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ARTICLE

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Development of Two Scalable Syntheses of 4-Amino-5-aminomethyl-2-methylpyrimidine: Key Intermediate for Vitamin B_1

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ABSTRACT: Two scalable processes for the synthesis of 4-amino-5-aminomethyl-2-methylpyrimidine (**2**) are described. In the first approach, the less expensive 2-cyanoacetamide was reacted with Vilsmeier reagent to afford enamine **18**, followed by the condensation with acetamidine to produce the 4-amino-2-methylpyrimidine-5-carbonitrile (**6**); subsequent hydrogenation gave **2** in 65% overall yield. In the second approach, malononitrile was treated with the ionic salt **21**, prepared in situ from DMF and dimethyl sulfate, to give **18**, which, without isolation was reacted with acetamidine hydrochloride to afford the common intermediate **6**. Overall yield of this approach was 70%. Both methods are performed in a convenient manner suitable for industrial use.

INTRODUCTION

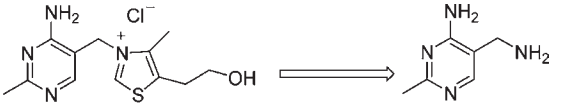
Since its isolation from yeast by Windaus in 1932,[1] vitamin B_1 (**1**), a water-soluble vitamin, has attracted considerable attention from both the academic community and the pharmaceutical industry due to its essential role for the growth and well being of animals as the antineuritic vitamin. To date, a considerable amount of effort has been devoted to the synthesis of **1** by utilizing different strategies. Currently, the synthetic strategy developed by Yoshida in 1952,[2] via the key intermediate 4-amino-5-aminomethyl-2-methylpyrimidine (**2**) remains a reliable approach towards **1** in industry (Scheme 1).

The synthesis of intermediate **2** has been described in a plethora of literature[3−5] and three procedures were selected as routes for the industrial production of **2**: (1) carbonitrile pyrimidine approach (Hoffmann-La Roche Co. process, Scheme 2);[3] (2) formyl pyrimidine approach (UBE Co. process, Scheme 3);[4] (3) formamide pyrimidine approach (Chinese producers process, Scheme 4).[5] The high overall yield and the minimum number of steps render the first approach attractive. However, 1.8 equiv. of expensive ethyl acetimidate hydrochloride is required for the cyclization of **5** in actual production process (Scheme 2). The limitation of the second approach is its long synthetic route (Scheme 3). The third process uses *o*-chloroaniline as amine, which is highly carcinogenic and traces of *o*-chloroaniline have been found in the end-product vitamin B_1 (Scheme 4). Thus, the development of practical syntheses of **2** is still in demand. Here we report two efficient and shorter routes to **2**, which start from 2-cyanoacetamide and malononitrile, respectively.

RESULTS AND DISCUSSION

2-Cyanoacetamide Approach. This synthetic route is shown in Scheme 5, which is based on the Hoffmann-La Roche Co. process (Scheme 2)[3] to synthesis **2** via the intermediate **6**. We initially focused on exploring a more efficient synthesis of **6**. We did pursue an intriguing report of a one-step conversion of enamine **18** to **6** using only 1 equiv of acetamidine hydrochloride in ethanol.[7] As enamine **18** is not commercially available, our endeavor included the synthesis of **18**. In the 2-cyanoacetamide approach, less expensive 2-cyanoacetamide (half the price of malononitrile) was selected as starting material for preparation of **18** (Scheme 5). Malononitrile can be obtained by the dehydration of 2-cyanoacetamide in presence of $POCl_3$.[6] Limitations of this method towards scale-up were its low conversion and the complex workup. If malononitrile, prepared in situ from 2-cyanoacetamide and $POCl_3$, would react with Vilsmeier reagent directly, the enamine **18** would be obtained via an economic process. Initially, the reaction for preparing **18** was carried out at −10 °C in the absence of pyridine, and a 1.14:1 mixture of **19** and **18** was formed (Scheme 6). Interestingly, the formation of **19** was minimized (<1%) by adding 0.1 equiv pyridine to the reaction mixture. At higher temperature, the formation of **19** increased.

