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Technical Notes

One-Pot Synthesis of 5-Methyl-3H-pyrrolo[2,3-*d*]pyrimidin-4(7H)-one

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Abstract:

An efficient and environmentally benign synthesis of 5-methyl-3H-pyrrolo[2,3-*d*]pyrimidin-4(7H)-one is described. An acyl-protected aminoacetone is reacted with cyanoacetamide to give 2-amino-4-methyl-1H-pyrrole-3-carboxamide, which is converted in one-pot to 5-methyl-3H-pyrrolo[2,3-*d*]pyrimidin-4(7H)-one in 60% overall yield. This process avoids the use of large excess Raney nickel which is required when known methods are practiced.

Introduction

Pyrrolo[2,3-*d*]pyrimidines have attracted much recent interest because of their biological importance.[1] Due to presence of multiple reactive sites, 3H-pyrrolo[2,3-*d*]pyrimidin-4(7H)-ones are important intermediates for preparation of pyrrolo[2,3-*d*]pyrimidines. While there are numerous synthetic examples for 3H-pyrrolo[2,3-*d*]pyrimidin-4(7H)-ones with a heteroatom substitution at the 2-position, only a limited number of synthetic methods with wide applicability have been reported for 5-alkyl-3H-pyrrolo[2,3-*d*]pyrimidin-4(7H)-ones.[2] Recently, we were in need of large quantities of 5-methyl-3H-pyrrolo[2,3-*d*]pyrimidin-4(7H)-one (**1**) to support an internal drug development program. Although **1** is known in literature, all reported syntheses utilize the desulfurization route. One such procedure consists of desulfurization of the 2-thioxopyrrolo[2,3-*d*]pyrimidinone (**2**), which is prepared from the appropriately substituted cyanoacetate **3** in two steps (Scheme 1).[3] Due to the lack of an efficient method for the preparation of the cyanoacetate **3**,[4] an in-house process was developed during the medicinal chemistry stage employing desulfurization of **4** as the final step (Scheme 2).[5,6] While this process was sufficient to support medicinal chemistry, the desulfurization step required a large excess of Raney nickel and suffered long reaction times and inconsistent yields during early process development.[7] We sought to develop a process that is more robust as well as more environmentally friendly.

Results and Discussion

While the Discovery synthesis of **1** starts with building the pyrimidine moiety, literature suggests that building the pyrrole moiety first may be more effective.[2] There are a number of such methods reported in literature for pyrroles. For example, pyrrole **5** was prepared from acetamidoacetone (**6**) (Scheme 3).[8] However, in our hands, the conversion of **5** to **1** using known procedures suffered poor yields. Thus, heating **5** in formic acid[9] gave only 10−15% yield of **1**. Alternatively, treating **5** with formic acid in the presence of acetic anhydride gave the *N*-formyl pyrrole **7** in good yield. However, conversion of **7** to the **1** by heating with concentrated phosphoric acid,[10] or phosphorus pentaoxide[10,11] gave only trace amounts of **1**.

Since the inefficient conversion of **5** to **1** may be due to the low reactivity of the nitrile in such an electron-rich pyrrole, we reasoned that replacing the nitrile with a primary

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(1) For example: (a) Choi, H.-S.; Wang, Z.; Richmond, W.; He, X.; Yang, K.; Jiang, T.; Karanewsky, D.; Gu, X.-J.; Zhou, V.; Liu, Y.; Che, J.; Lee, C. C.; Caldwell, J.; Kanazawa, T.; Umemura, I.; Matsuura, N.; Ohmori, O.; Honda, T.; Gray, N.; He, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2689−2692. (b) Choi, H.-S.; Wang, Z.; Richmond, W.; He, X.; Yang, K.; Jiang, T.; Sim, T.; Karanewsky, D.; Gu, X.-J.; Zhou, V.; Liu, Y.; Ohmori, O.; Caldwell, J.; Gray, N.; He, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2173−2176. (c) Smalley, T. L.; Peat, A. J.; Boucheron, J. A.; Dickerson, S.; Garrido, D.; Preugschat, F.; Schweiker, S. L.; Thomson, S. A.; Wang, T. Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2091−2094. (d) Gangjee, A.; Jain, H. D.; Phan, J.; Lin, X.; Song, X.; McGuire, J. J.; Kisliuk, R. L. *J. Med. Chem.* **2006**, *49*, 1055−1065. (e) Seela, F.; Peng, X. *J. Org. Chem.* **2006**, *71*, 81−90 and references therein. (f) Foloppe, N.; Fisher, L. M.; Howes, R.; Kierstan, P.; Potter, A.; Robertson, A. G. S.; Surgenor, A. E. *J. Med. Chem.* **2005**, *48*, 4332−4345. (g) Kempson, J.; Pitts, W. J.; Barbosa, J.; Guo, J.; Omotoso, O.; Watson, A.; Stebbins, K.; Starling, G. C.; Dodd, J. H.; Barrish, J. C.; Felix, R.; Fischer, K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1829−1833. (h) Traxler, P.; Bold, G.; Buchdunger, E.; Caravatti, G.; Furet, P.; Manley, P.; O'Reilly, T.; Wood, J.; Zimmermann, J. *Med. Res. Rev.* **2001**, *21*, 499−512.

