Synthesis of Pyrrolopyrimidones by a Chromous Ion-Mediated Reductive Cyclization

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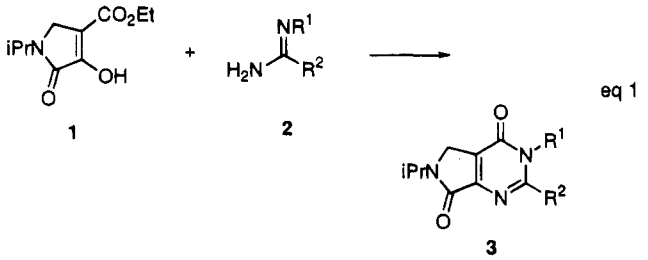
We required a general synthesis of pyrrolo[3,4-*d*]-pyrimidones **3** as a template from which the 4-position on the pyrimidine ring could be easily substituted. Synthetic approaches to **3**, based upon classical pyrimidine synthesis, were suggested from the literature.[1] Using amidines, guanidines, isoureas, and an appropriately functionalized pyrrolidinone **1** as reacting components, one could conceivably effect a cyclocondensation to form the targeted ring system (eq 1). In fact, related

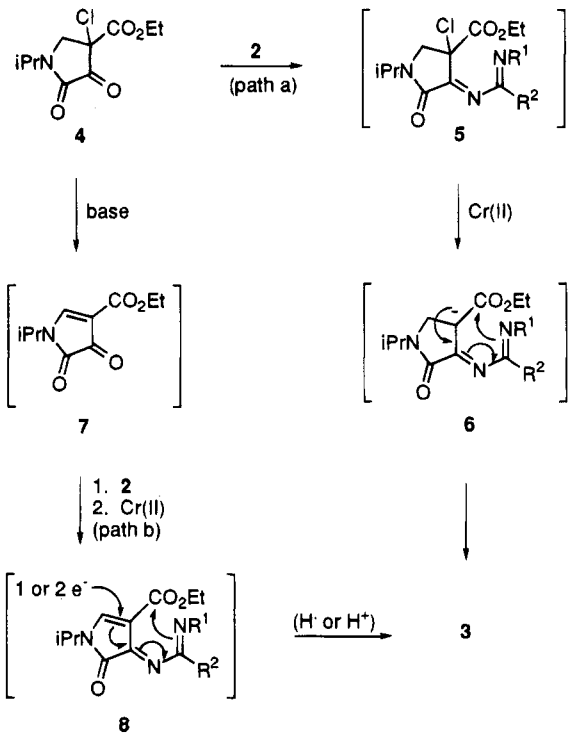


pyrrolopyrimidines and pyrrolopyrimidones have been obtained by such a cyclocondensation of β-dicarbonyls with guanidines, for example.[2]

Thus, the readily available pyrrolidinone **1**[3] was reacted with morpholinoformamidine (**2**) (R^1= H; R^2= 1-morpholinyl), as a representative reaction partner. However, reaction of **1** and **2** (R^1= H; R^2= 1-morpholinyl) in refluxing ethanol,[4] or refluxing acetic acid,[5] gave none of the desired pyrrolopyrimidone **3** (R^1= H; R^2= 1-morpholinyl). Even heating **1** and **2** together, neat at 150 °C, failed to afford any of pyrrolopyrimidone **3**. We suspected that the highly basic guanidine **2** (R^1= H; R^2= 1-morpholinyl) was simply functioning as a base to remove the very acidic enolic hydrogen from **1**.[6] This then would prevent the desired condensation from proceeding. In fact, a pyrrolidinone, similar in structure to **1**, has been reported to not produce the anticipated pyrrolopyrimidine upon reaction with guanidine.[2b] The failure of the reaction was attributed to proton transfer from the acidic pyrrolidinone to the basic guanidine.

