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A new and versatile synthesis of 5-substituted pyrrolo[2,3-*d*]pyrimidines

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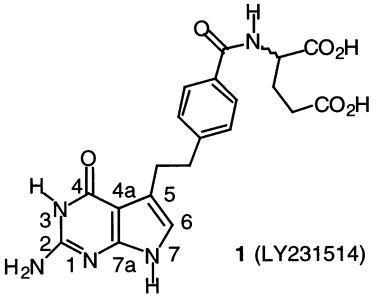
Abstract

We have developed a new methodology for the construction of 5-substituted pyrrolo[2,3-*d*]pyrimidines that involves the reduction of a nitroalkane to an oxime using the reducing ability of the $Sn(SR_3)^-$ species, followed by mild, acid-catalysed deoximation of the resulting adduct using Dowex-H^+ resin to form an intermediate aldehyde that spontaneously cyclises to the fused pyrrole ring. © 2000 Published by Elsevier Science Ltd.

Keywords: oxime; Dowex; deoximation; cyclisation; pyrrolo[2,3-*d*]pyrimidines.

Substituted 2-aminopyrrolo[2,3-*d*]pyrimidin-4-ones (7-deazaguanines) occur naturally within a number of minor nucleosidic constituents of tRNAs such as nucleoside Q[1] and archaeosine.[2] There are also several biologically active 2-aminopyrrolo[2,3-*d*]pyrimidin-4-ones, exemplified by the anticancer agent LY231514 **1**.[3] In each case, substitution at C5 is found. In addition, nucleoside analogues incorporating C5-substituted pyrrolo[2,3-*d*]pyrimidines have been widely studied as analogues of their purine counterparts, which permit the introduction of functional groups into the major groove of DNA.[4]



1 (LY231514)

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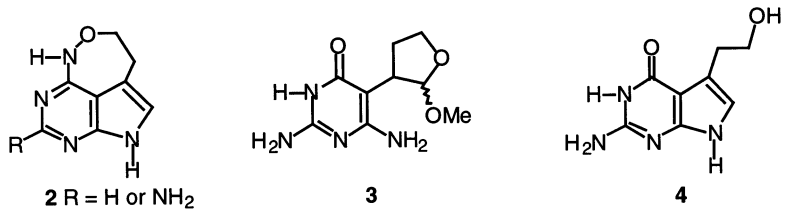
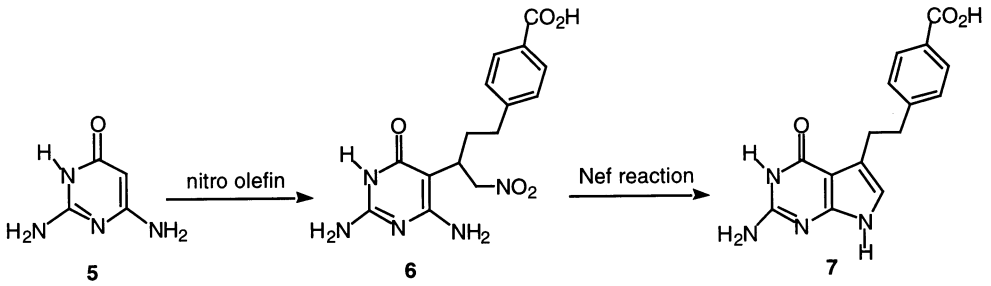
We have been interested for some time in the syntheses of analogues of type **2**,[5] which are derived from C5-substituted pyrrolo[2,3-*d*]pyrimidines. Whilst routes to such compounds using palladium catalysed cross-coupling reactions with 5-iodo-pyrrolo[2,3-*d*]pyrimidines[6] allows access to these molecules, the 5-iodo-substituted precursors are sometimes not readily available. Electrophilic substitution of 7-deazaguanine (2-aminopyrrolo[2,3-*d*]pyrimidin-4-one) occurs at C6[7] and consequently we have investigated routes to such compounds exemplified in the cyclisation of the pyrimidine acetal **3**, which upon treatment with aqueous acid gives the 5-substituted pyrrolo[2,3-*d*]pyrimidine **4**.



