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Selective Formation of Pyrrolo[3,2-*d*]pyrimidines from Methyl[(*N*-benzoyl-*S*-methylisothiocarbamoyl)amino]-1*H*-pyrrole-2-carboxylate

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Abstract:

A selective conversion of methyl 3-{[(benzoylamino)(methylsulfanyl)methylidene]amino}-4-(3-pyridinylmethyl)-1*H*-pyrrole-2-carboxylate (1a) to 2-amino-7-(3-pyridinylmethyl)-3,5-dihydro-4*H*-pyrrolo [3,2-*d*]pyrimidine-4-one (2a) in methanolic ammonia in the presence of sodium amide is described.

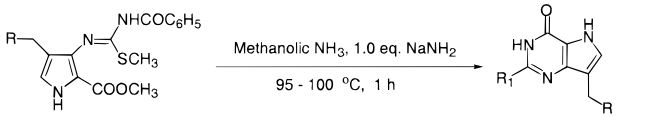
Purine nucleoside phosphorylase (PNP) catalyzes the reversible phosphorylation of guanosine, inosine, deoxyguanosine, and deoxyinosine, thus making PNP an essential enzyme in the purine salvage pathway.[1] This effect, combined with its role in the T-cell branch of the immune system,[2] has spawned interest in PNP inhibitors.

In our structure-based PNP inhibitor design program, we synthesized[3−5] 2-amino-3,5-dihydro-4*H*-pyrrolo[3,2-d]pyrimidine-4-one derivatives of the general structure **2**. The synthesis was carried out using a literature[6] multistep sequence starting from the corresponding heteroarylpropenenitriles [e.g., the precursor for **2a** was 3-(3-pyridinyl)-2-propenenitrile]. The 3-pyridylmethyl derivative **2a** (BCX-34, USAN peldesine) reversibly inhibits T-cell activity and is presently in clinical trials for topical use against psoriasis, T-cell proliferative diseases, as well as the other disease indications that are complex and not fully understood at this time. The clinical and stability studies required that the active material **2a** be available in bulk quantities, but the multistep synthesis used failed to provide such quantities. We contemplated optimizing the last step of the reaction sequence since it is at this step that the final product (**2**) was formed along with a byproduct **3**. The optimization of this step increased production of **2**. The conversion of methyl 3-{[(benzoylamino)(methylsulfanyl)methylidene]amino}-4-(3-pyridinylmethyl)-1*H*-pyrrole-2-carboxylate (**1a**) to 2-amino-7-(3-pyridinylmethyl)-3,5-dihydro-4*H*-pyrrolo[3,2-*d*]-pyrimidine-4-one (**2a**) involved 20−24 h exposure to saturated methanolic ammonia in a Parr reactor at 95−110 °C. These standard conditions[3] gave **2** (45−55%) and **3** (15−30%).

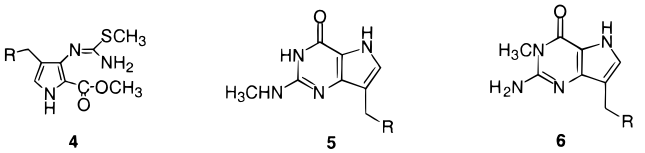
Table 1. **Various reaction conditions optimized for the production of 2[a]**

entry	additive	time, temp.	medium	ratio[b] **2:3**
1	no additive	24 h	NH_3−MeOH	35:10
2	no additive	3 h	NH_3−MeOH	39:10
3	0.1 equiv $NaNH_2$	3 h	NH_3−MeOH	23:10
4	1.0 equiv $NaNH_2$	3 h	NH_3−MeOH	96:4
5	1.0 equiv $NaNH_2$	1 h	NH_3−MeOH	95:5
6	1.0 equiv NaOMe	3 h	NH_3−MeOH	89:11
7	1.0 equiv Pyridine	3 h	NH_3−MeOH	54:46
8	no additive	24 h	NH_3−EtOH	78:22
9	no additive	3 h	NH_3−EtOH	86:14
10	1.0 equiv $NaNH_2$	3 h	NH_3−EtOH	97:3
11	1.0 equiv $NaNH_2$	12 h, 50 °C	NH_3−MeOH	91:9
12	no additive	60 h, 50 °C	NH_3−MeOH	3:1

[a] Reactions were carried out by mixing 100 mg of substrate (**1a**) in about 10 mL of saturated methanolic ammonia (prepared at 0 °C by passing anhydrous ammonia through anhydrous methanol until saturated) in a Parr steel vessel at 95−100 °C (except entries 11 and 12 for the time and temperature mentioned). In entry 3, the reaction was carried out using 1 g of the substrate. [b] Ratios of the products were calculated based on HPLC using ammonium formate−acetonitrile (85:15) buffer and detected at 233 nm. The peak area was translated to the actual molar amount based on the response factor of an individual compound, derived by injecting a known concentration under the same conditions. This was also supported by the isolated yield.



To improve the yield of **2a**, we investigated the mechanism of its formation and carried out a series of experiments, summarized in Table 1. On the basis of the formation of both products **2** and **3**, a feasible mechanism was postulated.[6] Accordingly, **3** is formed by the direct cyclization of **1** or alternatively via the deacylated (methylthio)pseudoureido intermediate **4**. The 9-deazaguanosine derivative, **2** on the other hand, might have been formed via either guanidine intermediate of type **7** and subsequent ring closure. However, the sequence for the debenzoylation was uncertain.



