Improved Syntheses of 3*H*,5*H*-Pyrrolo[3,2-*d*]pyrimidines

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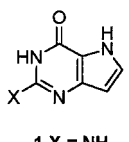
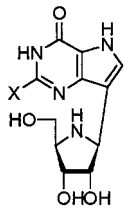
Received June 2, 1999

The synthesis of 3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidines is of renewed interest because both 2-amino-3*H*,5*H*-pyrrolo-[3,2-*d*]pyrimidin-4-one (**1,** 9-deazaguanine) and its deamino derivative **2** (9-deazahypoxanthine) are potential synthetic precursors of the newly discovered immucillins **3** and **4**, which are extremely potent inhibitors of purine nucleoside phosphorylase.[1]



1 X = NH_2
2 X = H



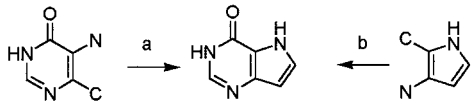
3 X = NH_2
4 X = H

There are relatively few routes to the pyrrolo[3,2-*d*]-pyrimidine ring system,[2] the most commonly used approach starting from pyrimidines with appropriate functional groups at the 5 and 6 positions to allow elaboration of the pyrrole ring (Scheme 1a). Otherwise, the pyrimidine ring can be constructed onto a substituted pyrrole[3] (Scheme 1b). Syntheses of compound **2** have previously been carried out by methods following route a,[4−6] and of **1** by routes a[7−9] and b,[3] but none of the methods is as straightforward and efficient as was required.

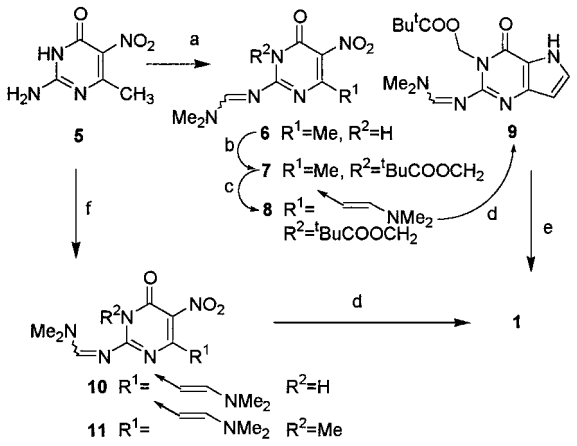
We report here new, abbreviated, and facile syntheses of compounds **1** and **2** that can be applied on a multigram scale.

After the report of a 10-step procedure to synthesize 9-deazaguanine (**1**) in 0.86% efficiency,[4] and of a further method[7] that could not be reproduced by others,[8,9] the latter workers developed a five-step, 20% efficient approach starting from 2-amino-6-methyl-5-nitropyrimidin-4-one (**5**) which is readily made by the nitration of the commercially available 2-amino-6-methylpyrimidin-4-one.[10] Their reaction of compound **5** with DMF dimethyl acetal in CH_2Cl_2 gave the imine **6** in excellent yield, and

Scheme 1



Scheme 2[a]



[a] Key: (a) $(MeO)_2CHNMe_2$, CH_2Cl_2, rt; (b) NaH, $^tBuCO_2CH_2Cl$; (c) $(MeO)_2CHNMe_2$, DMF, rt, (d) $Na_2S_2O_4$; (e) NaOH, EtOH; (f) $(MeO)_2CHNMe_2$, DMF, 100 °C.

this was N-protected using pivaloyloxymethyl chloride to give compound **7** (60%). Treatment with DMF dimethyl acetal in DMF at room temperature then gave the enamine **8** (86%), reduction of which with dithionite led to the pyrrolo[3,2-*d*]pyrimidine ring system of compound **9**, presumably following reduction of the nitro group, ring closure, and loss of dimethylamine. Alkaline N-deprotection of compound **9** gave the required 9-deazaguanine (**1**) in 48% yield.

These earlier workers[8,9] observed that the reaction of compound **5** with DMF dimethyl acetal in DMF caused the formation of the product **11** of N-methylation as well as imine formation. The N-alkylation of the amide group of heterocyclic bases using DMF dialkyl acetals has been well documented.[11−13] Our further investigation of the reaction led to the finding that the product obtained when the nitro derivative **5** was treated with 6 equiv of DMF dimethyl acetal in DMF at 100 °C was compound **10** (80%) without any of the *N*-methyl analogue **11**. When fewer mole equivalents of DMF dimethylacetal were used, the formation of some *N*-methyl compound **11** was observed, suggesting that a sufficient excess of the acetal is required for exclusive formation of **10**. Dithionite reduction of this product **10** in boiling water afforded 9-deazaguanine (**1**) in 61% isolated yield without chromatographic separation (Scheme 2).

