Facile Synthesis of 5,6,7,8-Tetrahydropyrido[2,1-*b*]purin-10-one

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A convenient synthesis of a new heterocycle, 5,6,7,8-tetrahydropyrido[2,1-*b*]purin-10-one **1** was described. 4-Amino-*N*-(5-chloropentanoyl)-5-imidazolecarboxamide **3a** was successively cyclized to **1** with polyphosphoric acid at 150°. Methylation of **1** under basic condition proceeded selectively at *N*-1 to afford **6** as the sole product.

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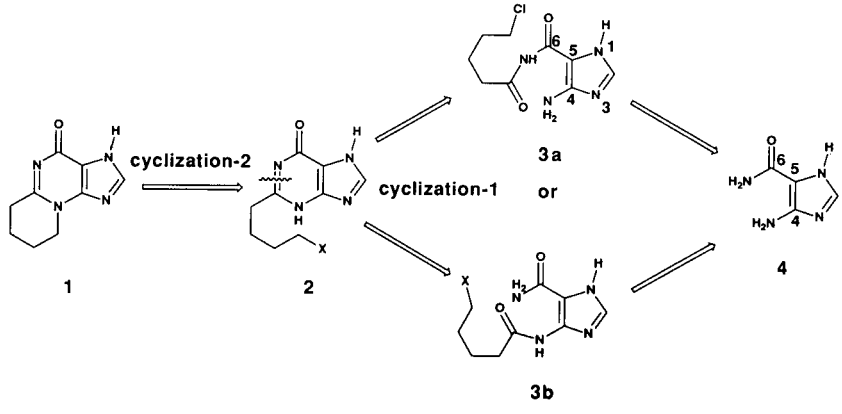
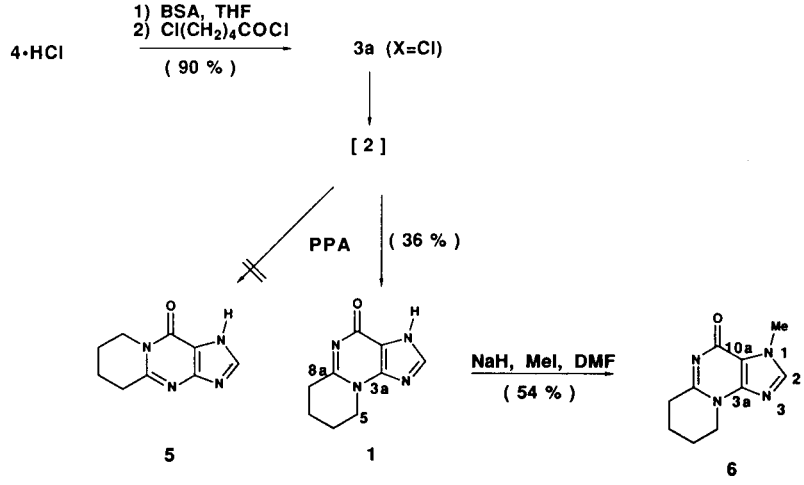
As part of our ongoing effort to screen for new bronchodilators and antiviral agents [1,2], we have studied the synthesis and pharmacological activity of new tricyclic heterocycles such as 5,6,7,8-tetrahydropyrido[2,1-*b*]purin-10-one **1** [3]. Retrosynthetic analysis suggested that a target compound **1** could be prepared *via* two intramolecular cyclizations from urea **3a** or amide **3b**, which would be prepared by acylation of a commercially available starting material **4** (Scheme 1).

First, acylation of 4-amino-5-imidazolecarboxamide **4** with 5-chlorovaleryl chloride was examined. Though basic conditions (triethylamine, pyridine, and lutidine *etc.*) were tried, none of the desired acylated products were obtained and the starting material was recovered. Reduced basicity may play a role in this lack of reactivity. Raucher and Jones [4] reported that treatment of primary or secondary amines with bis(trimethylsilyl)acetamide (BSA) followed by addition of acid chlorides provides a convenient one-pot

Scheme 1



Scheme 2



procedure for the preparation of the corresponding amides. This transformation is mechanistically similar to that reported by Bowser [5]. We applied this reaction to the synthesis of **3**. Treatment of hydrochloride salt of **4** with BSA in THF, followed by addition of 5-chlorovaleryl chloride gave an acylated product, 4-amino-*N*-(5-chloropentanoyl)-5-imidazolecarboxamide **3a** in satisfactory yield (Scheme 2).