(2) For a review on synthesis of pyrrolopyrimidines, see: Amarnath, V.; Madhav, R. *Synthesis* **1974**, 837−859.

(3) West, R. A. *J. Org. Chem.* **1961**, *26*, 4959−4961.

(4) Luepke, U.; Seela, F. *Chem. Ber.* **1979**, *112*, 799−806. Okuma, K. *J. Antibiot.* **1961**, *14*, 343−52.

(5) For annulation of similarly substituted pyrimidines, see: Noell, C. W.; Robins, R. K. *J. Heterocycl. Chem.* **1964**, *1*, 34−41. Williams, D. M.; Loakes, D.; Brown, D. M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3565−3570.

(6) For desulfurization of 2-(methylthio)-3H-pyrrolo[2,3-*d*]pyrimidin-4(7H)-one, see: Gerster, J. F.; Hinshaw, B. C.; Robins, R. K.; Townsend, L. B. *J. Heterocycl. Chem.* **1969**, *6*, 207−213.

(7) It should be noted that this process was eventually optimized and scaled up by a contract research organization to produce about 500 g of **1** to support preclinical studies. The key to a reproducible desulfurization was to start with a large excess of Raney nickel.

(8) Wamhoff, H.; Wehling, B. *Synthesis* **1976**, *51*.

(9) Traxler, P. M.; Furet, P.; Mett, H.; Buchdunger, E.; Meyer, T.; Lydon, N. *J. Med. Chem.* **1996**, *39*, 2285−2292. El-Bayouki, K. A. M.; Basyouni, W. M.; Hosni, H.; El-Deen, A. S. *J. Chem. Res., Synop.* **1995**, 314−315.

(10) Girgis, N. S.; Joergensen, A.; Pedersen, E. B. *Synthesis* **1985**, 101−104.

(11) Hess, S.; Mueller, C. E.; Frobenius, W.; Reith, U.; Klotz, K.-N.; Eger, K. *J. Med. Chem.* **2000**, *43*, 4636−4646.

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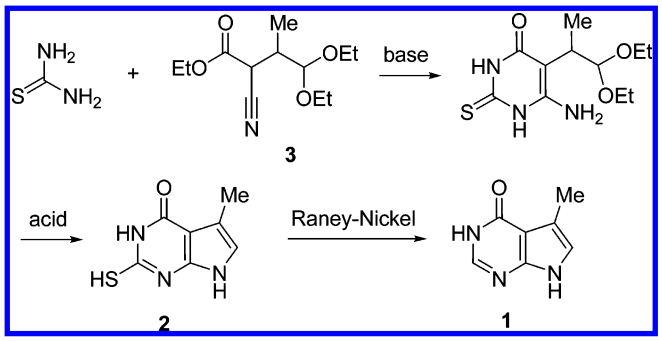
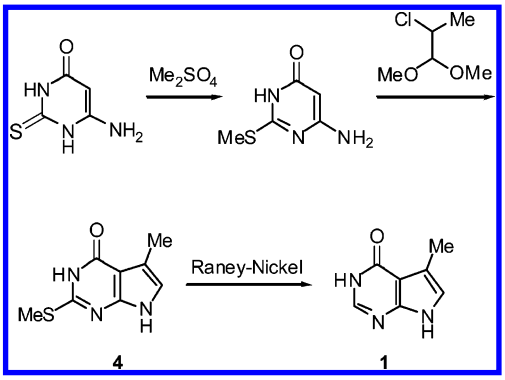
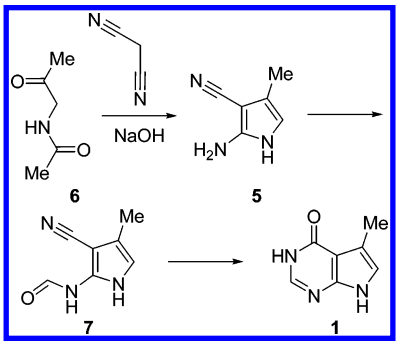
Scheme 1