From the above findings, the obvious starting material for making 9-deazahypoxanthine (**2**) is the deamino analogue of compound **5**, but it is difficult to obtain, and the alternative general approach to pyrrolo[3,2-*d*]pyrimidines (Scheme 1b), as exemplified by the conversion of the C-nucleoside **12** on treatment with formamidine

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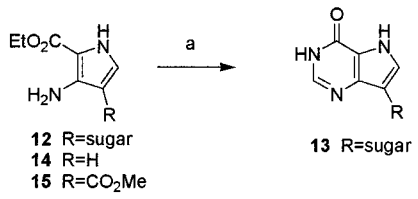
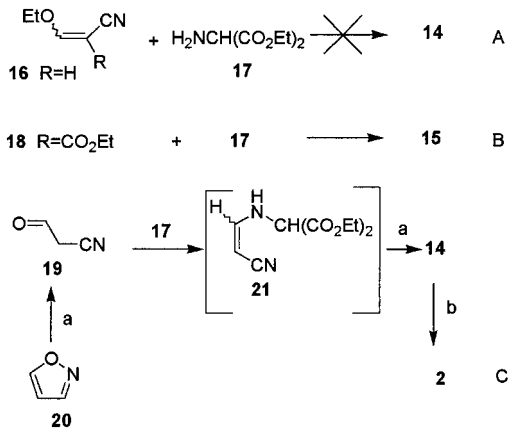
10.1021/jo990903e CCC: $18.00
Published on Web 10/14/1999

Scheme 3[a]



[a] Key: (a) $H_2NCH{=}NH{\cdot}HOAc$.

Scheme 4[a]



[a] Key: (a) NaOEt, EtOH; (b) $H_2NCH{=}NH{\cdot}HOAc$.

acetate to compound **13** (Scheme 3),[14] was employed. For the purpose of producing compound **2**, the previously unreported pyrrole **14** was therefore required, and the first attempt to make it involved reaction of 3-ethoxyacrylonitrile (**16**) with diethyl aminomalonate (**17**, Scheme 4A) following the successful synthesis of pyrrole **15** by condensation of ethyl (ethoxymethylene)cyanoacetate (**18**) with the same malonate ester[3] (Scheme 4B) but none of the required product **14** was formed. However, when the malonate **17** was treated with 3-oxopropionitrile (**19**), formed from its isomer isoxazole (**20**) on treatment with base,[15] the required pyrrole (**14**) was obtained in 55% yield based on malonate **17**, presumably by way of the 3-aminoacrylonitrile compound **21**. From the pyrrole **14** the required 9-deazahypoxanthine (**2**) was produced in 82% yield (without chromatography) following condensation in boiling ethanol with formamidine acetate (Scheme 4C).

With pyrrole **14** now readily available, its condensation with 1,3-bis(carbomethoxy)-*S*-methylisothiourea would offer a further possible route to compound **2**,[16] but in our opinion this option is unlikely to prove superior to our new procedure.

In conclusion, we have developed a convenient, direct synthetic route involving the condensation of isoxazole and diethyl aminomalonate to the pyrrole derivative **14** (55%) from which 9-deazahypoxanthine (**2**) is readily available by treatment with formamidine acetate (overall yield 45%). An abbreviation of a published synthesis of 9-deazaguanine (**1**) from the readily available nitro compound **5** (two steps, overall yield 49%) also makes this compound much more accessible.

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Experimental Section

General Methods. Microanalyses were performed by the Campbell Laboratory, Otago University, New Zealand. Aluminum-backed silica gel sheets (Merck or Riedel de Haen) were used for TLC. Column chromatography was performed on silica gel (230−400 mesh, Merck). Chromatography solvents were distilled prior to use. Anhydrous solvents were obtained from Aldrich.

2-[(*N*,*N*-Dimethylamino)methylene]amino-6-[(2-*N*,*N*-dimethylamino)vinyl]-5-nitropyrimidin-4-one (10). A mixture of **5**[10] (20 g, 117 mmol) with dry DMF (250 mL) and DMF dimethyl acetal (75 mL, 700 mmol) was stirred at 100 °C for 24 h and then cooled. Acetone (500 mL) was added, and the mixture was filtered and washed with acetone, affording **10** as an orange/brown solid (26.3 g, 80%). A sample purified by chromatography ($CHCl_3$/EtOAc/MeOH 5:2:1) and crystallized from methanol had mp ∼270 °C dec; ^{1}H NMR (DMSO-d_6) δ 8.59 (s, 1H), 7.81 (d, J = 12.5 Hz, 1H), 5.30 (d, J = 12.5 Hz, 1H), 3.12 (s, 3H), 3.00 (s, 3H), 2.93 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 168.4, 166.0, 159.2, 158.5, 149.5, 129.1, 90.6, 41.8, 35.7. Anal. Calcd for $C_{11}H_{16}N_6O_3$: C, 47.14; H, 5.75; N, 29.98. Found: C, 46.87; H, 5.72; N, 29.83.