The location of the valeryl group in **3a** was determined with the aid of spectroscopic analysis. The ^{13}C nmr C-5 and C-6 signals in **3a** shift to lower field compared with those in **4** (C-5: from 102.5 to 110.8 ppm; C-6: from 161.1 to 166.2 ppm). Little difference between the C-4 chemical shifts in **4** and **3a** was observed (**4**: 143.1 ppm; **3a**: 143.2 ppm). These features are consistent with the formation of **3a** instead of **3b**. This selectivity is in contrast with isothiocyanation of the same compound. Clausen *et al.* recently reported that treatment of 1-alkyl-5-aminoimidazole-4-carboxamide with benzoyl isothiocyanate in acetone afforded the corresponding 1-alkyl-5-[[*N'*-benzoyl(thiocarbamoyl)]amino]imidazole-4-carboxamide in high yield [6]. Trimethylsilylation or 1-alkyl substitution in the imidazole influenced the selectivity of this type of reaction dramatically.

The cyclization of **3a** was examined next. Neutral or mild acidic conditions (Dowtherm A, 220°, *p*-TsOH or PPSE (polyphosphoric acid trimethylsilyl ester), toluene, reflux) did not change the starting material. Treatment of **3a** with more forcing conditions (polyphosphoric acid (PPA), 150°) gave a sole product. Examination of the long range couplings between 5-H and C-3a and between 5-H and C-8a confirmed that the product was **1** instead of **5** as illustrated in Scheme 2. Thus, successive double intramolecular cyclization was achieved in 36% yield. Methylation of **1** in the presence of sodium hydride in DMF proceeded selectively at *N*-1 to afford **6** as a sole product. The location of the *N*-1 methyl group in **6** also was confirmed by the analysis of the long range decoupling experiments.

The coupling constant between 2-H and C-10a and between 2-H and C-3a is 4.8 and 12.9 Hz, respectively. This regioselectivity is also supported by results from similar systems. Monoalkylation of 6-chloropurine [7] and hypoxanthine (6-hydroxypurine) [8] proceed mainly at the 9-position (equivalent to the 3-position in **6**) under basic conditions, whereas 3-substitued hypoxanthine and 1,3-disubstituted xanthines alkylate exclusively at the 7-position (equivalent to the 1-position in **6**) [9]. Electronic (cross conjugation with carbonyl) and steric interactions by substitution at *N*-3 presumably favour *N*-1 substitution.

In conclusion, a convenient route to a new heterocycle, 5,6,7,8-tetrahydro[2,1-*b*]purin-10-one has been developed by using successive double intramolecular cyclization with PPA.

EXPERIMENTAL

Melting points were determined on a Yanagimoto hot plate micro melting point apparatus and are uncorrected. Infrared (ir) spectra were measured on a JASCO IR-810 spectrometer. Proton nuclear magnetic resonance (^1H nmr) spectra were measured on a JEOL JNM GX-270 spectrometer or a Hitachi R-90H spectrometer with tetramethylsilane (TMS) as an internal standard. The ^{13}C nmr spectra were recorded on a Bruker AMX400 spectrometer. Mass spectra (ms) were determined on a JEOL JMS-D300 instrument at an ionization potential of 70 eV. High resolution EI mass spectra were determined at 70 eV on a JEOL JMS-SX102. Elemental analyses were performed with a Perkin-Elmer 2400 CHN. For column chromatography, silica gel 60 (E. Merck, 0.063-0.200 mm) was used. Silica gel preparative thin layer chromatography was performed with Merck Kieselgel F254S.

4-Amino-*N*-(5-chloropentanoyl)-5-imidazolecarboxamide (**3a**).

To the suspension of 15 g (0.093 mole) of 4-amino-5-imidazolecarboxamide **4** hydrochloride and 400 ml of THF, was added dropwise 68 ml (0.28 mole) of bis(trimethylsilyl)acetamide. After stirring at room temperature for 30 minutes, 19 g (0.12 mole) of 5-chlorovaleryl chloride was added to the mixture with ice cooling. After stirring at room temperature again for 1 hour, the solvent was evaporated under reduced pressure. After adding 200 ml of water, the mixture was neutralized with 50% aqueous sodium hydroxide solution with ice cooling followed by extraction with ethyl acetate. The combined extracts were washed with brine, dried and evaporated under reduced pressure to give 22 g (90%) of **3a** as white crystals. An analytical sample was recrystallized from methanol-water, mp 176-178°; ir (potassium bromide): ν 1664 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): 1.62-1.90 (m, 4 H, pentanoyl 3-H and 4-H), 3.05 (t, 2 H, pentanoyl 2-H, J = 7 Hz), 3.70 (t, 2 H, pentanoyl 5-H, J = 7 Hz), 6.40-7.10 (m, 4 H, imido NH, NH_2, and imidazole NH), 7.80 (s, 1 H, imidazole 2-H); ^{13}C nmr (DMSO-d_6): 20.6 ($ClCH_2CH_2$), 31.0 ($ClCH_2CH_2CH_2$), 34.3 (CH_2CO), 44.9 ($ClCH_2$), 110.8 (C-5), 127.7 (C-2), 143.2 (C-4), 166.2 (C-6), 173.1 (CH_2CONH); ms: m/z 246, 244 molecular ion); hrms: m/z Calcd. for $C_9H_{13}N_4O_2Cl$: 244.0742. Found: 244.0757. *Anal.* Calcd. for $C_9H_{13}N_4O_2Cl$: C, 44.18; H, 5.36; N, 22.90. Found: C, 43.92; H, 5.45; N, 23.10.