We reasoned that if the offending proton transfer could be suppressed, or eliminated, successful cyclocondensation-based synthetic approaches to form **3** may be achievable. One method to accomplish this would be to introduce a blocking group α to the ester carbonyl in **1** to prevent enolization. Furthermore, selection of an easily reducible α-blocking group then might permit a reductively driven cyclization to annulate the pyrimidine ring onto the pyrrolidinone (Scheme 1, path a).

Scheme 1



To test this, α-chloropyrrolidinone **4** was chosen as a reducible α-substituted pyrrolidinone. The α-chloro substituent should be readily reduced and also enhance the reactivity of the already very electrophilic "keto" carbonyl group of the pyrrolidinone. Reaction of **1** with sodium hypochlorite in the presence of aqueous acetic acid afforded the desired pyrrolidinone **4** in excellent yield, as a white crystalline solid.[7] Pyrrolidinone **4** was then mixed with **2** (R^1 = H; R^2 = 1-morpholinyl) at 0 °C, and the mixture was subsequently exposed to excess freshly prepared chromous chloride as the reducing agent.[8] The desired pyrrolo[3,4-*d*]pyrimidone **3** was identified as the exclusive nonpolar product in a 16% yield. Evaluation of several other reducing agents (e.g. activated zinc dust, samarium diiodide,[9] and Rieke zinc[10]) gave poorer yields of **3** compared to those obtained with chromous ion and tended to produce more complex mixtures.

We suspected that the very basic guanidine[11] derivative **2** may be dehydrohalogenating pyrrolidinone **4**. This would give the Δ^2-pyrrolidinone **7** and the corresponding hydrochloride salt of **2** preventing the desired cyclocon-

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(7) Based on a procedure of Suprin: Suprin, J. *Ann. Chem.* **1951**, *6*, 294. The chlorination may also be accomplished with sulfuryl chloride or *tert*-butyl hypochlorite.

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Table 1. Pyrrolopyrimidones 3 by a Chromous Chloride-Induced Reductive Cyclization

entry	R^1	R^2	% yield[a]
1	H	1-morpholinyl	62
2[b]	H	1-morpholinyl	55
3	H	phenyl	70
4	H	*S*-benzyl	75
5	H	OCH_3	65
6	H	H	22
7	H	4-(*tert*-butoxycarbonyl)-1-piperazinyl	45
8		$-(CH_2)_4-$	58

[a] Yields are of isolated, recrystallized products. [b] Morpholinoformamidine and DBU (1.3 equiv of each) were admixed and reacted with **4**, followed by addition of the mixture to the low-valent chromium.

densation. However, we reasoned that if 2 equiv of **2** were employed in the reaction with pyrrolidinone **4**, 1 equiv could be sacrificed to induce the dehydrohalogenation allowing the other equivalent to condense with the electrophilic pyrrolidinone "keto" carbonyl (Scheme 1, path b). The resulting guanimine **8** could then be reacted with a suitable reducing agent to promote cyclization to form **3**.

Thus, reaction of **4** with 2.5 equiv of **2** (R^1 = H; R^2 = 1-morpholinyl) at 0 °C followed by exposure to chromous chloride at ambient temperature gave a 62% isolated yield of pyrrolopyrimidone **3**, after recrystallization. The reaction proved to be general for the synthesis of several pyrrolo[3,4-*d*]pyrimidone derivatives using several other reaction partners (Table 1). Conducting the reductive cyclocondensation of **4** with only 1.3 equiv of **3** (R^1 = H; R^2 = 1-morpholinyl) and 1.3 equiv of DBU, as an admixture, gave a 55% isolated yield of **3**, after recrystallization. The success of the procedure using DBU does provide some support for the proposed mechanism (Scheme 1, path b).[12] The DBU presumably can function as the dehydrohalogenating agent in place of the "extra" equivalent of **2**. Also, by employing DBU, very valuable or expensive guanidine derivatives can be more efficiently used.