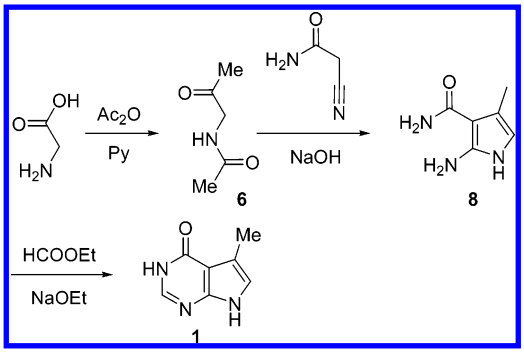
Scheme 2



Scheme 3



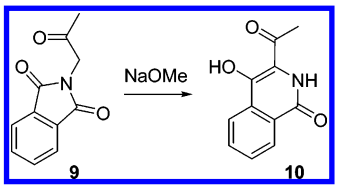
Scheme 4



amide could ease the construction of the pyrimidinone ring. Indeed, when 2-amino-4-methyl-1H-pyrrole-3-carboxamide (**8**) was prepared from **6** using similar conditions, it underwent annulation with ethyl formate to **1** in about 80% yield (Scheme 4). However, the yield of **8** was low, and the pyrrole was found to be unstable.[12] Consequently, we decided

(12) For a review on aminopyrroles, see: Cirrincione, G.; Almerico, A. M.; Aiello, E.; Dattolo, G. in *Chemistry of Heterocyclic Compounds*; Chichester: United Kingdom, 1992; Vol. 48 (Pyrroles, Pt. 2), pp 299−523.

Scheme 5



to carry out the two annulation reactions in one pot. Although acetamidoacetone (**6**) can be prepared by the Dakin−West reaction,[13] the reaction and isolation is somewhat tedious.[14] We decided to use phthalimidoacetone (**9**),[15] which is easier to monitor during the reaction due to the presence of a chromophore, as the aminoacetone surrogate.[16]

Since the pyrimidinone-formation step requires an alkoxide, such as sodium ethoxide, as the base, it was chosen as the base for the pyrrole-formation step as well. Thus, the cyanoacetamide was treated with sodium ethoxide followed by **9** at 40−50 °C. Upon consumption of **9**, ethyl formate was added along with additional sodium ethoxide. After heating at 50−60 °C for 4 h, HPLC showed the disappearance of **8**. The reaction mixture was then quenched with water, and solvent was removed. The product **1** was isolated by adjusting the pH to 7−8. Although this procedure gave about 30−35% yield at 10-g scale, the yield fell dramatically to about 10% when the procedure was scaled up to 50-g scale. It is noteworthy that the product **1** isolated from this low-yielding experiment was still very clean by HPLC and NMR.

We suspected that self reactions of cyanoacetamide and **9** under the reaction conditions were responsible for the scale-up issues since longer addition times may allow self reactions to proceed to a greater extent. Indeed, **9** is known to undergo a Gabriel−Coleman-type rearrangement in the presence of alkoxide bases to give 3-acetyl-4-hydroxyisoquinolin-1(2H)-one (**10**, Scheme 5).[17,18] It is also reported in the literature that cyanoacetamide undergoes self-condensation to give **11** in the presence of sodium methoxide.[19] Indeed, when cyanoacetamide was heated with 0.8 equiv of sodium methoxide in methanol for 6 h at 40 °C and then 5 h at 60 °C, a yellow solid was formed and isolated cleanly by filtration. This compound accounted for about 55% of the reaction mixture by HPLC area. The structure of the solid product was determined to be **12** based on HPLC/MS as well as NMR analysis. Further proof of the structure of **12** came

(13) Dakin, H. D.; West, R. *J. Biol. Chem.* **1928**, *78*, 91−105 and 745−756. For a review on the Dakin−West reaction, see: Buchanan, G. L. *Chem. Soc. Rev.* **1988**, *17*, 91−109.

(14) Hepworth, J. D. *Organic Syntheses*; Wiley & Sons: New York, 1973; Collect. Vol. V, pp 27−29. Wiley: R. H.; Borum, O. H. *J. Am. Chem. Soc.* **1948**, 70, 2005−2006. Yuan, C.; Chen, D. *Synthesis* **1992**, 531−532. Fadnavis, N. W.; Vadivel, S. K.; Bhalerao, U. T. *Tetrahedron: Asymmetry* **1997**, *8*, 2355−2359.