5,6,7,8-Tetrahydropyrido[2,1-*b*]purin-10-one (**1**).

To 10 g (0.041 mole) of **3a** was added 60 g of polyphosphoric acid. The mixture was stirred at 150° for 30 minutes. After cooling, the reaction mixture was poured into 100 ml of a mixture of ice and water and neutralized with 50% aqueous sodium hydroxide solution. The resulting precipitate was collected by filtration, washed with water, dried, and recyrstallized from DMF to give 2.8 g (36%) of **1** as white crystls, mp >300°; ir (potassium bromide): ν 1635 (C=O) cm^{-1}; ^1H nmr deuteriochloroform/perdeuteriomethanol = 4/1): 2.03-2.22 (m, 4 H, 6-H_2 and 7-H_2), 3.07 (t, 2 H, 5-H, J = 7 Hz), 4.36 (t, 2 H, 8-H, J = 7 Hz), 8.03 (s, 1 H, 2-H); ^{13}C nmr (deuteriotrifluoroacetic acid): 18.3 (C-7), 21.7 (C-6), 28.9 (C-8), 50.6 (C-5), 116.7 (C-10a), 146.6 (C-2), 149.3 (C-3a), 153.4 (C-10), 162.5 (C-8a); ms: m/z 190 (molecular ion); hrms: m/z Calcd. for $C_9H_{10}N_4O$: 190.0854. Found: 190.0872.

Anal. Calcd. for $C_9H_{10}N_4O$: C, 56.83; H, 5.30; N, 29.46. Found: C, 56.56; H, 5.55; N, 29.71.

1-Methyl-5,6,7,8-tetrahydropyrido[2,1-*b*]purin-10(1*H*)-one (**6**).

To the suspension of 1.20 g (6.32 mmoles) of **1** in DMF was

added 0.265 g (6.63 mmoles) of 60% of sodium hydride at 0°. After 30 minutes, 0.433 ml (6.95 mmoles) of iodomethane was added and the mixture was stirred at room temperature for 90 minutes. The precipitate was collected by filtration and recrystallized from 2-propanol-diisopropyl ether to afford 0.700 g (54%) of **6** as colorless crystals, mp 158-161°; ir (potassium bromide): ν 1622 (C=O) cm^{-1}, ^1H nmr (DMSO-d_6): 2.08-1.84 (m, 4 H, 6-H_2 and 7-H_2), 2.91 (t, 2 H, 5 H, J = 7 Hz), 3.98 (s, 3 H, CH_3), 4.18 (t, 2 H, 8-H, J = 7 Hz), 8.25 (s, 1 H, 2-H); ^{13}C nmr (DMSO-d_6): 18.1 (C-7), 20.3 (C-6), 28.4 (C-8), 33.2 (CH_3), 45.2 (C-5), 113.9 (C-10a), 143.6 (C-2), 147.3 (C-3a), 156.8l (C-10), 157.0 (C-8a); ms: m/z 204 (molecular ion); hrms: m/z Calcd. for $C_{10}H_{12}N_4O$: 204.0989. Found: 204.1011.

Anal. Calcd. for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.92; N, 27.43. Found: C, 59.08; H, 6.21; N, 27.60.

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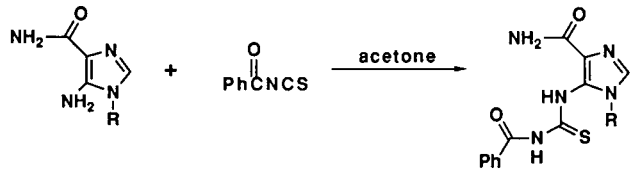

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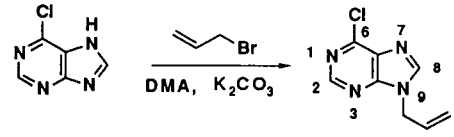

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