A scope for this novel chromous ion-mediated reductive cyclization for the synthesis of pyrimidines and pyrimidones has yet to be defined. Presently, the reductive cyclization augments existing procedures, which include cyclocondensation approaches to pyrimidine and pyrimidone ring construction.[1] Extension of the procedure to other related substrates such as β-diketones and β-keto nitriles, with very high enol or α-hydrogen acidity, may considerably expand the scope of the reaction.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. THF was distilled from sodium benzophenone ketyl immediately prior to use. TLC analyses were performed on silica gel GHLF. Flash chromatography refers to the method reported by Still.[13] All reactions were performed under a nitrogen or argon atmosphere using standard techniques for manipulation of air- and moisture-sensitive reagents.[14] Ambient temperature refers to 23 ± 3 °C. Melting points were taken on a capillary apparatus. Unless otherwise specified, recrystallization solvents for solid products are given in parentheses, prior to the melting point. ^{1}H NMR spectra were obtained at either 250 or 300 MHz. Mass spectra (CI) used methane as the ionization gas. Elemental analyses were performed by the departmental analytical laboratory at Zeneca Pharmaceuticals, Inc.

1-Isopropyl-4-carbethoxy-5,6-dihydropyrroline-2,3-dione (1). Freshly distilled ethyl acrylate (54 mL, 500 mmol) was added slowly to a solution of isopropylamine (42.6 mL, 500 mmol) in ethanol (250 mL) at ambient temperature. The solution was stirred for 24 h, which was followed by the addition of diethyl oxalate (67.8 mL, 500 mmol). The reaction solution was stirred at ambient temperature for 2 h. A solution of sodium ethoxide in ethanol, prepared from sodium metal (11.5 g, 500 mmol) and ethanol (100 mL), was added and the reaction solution heated to reflux. After 30 min, the reaction mixture formed a thick solid. The mixture was cooled to ambient temperature and the solid was removed by filtration. The solid was washed with ethanol (500 mL), then dissolved in hot water (350 mL), and acidified to a pH of 1 with 20% aqueous hydrochloric acid (about 70 mL). The solution was allowed to cool slowly and was then stored overnight at 5 °C which resulted in the precipitation of white needles. The solid was removed by filtration and washed with cold water and then was dried under high vacuum at 60 °C overnight. The title compound was obtained as a white crystalline solid (61.9 g, 58%): mp 134–135 °C; ^{1}H NMR ($CDCl_3$) 1.24 (d, 6H, J = 6.8 Hz), 1.36 (t, 3H, J = 7.2 Hz), 3.95 (s, 2H), 4.33 (q, 2H, J = 7.2 Hz), 4.51 (sep, 1H, J = 6.8 Hz), 8.90 (bs, 1H); mass spectrum, m/z = 214 [m + H]. Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.08; H, 7.09; N, 6.55.

4-Carbethoxy-4-chloro-1-isopropyl-5,6-dihydropyrroline-2,3-dione (4). To a suspension of **1** (12 g, 56.3 mmol) in acetic acid (15 mL) and water (50 mL) in an ice bath was added dropwise an aqueous solution of sodium hypochlorite (92 mL, 64 mmol, 0.7 M solution). After the addition was complete, the ice bath was removed and the reaction allowed to warm to ambient temperature. The solution was stirred for 1 h and then was saturated with excess solid sodium chloride. The mixture was extracted 5 times with dichloromethane. The extracts were combined, dried over anhydrous Na_2SO_4 and concentrated under high vacuum. The resulting solid was triturated with ether and collected by filtration to afford a white solid. Recrystallization from *tert*-butyl methyl ether/hexanes afforded fine white needles, 12.4 g (89%): mp 84–85 °C; ^{1}H NMR ($CDCl_3$) 1.30 (m, 9H), 3.77 (d, 1H, J = 11.5 Hz), 4.28–4.38 (m, 3H), 4.64 (sep, 1H, J = 6.8 Hz); mass spectrum, m/z = 248 [m + H]. Anal. Calcd for $C_{10}H_{14}NO_4Cl$: C, 48.49; H, 5.70; N, 5.66. Found: C, 48.64; H, 5.76; N, 5.68.