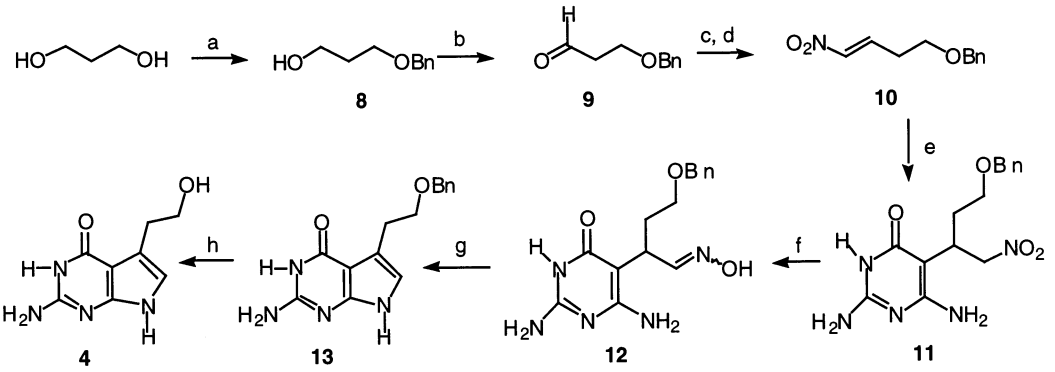
Recently, Taylor and Liu[8] have reported a concise synthesis of **1** by Michael addition of 2,6-diamino-4(3*H*)-pyrimidinone **5** to a nitro olefin to produce **6**, which cyclises to **7** under conditions of the Nef reaction (Scheme 1). We envisaged applying a similar route for a general synthesis of 5-substituted pyrrolo[2,3-*d*]pyrimidines such as **4**, which we have described previously, but only in moderate yield.[7]



Scheme 1.

We report here a novel and efficient synthesis of **4** from commercially available 2,6-diamino-4-(3*H*)-pyrimidinone **5** and an acyclic nitro alkene precursor, followed by subsequent acid catalysed cyclisation of an oxime to give the pyrrolopyrimidine.

Thus, 1,3-propandiol was monobenzylated to give **8**, which was oxidised to the corresponding aldehyde **9**.[9] Aldol condensation of **9** with nitromethane,[10] followed by dehydration[11] with methanesulfonyl chloride/triethylamine gave the nitro olefin **10**. Michael addition[12] of **5** to **10** gave **11** in good yield. Our initial attempts to effect cyclisation of **11** using the Nef reaction to generate an intermediate aldehyde analogously to that described[8] resulted in only poor yields (29%) of the desired product. As an alternative route, we envisaged the generation of the intermediate aldehyde from an oxime rather than from the nitro alkane **11**. Thus, compound **11**, when treated with 1.5 equiv. of a mixture of $SnCl_2$/3 PhSH/3 Et_3N in acetonitrile readily gave the oxime[13] **12** in 79% yield. The aldehyde intermediate was generated by deoximation[14] using Dowex-50 H^+ form resin in water at neutral pH and spontaneously cyclised to the pyrrolo[2,3-*d*]pyrimidine **13** (56% overall yield from **11**). Debenzylation of **13** with boron trichloride[15] gave **4** (Scheme 2).



Scheme 2. Reagents and conditions: (a) $PhCH_2Br$, NaH, DMF, Ref. 9; (b) PCC, CH_2Cl_2, Ref. 9; (c) CH_3NO_2/NaOH/EtOH, 64% yield; (d) CH_3SO_2Cl/Et_3N, 90% yield; (e) **5**, 1:1 EtOAc/H_2O, 50°C, 24 h, 69% yield; (f) 1.5 equiv. $SnCl_2$/3 PhSH/3 Et_3N, CH_3CN, 79% yield; (g) H_2O, Dowex-50, reflux, 71% yield; (h) CH_2Cl_2, 9 equiv. BCl_3, −78°C, 51% yield

In summary, we have developed a new and simple methodology to synthesise 5-substituted-7-deazaguanines which provides an alternative to the Nef-mediated cyclisation from a nitroalkane, especially in circumstances where yields of the latter route are poor. The method employed for the conversion of a nitroalkane into an aldehyde under mild and neutral conditions is envisaged to be of general interest as an alternative to the Nef reaction.

Acknowledgements

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10. 4-(Benzyloxy)-1-nitro-2-butanol: A solution of nitromethane (4.92 g, 80.69 mmol) and **9**[9] (13.25 g, 80.69 mmol) in EtOH (15 ml) was stirred at 0°C and an aqueous NaOH solution (3.16 g in 7.9 ml) was slowly added, maintaining the temperature below 10°C. The solution was warmed to room temp. over 3 h, then ice was added, followed by glacial acetic acid until the precipitate dissolved and the pH was 6. The crude product was extracted into EtOAc, which was washed with water, dried ($MgSO_4$) and evaporated. Purification by chromatography (CH_2Cl_2) gave a pale yellow oil (7.6 g, 64%); δ_H ($CDCl_3$) 1.78–1.85 (2H, m, CH_2), 3.43 (1H, s, OH), 3.65–3.71 (3H, m, CH and CH_2O), 4.41 (2H, dd, *J* 6.41 and 1.22 Hz, CH_2NO$_2$), 4.51 (2H, s, CH_2Ph), 7.29–7.36 (5H, m, *P*h); δ_C ($CDCl_3$) 33.26 (*C*H$_2$), 67.17 (*C*H$_2$O), 67.71 (*C*HOH), 73.43 (*C*H$_2$Ph), 80.47 (*C*H$_2$NO$_2$), 127.79 (2C, *P*h), 128.00 (1C, *P*h), 128.58 (2C, *P*h), 137.52 (1Cq, *P*h).