Scheme 1. Synthetic strategy of vitamin B_1



1 **2**

Typically, the reaction is quenched with excess ice−water to deactivate any remaining $POCl_3$. Adjusting the solution to pH 3, by the addition of 30% aqueous NaOH solution, resulted in the precipitation of **18**. The impurity **20** is observed when the pH is above 3. Although **20** was readily rejected at the final isolation stage and had no impact on the purity of final product **2**, the formation of **20** did represent considerable yield loss. Crude **18** that contained 0.7% of impurity **19** and 4.1% of DMF was used directly in the next step. It is worth mentioning that compound **18** is prepared via a solvent-free process.

From a safety perspective, the reaction enthalpy measurement was carried out using a Setaram micro DSC III calorimeter. The addition of $POCl_3$ to the mixture of 2-cyanoacetamide and DMF, an operation employed in this solvent-free reaction, was studied.

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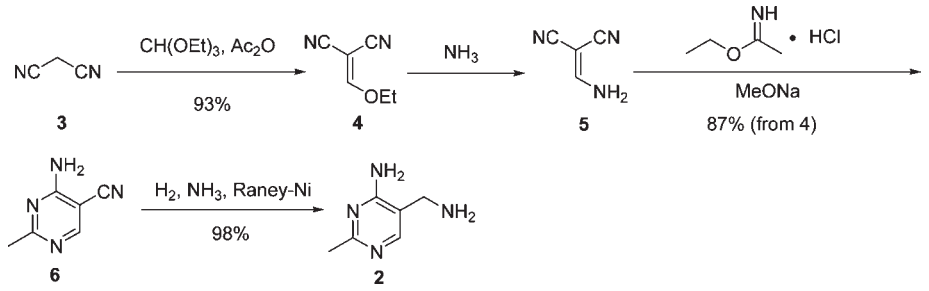
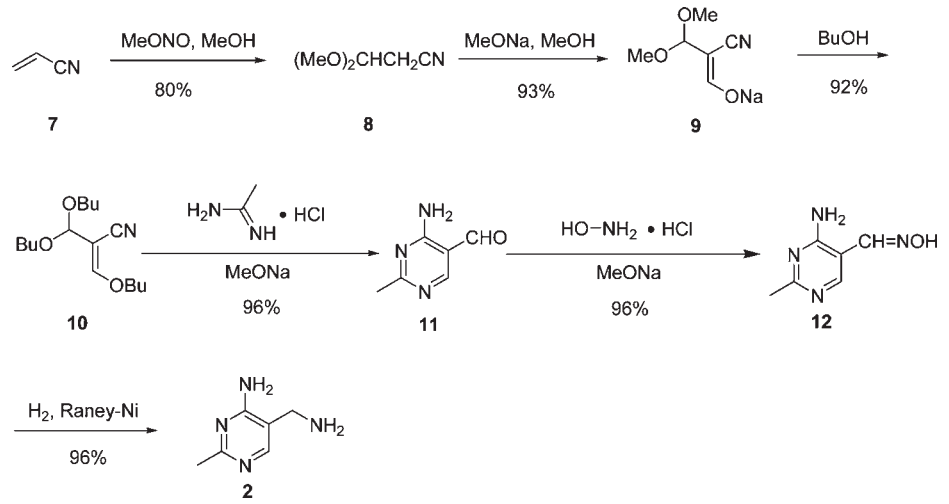
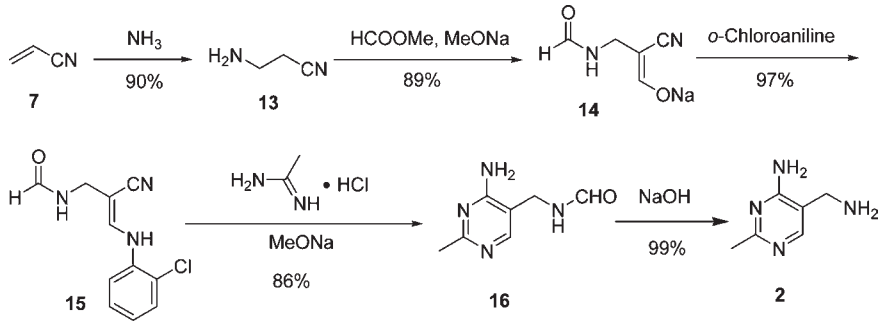
Scheme 2. Carbonitrile pyrimidine approach (Hoffmann-La Roche Co. process)



