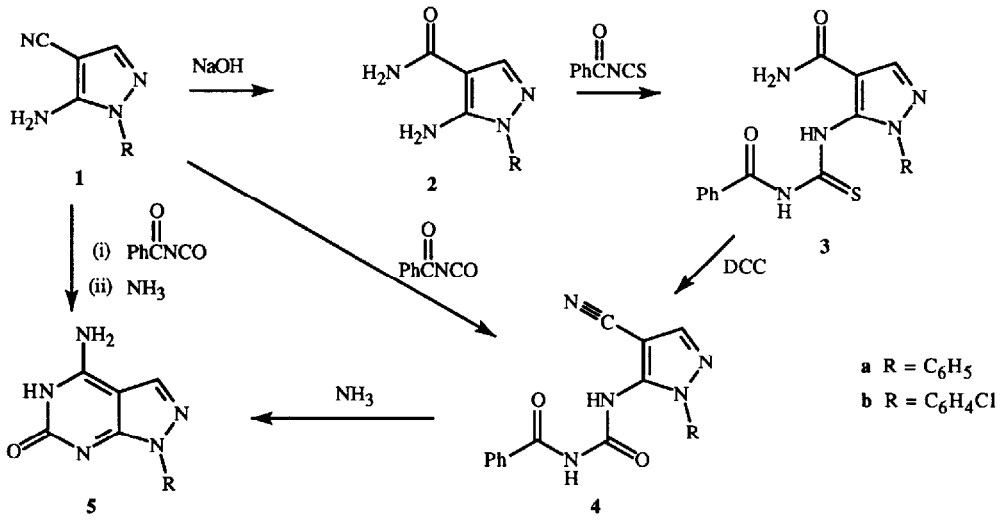

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7. Compound **4a** : mp 194-195.5°C. IR (KBr) : 3250, 3200, 1700, 1670 cm^{-1}. ^{1}H-NMR (250.12 MHz, DMSO-d_6) : δ 7.49-7.99 (m, 10H, $C_{arom}H$), 8.30 (s, 1H, C_3H), 10.98 (br s, 1H, NH), 11.33 (br s, 1H, NH). ^{13}C-NMR (62.8 MHz, DMSO-d_6) : δ 89.2 (s, C_4), 112.9 (s, CN), 124.4 (d), 128.4 (d), 128.6 (d), 129.1 (d), 129.5 (d), 131.7 (s), 133.4 (d), 137.2 (s), 140.4 (s, C_5), 142.4 (d, C_3), 150.9 (s, C=O), 168.5 (s, C=O).
8. Compound **5a** : mp 345-348°C. IR (KBr) 3350, 3180, 1670 cm^{-1}. ^{1}H NMR (250.12 MHz, DMSO-d_6) : δ 7.21-8.13 (m, 5H, $C_{arom}H$), 7.27 (br s, 1H, NH), 8.14 (s,1H, H_3), 8.71 (br s, 1H, NH), 11.92 (br s, 1H, NH). ^{13}C NMR (62.8 MHz, DMSO-d_6) : δ 92.7 (s, C_{3a}), 120.3 (d, $C_{2',6'}$), 125.4 (d, $C_{4'}$), 128.8 (d, $C_{3',5'}$), 135.5 (d, C_3), 139.3 (s, $C_{1'}$), 153.9 (s,C_4), 156.5 (s, C_{7a}), 157.8 (s, C_6). Anal. Calcd. for $C_{11}H_9N_5O$: C, 58.14; H, 3.99; N, 30.82. Found : C, 57.9; H, 4.1; N, 30.5.
9. Compound **4b** : mp 146-149°C. IR (KBr) 3450, 2220, 1720, 1660 cm^{-1}. ^{1}H NMR (250.12 MHz, DMSO-d_6) : δ 7.50-8.00 (m, 4H, $C_{arom}H$), 8.32 (s, 1H, C_3H), 10.96 (br s,1H, NH), 11.40 (br s, 1H, NH). ^{13}C NMR (62.8 MHz, DMSO-d_6) : δ 89.6 (s, C_4), 112.7 (s, CN), 122.9 (d), 124.2 (d), 128.4 (d), 128.6 (d), 128.9 (d), 131.2 (d), 131.8 (s), 133.4 (d), 138.4 (s), 140.9 (s, C_5), 142.8 (d, C_3), 150.9 (s, C=O), 168.5 (s, C=O).
10. Compound **5b** : mp 355-358°C. IR (KBr) 3450, 3100, 1675 cm^{-1}. ^{1}H NMR (250.12 MHz, DMSO-d_6) : δ 7.28-8.36 (m, 4H, $C_{arom}H$), 7.51 (br s, 1H, NH), 8.17 (s, 1H, H_3), 8.79 (br s, 1H, NH), 10.99 (br s, 1H, NH). ^{13}C NMR (62.8 MHz, DMSO-d_6) : δ 92.6 (s, C_{3a}), 118.1 (d, $C_{6'}$), 119.2 (d, $C_{2'}$), 124.9 (d, $C_{4'}$),130.6 (d, $C_{5'}$), 133.2 (s, $C_{3'}$), 136.1 (d, C_3), 140.5 (s, $C_{1'}$), 153.6 (s, C_4), 156.2 (s, C_{7a}), 158.5 (s, C_6). Anal. Calcd. for $C_{11}H_8N_5OCl$: C, 50.49; H, 3.08; N, 26.76. Found : C, 50.6; H, 3.0; N, 26.9.

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