11. {[(3*E*)-4-Nitro-3-butenyl]oxy}methyl)benzene **10**: Methanesulfonyl chloride (2.7 ml, 33.77 mmol) was added in one portion to a stirred solution of 4-(benzyloxy)-1-nitro-2-butanol (7.6 g, 33.77 mmol) in CH_2Cl_2 (34 ml) at 0°C under nitrogen. Et_3N (9.35 ml, 67.54 mmol) was then added via a syringe pump over 1.5 h and the mixture stirred for 15 min at 0°C. (**Note**: poor yields result if addition is too rapid). CH_2Cl_2 (40 ml) was then added, the mixture transferred to a separating funnel and the organic layer was washed with water, 5% aqueous HCl, and brine. After evaporation, the product (6.3 g, 90%) was used without further purification; δ_H ($CDCl_3$) 2.5–2.59 (2H, m, CH_2), 3.61 (2H, t, *J* 5.8 Hz, CH_2O), 4.52 (2H, s, CH_2Ph), 7.04 (1H, td, *J* 1.22 and 13.73 Hz, *H*2), 7.24–7.37 (6H, m, *H*1 and *P*h); δ_C ($CDCl_3$) 28.97 (*C*H$_2$), 67.29 (*C*H$_2$O), 73.22 (*C*H$_2$Ph), 127.74 (2C, *P*h), 127.92 (*C*2), 128.08 (1C, *P*h), 128.54 (2C, *P*h), 137.67 (1Cq, *P*h), 139.59 (*C*1).

12. 2,6-Diamino-5-[3-(benzyloxy)-1-(nitromethyl)propyl]-4(3*H*)-pyrimidinone **11**: A solution of 2,6-diamino-4(3*H*)-pyrimidinone (3.63 g, 27.66 mmol) and **10** (6.3 g, 30.43 mmol) in 50% EtOAc/H_2O (60 ml) was heated at 50°C overnight. The crude product was extracted into EtOAc, which was washed with water, dried ($MgSO_4$) and evaporated. Purification by column chromatography (9:1 CH_2Cl_2/MeOH) gave a pale yellow solid (6.37 g, 69%); R_f (8:2 CH_2Cl_2/MeOH), 0.62. The compound can be recrystallised from CH_3CN; mp 95.3°C; δ_H (DMSO-d_6) 1.65–1.85 (1H, m, CH_2), 1.95–2.15 (1H, m, CH_2), 3.35–3.62 (3H, m, CH and CH_2O), 4.41 (2H, q, *J* 3.05 and 11.6 Hz, CH_2Ph), 4.76 (1H, dd, *J* 6.1 and 12.51 Hz, CH_2NO$_2$), 5.03 (1H, dd, *J* 3.66 and 12.51 Hz, CH_2NO$_2$), 5.81 (2H, s, NH_2), 6.06 (2H, s, NH_2), 7.29–7.34 (5H, m, *P*h), 9.81 (1H, s, NH); δ_C (DMSO-d_6) 30.02 (*C*H$_2$), 32.56 (*C*H), 68.40 (*C*H$_2$O), 72.34 (*C*H$_2$Ph), 78.08 (*C*H$_2$NO$_2$), 84.34 (*C*q), 127.79 (1C, *P*h), 127.97 (2C, *P*h), 128.67 (2C, *P*h), 138.98 (1Cq, *P*h), 154.01 (*C*q), 162.33 (*C*q), 163.28 (*C*=O); *m*/*z* (FAB$^+$) 334.152277 (M+H$^+$; calc. for $C_{15}H_{20}N_5O_4$, 334.151529).