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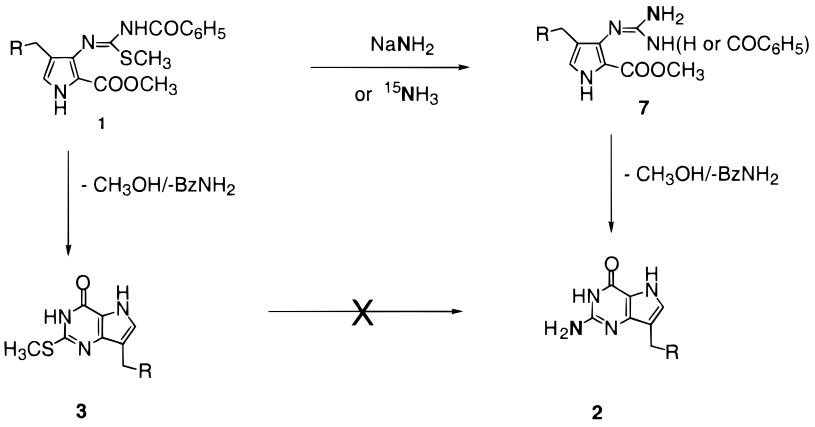
Scheme 1



We envisioned improving the yield by replacing the thiomethyl group in **1** by an amino group before cyclization. The addition of 1.0 equiv of sodium amide boosted the overall yield of **2a** to more than 70% and reduced the formation of **3** by 5-fold (Table 1, Entry 5). However, the use of one equivalent of pyridine shifted the equilibrium towards the formation of **3** (**2a**:**3a**, 54:46, Table 1, Entry 7). Since one equivalent of sodium amide was essential for the reaction, it would be fair to assume that sodium amide is involved directly or indirectly in the reaction. On the other hand the difficult ammonolysis of the carboalkoxy group in **1** was reported,[6] and easy access to the required amide was thus not easy. Assuming the carbomethoxy group was not converted to an amide group, the next possibility was the substitution of the thiomethyl group in **1** by an amino group (intermediate **7**) before cyclization to block the formation of **3**. The intermediate **7** could then cyclize losing methanol and benzamide to give **2**. The proposed mechanism is shown by Scheme 1.

The support for this mechanism came from the following two experiments. First, when the reaction was carried out in saturated methanolic methylamine (instead of ammonia) in the presence of sodium amide, only **5** was formed, not **6**, suggesting the amino nitrogen of **2** was coming from ammonia. Second, an experiment using ^{15}N labeled ammonia ($^{15}NH_3$) introduced ^{15}N on the amino nitrogen[8] (i.e., ^{15}N-3) and not on the ring N-1 nitrogen. We therefore concluded that the benzamido nitrogen of **7** cyclized to become the N-1 nitrogen (ring nitrogen) in **2**.

In conclusion, the presence of 1.0 equiv of sodium amide gave exclusively **2,** while the presence of a weaker base like pyridine shifted equilibrium towards the formation of **3**. The best conditions for the formation of **2** from **1** were the treatment of **1** with 1.0 equiv of sodium amide in about 10-fold volume (0.02 M) of saturated methanolic ammonia at 95−100 °C for 1 h in a closed vessel. After the vessel cooled to ambient temperature, the crystallized product was isolated by filtration. The product thus obtained routinely showed 95%+ purity by HPLC. With this new procedure the yield of **2** was significantly improved from about 45% to more than 70%. In the case of the cyclopentylmethyl- and 3-furano-substituted compounds (**2b** and **2c**), the yield obtained exceeded 80%. The optimized reaction conditions increased the yield, facilitated the purification of **2**, and decreased the reaction time from 12 to 24 h to 1 h. Subsequently, these conditions were routinely used for the preparation of various substituted 9-deazaguanines at a 350 mmol scale using a 2 L Parr steel vessel. Finally, multiple batches of 10 kg each of **2a** were prepared at the process plant.

(7) (R = 3-pyridyl): mp 253−255 °C, ^1H NMR (DMSO-d_6, 400 MHz) δ 11.25 (br s), 8.48 (d, 1.8 Hz), 8.35 (dd, 1.6, 4.7 Hz), 7.61 (dt, 1.8, 7.8 Hz), 7.26 (ddd, 0.5, 4.7, 7.7 Hz), 6.99 (d, 2.9 Hz), 6.34 (s), 3.83 (s), and 3.33 (s, superimposed with H_2O); ^{13}C NMR 153.9, 151.2, 149.4, 146.8, 143.0, 137.4, 135.7, 125.8, 123.3, 112.1, 111.9, 27.7, 26.6. ($M^+ + H$) *m*/*z* 255.

(8) The ^{15}N signal was observed at δ 25 ppm in DCl−D_2O, using formamide as standard, and therefore assigned to an amino nitrogen, N-3. The assignment was based on comparison to guanosine ^{15}N chemical shifts, where the amino nitrogen shows at δ 72.0 ppm and N-1 appears at δ 146 ppm (Levy, G. C., Lichter, R. L. In *Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy*; John Wiley & Sons: New York, 1979; pp 203−205. The ^{15}N shift of an amino group is pH dependent, and ammonium appears at δ 42.5 (p 174).

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