Scheme 3. Formyl pyrimidine approach (UBE Co. process)



Scheme 4. Formamide pyrimidine approach (Chinese producers process)



The addition was exothermic, and reaction enthalpy was determined to be −19.8 kJ/mol of **17**, which corresponded to an adiabatic temperature rise of 26 °C. The calorimeter study revealed the total energy given off during quenching the reaction with ice−water to be 165.7 kJ/mol of **17**, and the associated adiabatic temperature rise was estimated to be 34 °C. These results show that this solvent-free process can be run safely.

Cyclization was further carried out by the addition of **18** to a methanol solution of acetamidine (1.1 equiv) at −5 °C.[7] As the reaction proceeded, product **6** precipitated. Product **6**, obtained by filtration, is quite pure and the impurity **19** was undetected.

Finally, following the reported protocol,[8] the catalytic hydrogenation of **6** provided **2**. The reaction is very clean, and no further purification is required to obtain spectrally pure **2**. The overall yield of **2** from 2-cyanoacetamide is typically 65%.

Malononitrile Approach. In order to avoid the isolation of unstable **18**, we tried to design the reaction in a single pot, wherein generation of **18** and its subsequent reaction with acetamidine would happen in a tandem manner to provide **6**. The second route explored for the industrial synthesis of **2** involved the condensation of malononitrile with an ionic salt compound **21** in the presence of sodium methanolate to give **18** that, without isolation, condensed directly with acetamidine to

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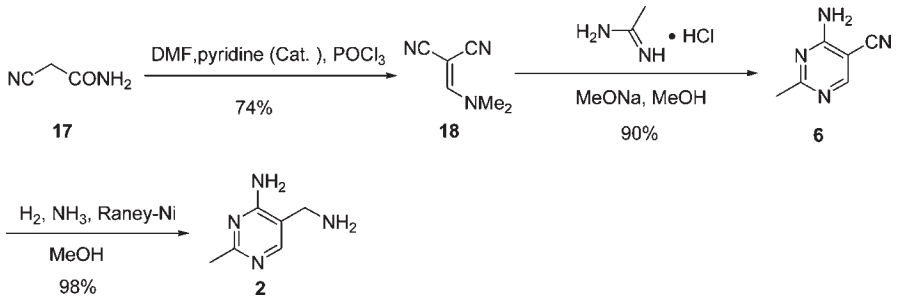
Scheme 5. 2-Cyanoacetamide approach



produce **6**, then underwent reduction to produce **2** (Scheme 7). This synthetic strategy is attractive because it uses a cheap and efficient ionic salt and leads to the formation of the desired **6** via a one-pot procedure under mild conditions. Thus, we were able to achieve the shortest synthesis of **2**.

On addition of malononitrile to the mixture of ionic salt compound **21** (prepared in situ from DMF and dimethyl sulphate)[9] and methanol at −5 °C, the formation of **18** was observed (monitored by GC/MS). GC analysis revealed the maximum concentration of **18** was obtained after stirring 30 min at −5 °C, followed by the addition of a solution of acetamidine[12] (1.1 equiv) in methanol to achieve the conversion of **18** to **6**. Product **6** can be obtained directly from the reaction mixture by filtration; the product thus obtained is contaminated with methanesulfinic acid sodium salt. The product was washed with water to remove methanesulfinic acid sodium salt and obtain free **6** in 71% yield. Crude **6**, obtained as an off-white solid, was used directly in the next step.

Following the first method's procedure, the conversion of **6** to **2** was achieved. The overall yield of **2** from malononitrile is typically 70%.