13. 4-(Benzyloxy)-2-(2,4-diamino-6-oxo-1,6-dihydro-5-pyrimidinyl)butanal oxime **12**: Benzene thiol (1.65 ml, 16.06 mmol) and Et_3N (2.5 ml, 17.93 mmol) were added to a stirred solution of anhydrous $SnCl_2$ (1 g, 5.26 mmol) in dry CH_3CN (54 ml) at room temp. Then, **11** (1.2 g, 3.60 mmol) in dry CH_3CN (73 ml) was added. After 30 min, the reaction mixture was evaporated and the crude product was purified by column chromatography eluting with 95:5 CH_2Cl_2/MeOH (eluting PhSH, PhSSPh) and then 9:1 CH_2Cl_2/MeOH to afford a white solid (901 mg, 79%) as an *E*/*Z* mixture (2:1.5 by ^{1}H NMR); R_f (8:2 CH_2Cl_2/MeOH), 0.41; spectral data of isomer *E*: δ_H (DMSO-d_6) 1.9–2.05 (2H, m, CH_2), 3.45 (2H, t, *J* 7.05 Hz, CH_2O), 3.40–3.50 (1H, m, CH), 4.32 (2H, s, CH_2Ph), 5.75 (2H, s, NH_2), 6.07 (2H, s, NH_2), 7.2–7.4 (5H, m, *P*h), 7.55 (1H, d, *J* 8.6 Hz, CH=N), 9.81 (1H, s, NH), 10.21 (1H, s, OH); δ_C (DMSO-d_6) 30.73 (*C*H$_2$), 32.94 (*C*H), 68.71 (*C*H$_2$O), 72.35 (*C*H$_2$Ph), 86.69 (*C*q), 126.28 (1C, *P*h), 127.74 (2C, *P*h), 128.66 (2C, *P*h), 139.13 (1Cq, *P*h), 152.49 (*C*H=N), 153.92 (*C*q), 154.24 (*C*q), 162.37 (*C*=O); *m*/*z* (FAB$^+$) 318.158495 (M+H$^+$; calc. for $C_{15}H_{20}N_5O_3$, 318.156615).

14. Cyclisation with Dowex-50 H$^+$: **12** (324 mg, 1.02 mmol) was heated for 3 h at reflux with Dowex-50 (H$^+$ form, 160 mg) in water (30 ml). The reaction mixture was then diluted with MeOH, and the Dowex resin filtered. The methanol was evaporated under vacuum and the precipitate was filtered and washed with water to give **13** as a white solid (206 mg, 71%); R_f (8:2 CH_2Cl_2/MeOH), 0.52; δ_H (DMSO-d_6) 2.91 (2H, t, *J* 7.02 Hz, CH_2), 3.71 (2H, t, *J* 7.02 Hz, CH_2O), 4.53 (2H, s, CH_2Ph), 6.06 (2H, s, NH_2), 6.48 (H, s, *H*-6), 7.30–7.45 (5H, m, *P*h), 10.21 (1H, s, NH), 10.76 (1H, s, NH); δ_C (DMSO-d_6) 27.0 (*C*H$_2$), 71.1 (*C*H$_2$O), 72.1 (*C*H$_2$Ph), 99.3 (*C*q), 114.6 (*C*6), 114.9 (*C*q), 127.7 (1C, *P*h), 127.8 (2C, *P*h), 128.6 (2C, *P*h), 139.3 (Cq), 151.6 (*C*q), 152.6 (*C*q), 159.7 (*C*=O); *m*/*z* (Fab$^+$) 285.137312 (MH$^+$; calc. for $C_{15}H_{17}N_4O_2$, 285.135151).

15. 2-Amino-5-(2-hydroxyethyl)-3,7-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one **4**: A solution of boron trichloride (1 M) in heptane (26 ml, 23.4 mmol) was added to a solution of **13** (700 mg, 2.46 mmol) in CH_2Cl_2 (90 ml) at −78°C with exclusion of moisture. The mixture was stirred for 6 h at −78°C and a solution of CH_2Cl_2/EtOH (1:1; 90 ml) was added dropwise while the mixture was allowed to warm to room temp. The mixture was then evaporated,

redissolved in a small volume of EtOH, and neutralised with a 1N NaOH solution. The residue was adsorbed onto silica gel and chromatographed eluting with 9:1 and 8:2 CH_2Cl_2/MeOH to give a white solid (244 mg, 51%); R_f (8:2 CH_2Cl_2/MeOH), 0.18; δ_H (DMSO-d_6) 2.71 (2H, t, *J* 7.02 Hz, CH_2), 3.56 (1H, t, *J* 7.02 Hz, CH_2O), 3.60 (1H, d, *J* 5.19 Hz, CH_2O), 4.64 (1H, t, *J* 5.19, O*H*), 6.06 (2H, s, NH_2), 6.37 (1H, s, *H*-6), 10.25 (1H, s, N*H*), 10.69 (1H, s, N*H*); δ_C (DMSO-d_6) 30.5 (*C*H_2), 62.6 (*C*H_2O), 99.3 (*C*q), 114.5 (*C*6), 115.6 (*C*q), 151.7 (*C*q), 152.6 (*C*q), 159.9 (*C*=O).