2-Amino-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (1). A mixture of **10** (24 g, 86 mmol) and sodium dithionite (48 g) in water (240 mL) was heated under reflux for 2 h. The suspension was hot filtered, cooled, and refiltered to give **1** (7.84 g, 61%) as a yellow/brown solid. This material was suitable for synthetic purposes but contained about 10% of inorganic material that was difficult to remove. A portion (0.5 g) was chromatographed ($CHCl_3$/EtOAc/MeOH 5:2:2) on silica gel, and the material obtained (0.42 g) was recrystallized from methanol affording compound **1** as a white solid: mp > 300 °C; ^{1}H NMR (DMSO-d_6) as previously reported;[4] ^{13}C NMR (DMSO-d_6) δ 155.9, 152.0, 146.6, 128.3, 113.6, 101.2. Anal. Calcd for $C_6H_6N_4O$: C, 48.00; H, 4.03; N, 37.32. Found: C, 47.57; H, 4.13; N, 36.87.

3-Amino-2-ethoxycarbonylpyrrole Hydrochloride (14·HCl). A solution of sodium ethoxide in ethanol (2 M, 152 mL, 305 mmol) was added slowly to a stirred solution of isoxazole **20** (20 g, 290 mmol) in ethanol (80 mL) in an ice bath with a reaction temperature of ≤8 °C. After an additional 0.5 h with stirring, acetic acid (5.5 mL, 100 mmol), diethyl aminomalonate hydrochloride (40.9 g, 193 mmol), and sodium acetate (16.4 g, 200 mmol) were added, and the mixture was stirred at rt for 2 d, after which most of the ethanol was removed under vacuum. The residue was partitioned between chloroform and water, and the organic phase was dried and filtered through a pad of silica gel. Evaporation afforded a syrup that was dissolved in a solution of sodium ethoxide in ethanol (0.5 M, 400 mL), and the solution was stirred at room temperature for 3 d. Acetic acid (12 mL, 210 mmol) was added and the ethanol removed under vacuum. The residue was dissolved in chloroform and washed with $NaHCO_3$ (aqueous, pH kept ∼7). The organic phase was dried and filtered through a thick pad of silica gel to give crude syrupy **14** (16.4 g, 106 mmol), with clean ^{1}H and ^{13}C NMR spectra, that was suitable for synthetic use. A portion in ether was treated with HCl in dioxane to precipitate the hydrochloride salt **14·HCl** (recrystallized from ethyl acetate/ethanol): mp 197−200 °C; ^{1}H NMR (DMSO-d_6) δ 7.02 (t, J = 3.0 Hz, 1H), 6.34 (t, J = 2.5 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 1.31 (t, J = 7 Hz, 3H); ^{13}C NMR δ 159.7, 123.2, 121.6, 114.7, 106.1, 60.6, 14.6. Anal. Calcd for $C_7H_{11}ClN_2O_5$: C, 44.10; H, 5.82; N, 14.70. Found: C, 44.02; H, 6.13; N, 14.55.

3*H*,5*H*-Pyrrolo[3,2-*d*]pyrimidin-4-one (2). Formamidine acetate (16.6 g, 158 mmol) was added to a solution of crude **14** (16.4 g, 106 mmol) in ethanol (150 mL), and the solution was heated under reflux for 16 h and then cooled. The solid that formed was isolated by filtration, washed with ethanol, and dried to give **2** (11.8 g, 87 mmol) (recrystallized from water): mp > 300 °C; ^{1}H NMR (DMSO-d_6) as previously reported;[4] ^{13}C NMR (DMSO-d_6) δ 154.0, 145.0, 141.8, 127.7, 118.2, 103.3. Anal. Calcd for $C_6H_5N_3O$: C, 53.33; H, 3.73; N, 31.10. Found: C, 53.41; H, 3.43; N, 31.21.

Acknowledgment. Dr. Herbert Wong kindly recorded the NMR spectra and Professor Robin Ferrier assisted with the preparation of the manuscript.

JO990903E