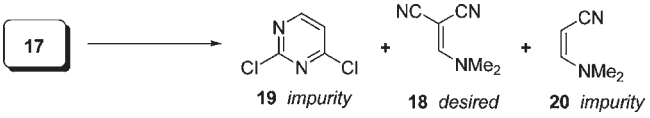
■ CONCLUSION

We have developed two efficient methods for the preparation of **2**. The first method starting from 2-cyanoacetamide gave the desired product in three steps and 65% overall yield. The second method, which is based on a one-pot procedure for preparing **6**, gave **2** in two steps and 70% overall yield. These two processes were readily scaled up with the target molecule being isolated in high yield and high chemical purity. After optimization, these two protocols were finally carried out on 10 kg scale and 8.8 kg scale, respectively.

■ EXPERIMENTAL SECTION

General. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$, DMSO using tetramethylsilane (TMS), and $CDCl_3$ (^{13}C, δ 77.0 ppm) as internal standards. *J* values are given in hertz. Mass spectra were recorded on a Waters Quattro Micromass instrument using electrospray ionization techniques. IR spectra were recorded on a JASCO FT/IR-4200 spectrometer. HPLC analysis was performed by a standard method on a Kromasil 100-5 C_{18} column, 250 mm × 4.6 mm (5 μm); λ = 245 nm; mobile phase: MeOH/H_2O = 60/40. GC conditions: column, HP-5Ms, 30.0 m × 250 μm, 0.25-μm-thick coating; carrier gas, He, 19 psi; injection, 250 °C, split ratio of 1:50; temperature, 50−280 at

Scheme 6. Impurities



10 °C/min. The GC and HPLC analysis data is reported in area % and is not adjusted to weight %.

2-Cyanoacetamide Approach. *2-((Dimethylamino)methylene)malononitrile (**18**).* A mixture of 2-cyanoacetamide (**17**) (10.0 kg, 119 mol), pyridine (940 g, 12 mol), and DMF (18.2 kg, 249 mol) was cooled to −10 °C, $POCl_3$ (38.6 kg, 252 mol) was added to the cooled mixture dropwise over a period of 3 h. After addition was completed, the reaction mixture was allowed to stir for 12 h at −10 °C. The mixture was poured into ice−water (70 L) and then basified with 30% aqueous NaOH solution to pH 3.0 and extracted with ethyl acetate (60 L × 3). The organic phase was combined and concentrated to dryness (35 °C/15 mmHg) to give crude **18** (10.7 kg, 74%) as a yellow oil; 95% pure by GC analysis, containing 0.7% of 2,4-dichloropyrimidine (**19**) and 4.1% of DMF; IR (KBr):ν 3445, 3010, 2980, 2213, 1433 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.21 (s, 3 H), 3.33 (s, 3 H), 7.06 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.2, 47.7, 48.9, 115.3, 117.2, 158.0; *m*/*z* (MS-EI): 121, 106, 79, 54.

GC retention times: **19**, 6.11 min; **18**, 11.08 min; DMF, 2.99 min;

A sample of purified **19** was analyzed as follows:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (s, 1H), 8.83 (s, 1H); *m*/*z* (MS-EI): 148, 113, 86, 51.

*4-Amino-2-methylpyrimidine-5-carbonitrile (**6**).* To an ice-cooled solution of sodium methoxide (5.3k g, 98 mol) in methanol (80 L) was added acetamidine hydrochloride (9.3 kg, 98 mol); the mixture was stirred for 10 min and quickly filtered from precipitated sodium chloride. To the cooled filtrate was added a solution of **18** (10.8 kg, 89 mol) in methanol (5 L) over a period of 30 min. After stirring 12 h at room temperature, the mixture was cooled to 0 °C, and the precipitate was collected by filtration and dried by suction overnight to give **6** (10.8 kg, 90%) as an off-white solid; 99% pure by GC analysis (retention time: 9.38 min); mp: 249−250 °C (lit. mp 250−251 °C);[7] IR (KBr): ν 3386, 3336, 3034, 2849, 2225, 1677, 1604 cm^{-1}; ^{1}H NMR(DMSO, 400 MHz): δ = 2.38 (s, 3H), 7.77 (br s, 2H), 8.50 (s, 1H) ppm; ^{13}C NMR(DMSO, 100 MHz): δ = 25.9, 86.7, 115.7, 161.1, 162.3, 170.1 ppm; *m*/*z* (MS-EI):134, 94, 66.

