Efficient Synthesis of 3*H*,5*H*-Pyrrolo[3,2-*d*]pyrimidin-4-one

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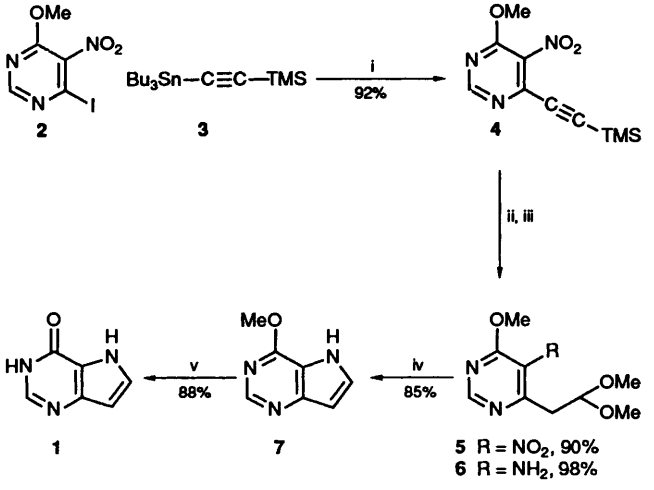
Palladium-catalysed cross-coupling of 4-iodo-6-methoxy-5-nitropyrimidine and trimethyl(tributylstannylethynyl)silane to form the corresponding 4-trimethylsilylethynylpyrimidine and subsequent construction of an annellated pyrrolo ring provides an efficient route to the pyrrolo[3,2-*d*]pyrimidine system.

The important 9-deaza-isostere of hypoxanthine,[1] 3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one **1**, although first reported in 1964[2] has not been readily available. Indeed, there are relatively few known routes to the pyrrolo[3,2-*d*]pyrimidine ring system.[3] We now report a new, efficient synthesis of **1** in which the key step is a palladium-catalysed cross-coupling reaction between 4-iodo-6-methoxy-5-nitropyrimidine * **2** and trimethyl(tributylstannylethynyl)silane **3** [prepared by reaction of trimethylsilylacetylene with (diethylamino)tributylstannane].† This cross-coupling reaction produced an intermediate **4** (92%) possessing the atoms needed for annellation of a pyrrolo ring onto the pyrimidine nucleus to produce the heterobicycle **1**.



Scheme 1 *Reagents and conditions:* i, $Pd(OAc)_2$, $AsPh_3$; ii, KOH, MeOH; iii, H_2, Pd–C; iv, HCl, 60 °C; v, HCl, 100 °C

Completion of the synthesis was accomplished in four routine operations: base-catalysed conversion of the silylacetylene function to a dimethylacetal (**4**→**5**), hydrogenation of the nitro group (5→6), acid-catalysed condensation to form the pyrrolo ring (**6**→**7**) and oxygen deprotection (**7**→**1**). The five-step synthesis, readily carried out on gram scale, was accomplished in 61% overall yield. The product, 3*H*,5*H*-pyrrolo[3,2-*d*]-pyrimidin-4-one[2] **1**, exhibited a ^1H NMR spectrum ([$^2H_6$]-Me_2SO) δ_H 6.40 (1 H, dd, $J_{6,7}$ 2.9, $J_{7,NH}$ 2.1, 7-H), 7.46 (1 H, dd, $J_{6,NH}$ 2.7, 6-H), 8.22 (1 H, s, 2-H) and 12.41 (br, exchangeable with D_2O, NH).

Experimental

^1H and ^{13}C (NMR) spectra were recorded with a Varian 200 XL spectrometer, *J* values are given in Hz. Electron impact (EI) and chemical ionization (Cl) mass spectra were recorded with a Hewlett Packard 5987A GC/MS system at 70 eV ionizing voltage. Isobutane was used as the reagent gas for Cl mass spectrometry. Column chromatography (Merck Silica gel: 230–400 mesh) was used for purification of crude reaction mixtures.