(15) Phthalimidoacetone (**9**) is commercially available from TCI America, Portland, Oregon. For a convenient preparation from chloroacetone, see: Lei, A.; Wu, S.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2004**, *126*, 1626−1627.

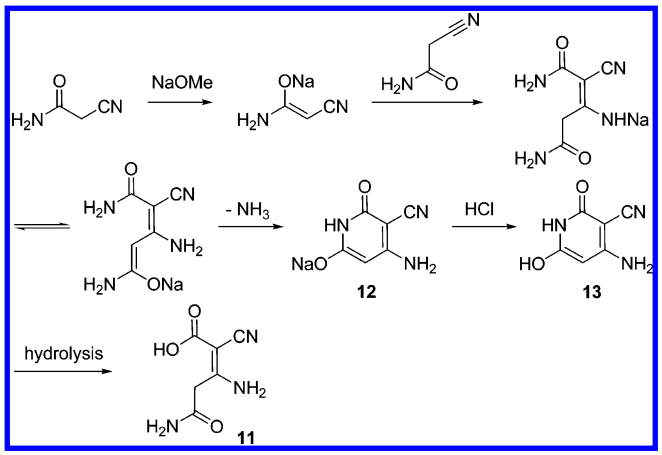
(16) A similar strategy was employed by Yumoto, M.; Kawabuchi, T.; Sato, K.; Takashima, M. Jpn. Kokai Tokkyo Koho, JP 10316654 A2, 1998.

(17) Howe, R.; Johnson, D. *J. Chem. Soc., Perkin Trans. 1* **1972**, 977−981. Nan, F.; Li, J.; Chen, Y.; Zhang, Y.; Gu, M.; Zhang, H. PCT Int. Appl. WO 2004111010 A1, 2004.

(18) Gabriel, S.; Colman, J. *Ber.* **1900**, *33*, 980−995.

(19) Fahmy, S. M.; Mohareb, R. M. *Synthesis* **1985**, 1135−1137.

Scheme 6

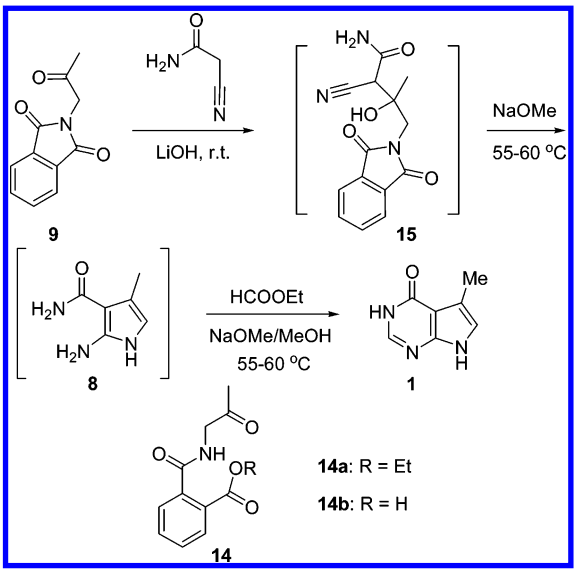


from NMR comparison of its protonated form **13** with that reported in literature.[20] We suspect that compound **11** reported in the literature[19] may be a secondary product produced during workup from **12**. A possible mechanism for this reaction is presented in Scheme 6.

Since both side reactions proceed under strongly basic conditions, lower basicity should be beneficial to the desired reaction. We decided to investigate the efficiency of the pyrrole formation vs strength of the base. Weak amine bases, such as triethylamine, gave only the ethanolysis product **14a** even after heating at reflux overnight. Some pyrrole **8** (about 10% by HPLC area) was observed when potassium carbonate was used as the base and the reaction mixture was heated at reflux overnight. In this case, the ethanolysis product **14a** and hydrolysis product **14b** predominated. With sodium hydroxide as the base, we were surprised to observe the aldol condensation product **15**. Thus, when a mixture of **9** and cyanoacetamide (1.5 equiv) was treated with 50% sodium hydroxide (1.5 equiv) at room temperature in DMF, **9** was converted within 30 min to aldol **15** and hydrolysis product **14b** in about 2:1 ratio. Aldol **15** was found to be unstable under reaction conditions and was gradually converted to pyrrole **8** upon heating. However, hydrolysis product **14b** resisted further reaction. To minimize hydrolysis, solid sodium hydroxide or lithium hydroxide was used, resulting in improved yields. After conversion to the pyrrole was complete, excess ethyl formate was added along with sodium methoxide to form the product in about 60% yield. Although reactions using lithium hydroxide gave similar yields to that using solid sodium hydroxide on small scale, they are more reproducible on larger scale (e.g., 100 g).