*4-Amino-5-aminomethyl-2-methylpyrimidine (**2**).* In an autoclave the mixture of **6** (2.0 kg, 15 mol), modified Raney nickel

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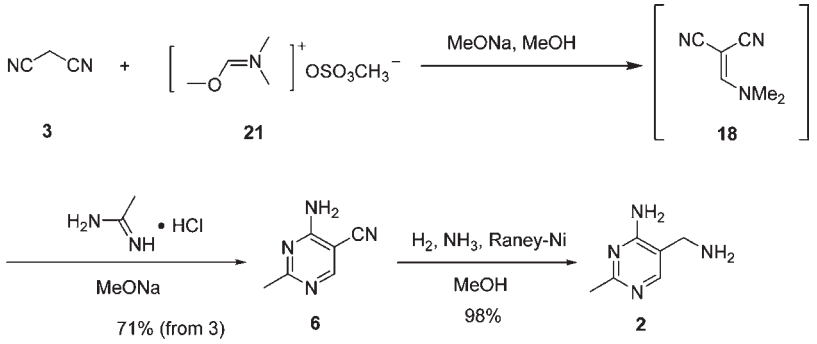
Scheme 7. Malononitrile approach



(wet weight 300 g), and saturated methanol solution of ammonia (20 L) was heated to 100 °C and stirred for 5 h at this temperature under 4 MPa hydrogen pressure.Then the mixture was cooled down to room temperature and filtered; **2** was obtained as white solid (2.0 kg, 98%) by concentrating the filtrate; 99% pure by HPLC analysis (retention time: 3.74 min.); mp: 133 °C (dec) (lit. mp 132 °C(dec));[10] Loss on drying: 0.12%; IR (KBr): ν 3351, 3138, 2906, 2360, 2342, 1665, 1560, 1468, 1418, 928, 603 cm^{-1}; ^1H NMR(DMSO, 400 MHz): δ = 2.29 (*s*, 5H[11]), 3.54 (*s*, 2H), 6.78 (*s*, 2H), 7.89 (*s*, 1H); ^{13}C NMR(DMSO,100 MHz): δ = 25.1, 48.1, 114.8, 152.9, 162.1, 164.9 ; ESI-MS: 139 $[M + 1]^+$.

Malononitrile Approach. *4-Amino-5-aminomethyl-2-methylpyrimidine (**6**).* A mixture of DMF (9.9 kg, 135 mol) and dimethyl sulfate (17.0 kg, 135 mol) was stirred at 70 °C for 3.5 h and then cooled down to −5 °C. Then a solution of sodium methylate (7.3 kg, 135 mol) in methanol (40 L) was added dropwise (maintaining the internal tempreature ≤−5 °C). After addition was completed, the reaction mixture was allowed to stir for 5 min. A solution of malononitrile (8.8 kg, 133 mol) in methanol (5 L) was added dropwise (maintaining the internal temperature ≤−5 °C), and then the mixture was stirred at −5 °C for 30 min. A solution of acetamidine[12] (8.5 kg, 146 mol) in methanol (44 L) was added. After stirring 12 h at room temperature, the mixture was cooled to 0 °C, and the precipitate was collected by filtration, washed with water (10 L × 3), and dried by suction overnight to give **6** (12.7 kg, 71%) as an off-white solid, 99% pure by GC analysis; mp: 249−250 °C (lit. mp 250−251 °C).[7]

GC retention time: **3**, 3.73 min.

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(11) This includes the two methylamino hydrogens.

(12) Acetamidine was prepared from acetamidine hydrochloride and sodium methoxide.