Trimethyl(tributylstannylethynyl)silane[6] **3**.—A mixture of (diethylamino)tributylstannane[7] (3.0 g, 8.3 mmol) and trimethylsilylacetylene (1.0 g, 10 mmol) was stirred at room temp. for 1 h. The reaction mixture was then poured into aqueous ammonium chloride and extracted with diethyl ether. The ether extract was washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. The product obtained, stable and pure enough for further use, was purified by column chromatography eluting with EtOAc and hexane to yield 2.8 g (86%) of the title compound **3** as a viscous oil; $\delta_H(CDCl_3)$ 0.13 (s, 9 H, $SiMe_3$) and 0.87–1.58 (m, 27 H, Bu).

4-*Iodo*-6-*methoxy*-5-*nitropyrimidine* **2**.—4-Chloro-6-methoxy-5-nitropyrimidine[4a] (5 g, 17.8 mmol) was added to hydroiodic acid[4b] (48%, 25 cm^3) and the mixture was stirred at room temp. for 3 h. The solid precipitate was collected and dissolved in water. The resulting solution was neutralized by addition of saturated aqueous sodium hydrogen carbonate and then extracted with chloroform. The chloroform extract was washed twice with aqueous sodium sulfite and then with water, dried ($MgSO_4$) and evaporated to produce 5.8 g (78%) of the title compound **2**, m.p. 165–166 °C, suitable for use in the coupling reaction; $\delta_H(CDCl_3)$ 4.11 (s, 3 H, Me) and 8.50 (s, 1 H, 2-H); $\delta_C(CDCl_3)$ 55.92, 119.88, 157.4 and 159.68; ClMS *m/z* (rel. int.) 282 (100, M + H^+) (Found: C, 21.7; H, 1.3; N, 15.0. Calc. for $C_5H_4IN_3O_3$: C, 21.4; H, 1.43; N, 15.0%).

4-*Methoxy*-5-*nitro*-6-(*trimethylsilylethynyl*)*pyrimidine* **4**.—To a mixture of palladium acetate (40 mg, 10 mol%), triphenylarsine (100 mg, 20 mol%), triethylamine (0.74 cm^3) and acetonitrile (7 cm^3) was added trimethyl(tributylstannylethynyl)silane **3** (1 g, 2.5 mmol) followed by 4-iodo-6-methoxy-5-nitropyrimidine **2** (500 mg, mmol) in acetonitrile (8 cm^3). The mixture was stirred under nitrogen at room temp. for 4 h. The solvent was removed at reduced pressure, water was added and the mixture was extracted with diethyl ether. The ether extract was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography eluting with light petroleum–dichloromethane 4:1 to yield 411 mg (92%) of the title compound **4**, m.p. 48–49 °C; $\delta_H(CDCl_3)$ 0.24 (s, 9 H, $SiMe_3$), 4.09 (s, 3 H, Me) and 8.72 (s, 1 H, 2-H); $\delta_C(CDCl_3)$ −0.89, 55.64, 88.53, 95.12, 109.60, 142.41, 158.38 and 160.69; ClMS *m/z* (rel. int.) 252 (100, M + H^+) (Found: C, 47.5; H, 5.0; N, 16.8. Calc. for $C_{10}H_{13}N_3O_3Si$: C, 47.8; H, 5.21; N, 16.7%).

* Prepared by treatment of the corresponding chloro compound[4a] with HI.[4b]

† A conceptually similar route to this ring system has been reported.[5]

6-(2,2-*Dimethoxyethyl*)-4-*methoxy*-5-*nitropyrimidine* **5**.—To a solution of 4-methoxy-5-nitro-6-(trimethylsilylethynyl)pyrimidine **4** (400 mg, 1.6 mmol) in methanol (14 cm^3) was added potassium hydroxide (270 mg, 4.8 mmol). The mixture was stirred at room temp. for 1 h, when the reaction was complete. Acetic acid (4.8 mmol) was added and most of the methanol was removed at reduced pressure. The concentrate was diluted with water and then extracted with dichloromethane. The organic extract was washed with water, dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The product obtained was purified by column chromatography eluting with EtAc–hexane, (3:2) to yield 350 mg (90%) of the title compound **5** as an oil; $\delta_H(CDCl_3)$ 3.14 (d, 2 H, *J* 5.5, CH_2), 3.33 (s, 6 H, 2 × Me), 4.09 (s, 3 H, Me), 4.85 (t, 1 H, *J* 5.5, CH) and 8.75 (s, 1 H, 2-H); $\delta_C(CDCl_3)$ 37.06, 53.55, 55.32, 102.47, 157.59, 158.35 and 160.83; ClMS *m/z* (rel. int.) 244 (12, M + H^+) and 212 (100, M + H^+ − CH_3OH) (Found: C, 44.3; H, 5.45; N, 17.0. Calc. for $C_9H_{13}N_3O_5$: C, 44.4; H, 5.38; N, 17.3%).