Preparation of Pyrrolopyrimidones 3 by Reductive Cyclization Using Chromous Chloride. General Procedure. The procedure for the preparation of 4-hydroxy-6-isopropyl-2-(1-morpholinyl)-6,7-dihydro-5*H*-pyrrolopyrimidin-7-one (Table, entry 1) serves as a representative example. A suspension of morpholinoformamidine hydrobromide (26.4 g, 125.6 mmol) in ethanol (75 mL) was treated with sodium ethoxide in ethanol, prepared from sodium metal (2.88 g, 125 mmol) in ethanol (75 mL), at ambient temperature. After stirring for 1h, the suspension was cooled in an ice bath and 4Å molecular sieves were added (12 g). A solution of **4** (12.4 g, 50 mmol) in ethanol was then added dropwise to the morpholinoformamidine/molecular sieve mixture. This mixture was stirred 2 h in the ice bath. A suspension of chromous chloride ($CrCl_2$) was prepared by adding solid lithium aluminum hydride (4.74 g, 125 mmol, added in five batches under gentle N_2 backflush) to a mechanically stirred suspension of chromium(III) chloride (39.6 g, 250 mmol) in THF (200 mL) at ice bath temperature. Following the addition of the hydride, the cooling bath was removed and the dark mixture was stirred for 15 min. The suspension containing the morpholinoformamidine and **4** was then transferred, by cannula, to the freshly prepared chromous reagent. The reaction mixture was cooled as necessary in a

(12) Due to apparent instability, we have been unable to isolate or characterize intermediates **5**, **7**, or **8**. We have also been unsuccessful in obtaining ^{1}H NMR or mass spectrometry evidence to detect even transient formation of **7**. Furthermore, pretreatment of **4** with 1 equiv of DBU, followed immediately by the addition of 1 equiv of **2** (R^1 = H, R^2 = morpholinyl), gave **3** (R^1 = H, R^2 = morpholinyl) in only a 12% yield.

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water bath to maintain the internal temperature below 30 °C. The reaction was stirred 3 h. Water was added (300 mL) and the resulting mixture extracted 4 times with methylene chloride. The extracts were dried (anhydrous Na_2SO_4) and concentrated to leave a light green solid. The product was purified by flash chromatography, primarily to remove some polar byproducts, using methylene chloride /methanol (49:1) as the eluent, followed by recrystallization from diethyl ether/methylene chloride to give 8.58 g (62%) of a white solid: mp 227–228 °C; TLC, $R_f = 0.38$, methylene chloride/methanol (19:1); ^{1}H NMR (DMSO-d_6) 1.28 (d, 6H, J = 6.8 Hz), 3.80 (bs, 8H), 4.12 (s, 2H), 4.63 (sep, 1H, J = 6.8 Hz), 10.8 (bs, 1H); mass spectrum, m/z = 279 [m + H]. Anal. Calcd for $C_{13}H_{18}N_4O_3 \cdot 0.2H_2O$: C, 55.39; H, 6.57; N, 19.87. Found: C, 55.71; H, 6.42; N, 19.31.

4-Hydroxy-6-isopropyl-2-phenyl-6,7-dihydro-5*H*-pyrrolopyrimidin-7-one (Table 1, Entry 3): Melting point (dichloroethane), 284–287 °C; ^{1}H NMR (DMSO-d_6) 1.25 (d, 6H, J = 7 Hz), 4.33 (s, 2H), 4.38 (sep, 1H, J = 7 Hz), 7.58 (m, 3H), 8.12 (m, 2H), 13.07 (bs, 1H); mass spectrum, m/z = 270 [m + H]. Anal. Calcd for $C_{15}H_{15}N_3O_2 \cdot 0.1H_2O$: C, 66.46; H, 5.65; N, 15.50. Found: C, 66.34; H, 5.64; N, 15.31.