Thus, cyanoacetamide and **9** are treated with lithium hydroxide in methanol at room temperature to form **15**. Sodium methoxide solution in methanol is then added, and the reaction mixture is heated to convert **15** to **8**. The pyrrolopyrimidinone **1** is formed by heating the reaction mixture with ethyl formate and additional sodium methoxide (Scheme 7). After quenching with water and removal of organic solvent, **1** is isolated by precipitation at pH 7.5 to 8.0. This process consistently produced **1** at 60% overall yield on 100-g (**9**) scale with purity greater than 99% by HPLC.

Scheme 7



Having established the reaction conditions for conversion of phthalimidoacetone (**9**) to **1**, we repeated the process using acetamidoacetone (**6**). The one-pot procedure gave an overall yield of 55% yield of **1**. If the preparation procedure for **6** can be streamlined, the process starting with **6** should be more attractive due to its higher atom efficiency.

In summary, we have developed a one-pot process for the preparation of 5-methyl-3H-pyrrolo[2,3-*d*]pyrimidin-4(7H)-one (**1**). This process avoids the use of hazardous Raney nickel and eliminates the resulting heavy metal waste stream. The process produces **1** in 60% yield from readily available starting material **9**.

Experimental Section

Reagents and solvents were obtained from commercial sources and used as received. All solvents used were of HPLC grade. NMR spectra were recorded with a Bruker ARX 300, Bruker DPX 400 or Varian Mercury 400. HPLC analysis was performed on a Shimadzu instrument with a PDA detector. HPLC/MS analysis was carried out on a Waters ZQ or Shimadzu instrument.

Representative Procedure To a solution of LiOH (17.25 g, 1.5 equiv) in anhydrous methanol (600 mL) was added cyanoacetamide (63 g, 1.5 equiv) under nitrogen atmosphere. The resulting mixture was stirred for 20 min at room temperature. To this was added a solution of phthalimidoacetone (101.5 g, 0.5 mol) in 700 mL of THF (anhydrous) over a period of 30 min. The resulting reaction mixture was stirred for 2 h at room temperature and then heated at 55 °C for 1 h. To this was added sodium methoxide solution (25% solution, 172 mL, 1.5 equiv) at 55 °C over a period of 40 min. After 3 h HPLC/MS indicated starting material and intermediates were converted to the pyrrole **8**. A crude sample of **8** was obtained by extractive aqueous workup. MS: $MH^+ = 140.1$. ^{1}H NMR (DMSO-d_6): δ 9.71 (br s, 1H), 6.08 (br s, 2H), 5.84 (s, 1H), 5.64 (s, 2H), 2.07 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 169.2, 146.7, 113.8, 108.0, 95.5, 13.4. To the above reaction mixture was added ethyl formate (200.8 mL, 5 equiv) over a period of 20 min followed by

(20) Junek, H.; Sarhan, E. T.; Sterk, H. *Monatsh. Chem.* **1988**, *119*, 717−726.

sodium methoxide (25% solution, 324 g, 3 equiv). The resulting reaction mixture was heated for 7 h at 55 °C at which time HPLC/MS indicated that the pyrrole **8** was converted to the pyrrolopyrimidinone **1**. The reaction mixture was diluted with 1.5 L water, heated at 60 °C for 1 h, and then concentrated to small volume (~1.5 L). Solution assay indicated that pyrrolopyrimidinone **1** was formed in 75% solution yield. This solution was neutralized to pH ≈ 7.5 with 6 N aq HCl, cooled to about 5 °C, and held at this temperature for 30 min. Solids were filtered, washed with water, dried at 50 °C under vaccum overnight to give the pyrrolopyrimidinone **1** as a light brown solid (45.8 g, 61% yield, purity: 99.0% by HPLC area). MS: $MH^+ = 150.1$. ^{1}H NMR (DMSO-d_6): δ 2.27(s, 3H), 6.74(s, 1H), 7.74(s, 1H), 11.53 (br s, 2H). ^{13}C NMR (DMSO-d_6): δ 11.6, 107.0, 113.8, 117.8, 143.5, 148.2, 159.6.

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