6-(2,2-*Dimethoxyethyl*)-4-*methoxypyrimidin*-5-*amine* **6**.—6-(2,2-Dimethoxyethyl)-4-methoxy-5-nitropyrimidine **5** (350 mg, 1.44 mmol) in methanol was shaken under 2 atm of hydrogen in the presence of 5% Pd/C at room temp. After 3 h, the catalyst was removed by filtration, the filtrate was evaporated under reduced pressure to yield 300 mg (98%) of the title compound **6** as an oil; $\delta_H(CDCl_3)$ 3.00 (d, 2 H, *J* 5.3, CH_2), 3.40 (s, 6 H, 2 Me), 4.02 (s, 3 H, Me), 4.64 (t, 1 H, *J* 5.3, CH) and 8.21 (s, 1 H, 2-H); $\delta_C(CDCl_3)$ 38.20, 53.77, 54.48, 105.58, 128.45, 146.39, 146.69 and 158.41; ElMS *m/z* (rel. int.) 213 (52, $M^{\bullet+}$) and 181 (20, $M^{\bullet+}$ − CH_3OH) (Found: C, 50.6; H, 7.18; N, 19.8. Calc. for $C_9H_{15}N_3O_3$: C, 50.7; H, 7.09; N, 19.7%).

4-*Methoxy*-5H-*pyrrolo*[3,2-d]*pyrimidine* **7**.—A mixture of 6-(2,2-dimethoxyethyl)-4-methoxypyrimidin-5-amine **6** (300 mg, 1.4 mmol) and 1 mol dm^{-3} HCl (6 cm^3) in 50% aqueous methanol was stirred at 60 °C for 4 h. After cooling, the reaction mixture was neutralized by slow addition of saturated aqueous sodium hydrogen carbonate. The mixture was then extracted with chloroform and the extract washed with water, dried ($MgSO_4$) and evaporated. The resulting residue was purified by recrystallization from water to yield 178 mg (85%) of the title compound **7**, m.p. 158–159 °C; $\delta_H(CDCl_3)$ 4.14 (s, 3 H, Me), 6.70 (dd, 1 H, $J_{7,6}$ 3.1, $J_{7,NH}$ 2.1, 7-H), 7.43 (t, 1 H, $J_{6,NH}$ 2.9, 6-H), 8.57 (s, 1 H, 2-H) and 8.94 (br, 1 H, exchangeable with D_2O, NH); ElMS *m/z* (rel. int.) 149 (80, $M^{\bullet+}$) and 148 (58, M − H) (Found: C, 56.7; H, 4.87; N, 28.2. Calc. for $C_7H_7N_3O$: C, 56.4; H, 4.73; N, 28.2%).

3H,5H-*Pyrrolo*[3,2-d]*pyrimidin*-4-*one*[2] **1**.—A solution of 4-methoxy-5*H*-pyrrolo[3.2-*d*]pyrimidine **7** (100 mg, 0.67 mmol) in HCl (6 mol dm^{-3}; 4 cm^3) was heated under reflux for 6 h. The reaction solution was then evaporated under reduced pressure and the resulting residue was twice dissolved in water and evaporated to dryness *in vacuo*. The crude product (70 mg, 88%) was collected and crystallized twice from water to give the title compound **1**[2] as colourless prisms: m.p. >300 °C; $\delta_H([^2H_6]$-$Me_2SO)$ 6.40 (dd, 1 H, $J_{7,NH}$ 2.1, $J_{6,7}$ 2.9), 7.46 (dd, 1 H, $J_{6,NH}$ 2.7, 6-H), 8.22 (s, 1 H, 2-H) and 12.41 (br, 1 H, exchangeable with D_2O, NH); ClMS *m/z* (rel. int.) 136 (100, M + H^+).

Acknowledgements

We thank the National Institutes of Health for financial support.

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Paper 2/02944H
Received 4*th June* 1992
Accepted 5*th June* 1992