4-Hydroxy-6-isopropyl-2-benzylthio-6,7-dihydro-5*H*-pyrrolopyrimidin-7-one (Table 1, Entry 4): Melting point (diethyl ether/methylene chloride), 236–239 °C dec; ^{1}H NMR (DMSO-d_6) 1.22 (d, 6H, J = 6.8 Hz), 4.23 (s, 2H), 4.36 (sep, 1H, J = 6.8 Hz), 4.48 (s, 2H), 7.28–7.48 (m, 5H), 13.11 (bs, 1H); mass spectrum, m/z = 316 [m + H]. Anal. Calcd for $C_{16}H_{17}N_3O_2S$: C, 60.93; H, 5.43; N, 13.32. Found: C, 60.58; H, 5.46; N, 13.33.

4-Hydroxy-6-isopropyl-2-methoxy-6,7-dihydro-5*H*-pyrrolopyrimidin-7-one (Table 1, Entry 5): Melting point (ethyl acetate/methanol), 215–218 °C; ^{1}H NMR (DMSO-d_6) 1.20 (d, 6H, J = 6.8 Hz), 3.94 (s, 3H), 4.18 (s, 2H), 4.32 (sep, 1H, J = 6.8 Hz), 13.2 (bs, 1H); mass spectrum, m/z = 224 [m + H]. Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.81; H, 5.87; N, 18.82. Found: C, 53.83; H, 5.85; N, 19.13.

4-Hydroxy-6-isopropyl-6,7-dihydro-5*H*-pyrrolopyrimidin-7-one (Table 1, Entry 6): Melting point (1,1,2-trichloroethane/ methanol), 242–244 °C dec; ^{1}H NMR (DMSO-d_6) 1.21 (d, 6H, J = 6.8 Hz), 4.27 (s, 2H), 4.36 (sep, 1H, J = 6.8 Hz), 8.31 (s, 1H), 13.2 (bs, 1H); mass spectrum, m/z = 194 [m + H]. Anal. Calcd for $C_9H_{11}N_3O_2 \cdot 0.2H_2O$: C, 54.93; H, 5.84; N, 21.35. Found: C, 55.10; H, 5.67; N, 21.20.

4-Hydroxy-6-isopropyl-2-[4-(*tert*-butoxycarbonyl)piperazinyl]-6,7-dihydro-5*H*-pyrrolopyrimidin-7-one (Table 1, Entry 7): Melting point (1,1,2-trichloroethane/ methanol), 240–242 °C dec w/gas evolution; ^{1}H NMR (DMSO-d_6) 1.18 (d, 6H, J = 6.8 Hz), 1.42 (s, 9H), 3.39 (m, 2H), 3.62 (m, 2H), 4.11 (s, 2H), 4.32 (sep, 1H, J = 6.8 Hz), 11.50 (bs, 1H); mass spectrum, m/z = 378 [m + H]. Anal. Calcd for $C_{18}H_{27}N_5O_4 \cdot 0.3H_2O$: C, 56.47; H, 7.26; N, 18.29. Found: C, 56.55; H, 7.15; N, 18.02.

4-Hydroxy-6-isopropyl-6,7-dihydro-5*H*-pyridopyrrolo[*b*,*e*]pyrimidin-7-one (Table 1, Entry 8): Melting point (ethyl acetate/methylene chloride), 243–246 °C dec; ^{1}H NMR ($CDCl_3$) 1.27 (d, 6H, J = 7 Hz), 1.93–2.01 (m, 4H), 3.10 (m, 2H), 4.05 (m, 2H), 4.24 (m, 2H), 4.67 (sep, 1H, J = 7 Hz); mass spectrum, m/z = 248 [m + H]. Anal. Calcd for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 62.74; H, 6.84; N, 16.84.

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