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An Alternative Scalable Process for the Synthesis of 4,6-Dichloropyrimidine-5-carbonitrile

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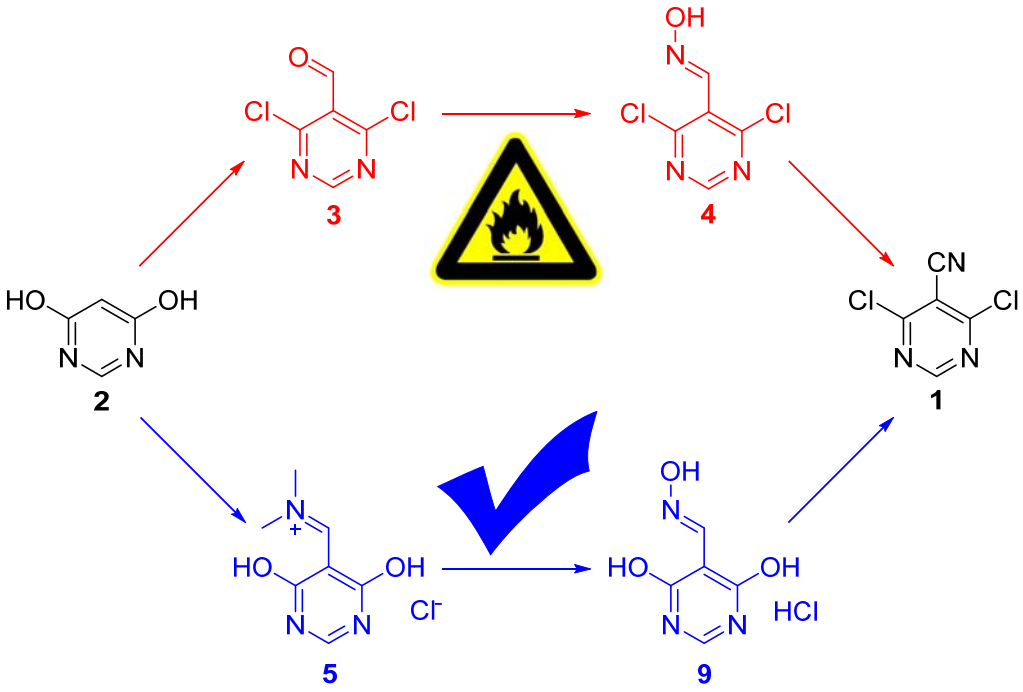
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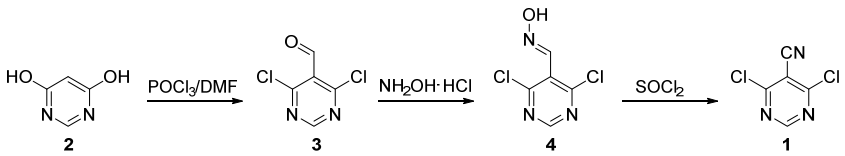
ABSTRACT: A robust, safe and scalable process for synthesis of 4,6-dichloropyrimidine-5-carbonitrile was described. All the intermediates in the process are storable at normal conditions. Significant process safety evaluation was undertaken in this route, and the highlights of these studies were presented. This scalable and safe synthetic strategy could be applied for multi-kilogram scale production.

KEYWORDS: 4,6-Dichloropyrimidine-5-carbonitrile, Synthesis, Safety, Scalable, Process.

▪ INTRODUCTION

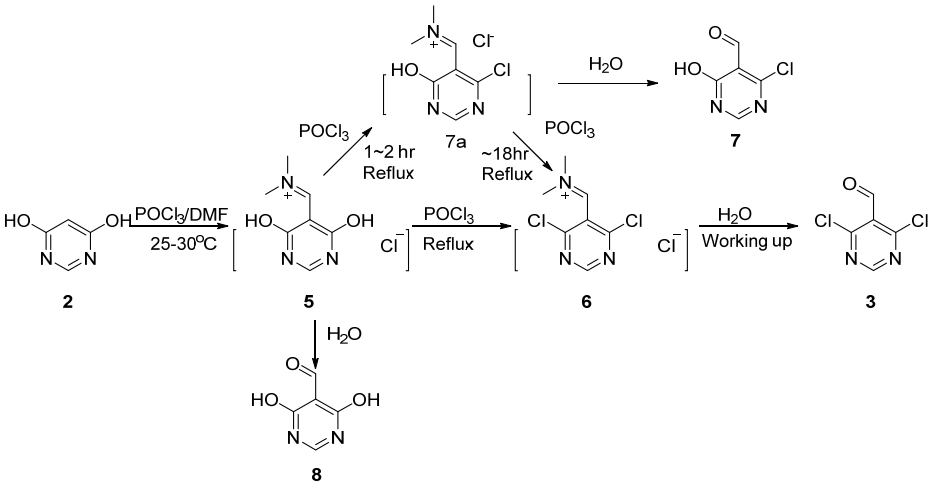
4,6-Dichloropyrimidine-5-carbonitrile **1** was a key intermediate and constituted one of the most important heterocyclic composition or subunits in pesticide[1-3], color coupler[4] and pharmaceutically active compounds[5-7]. Although the usefulness in many drug candidates and molecules for various applications, a truly convenient process for its large scale production had not been published to date[4, 8-10]. As part of an ongoing clinical program, a practical synthesis of 4,6-dichloropyrimidine-5-carbonitrile **1** was required. The extensive use of 4,6-dichloropyrimidine-5-carbonitrile intermediates in pharmaceutically active compounds had stimulated the synthetic developments for their synthesis.

Scheme 1. Original Synthetic Route of Nitrile **1**



Not many reports were available in literature for its novel or modified synthesis[4, 8-10]. A frequently employed approach for 4,6-dichloropyrimidine-5-carbonitrile synthesis began with readily available 4,6-dihydroxy pyrimidine **2**, Vilsmeier conditions were employed to accomplish two transformations: installation of a formyl group at the pyrimidine 5-position and chlorination of both hydroxyl moieties into chlorides. Exposure of the formyl group to hydroxyl amine hydrochloride under acidic aqueous conditions followed by thionyl chloride yielded the nitrile **1** (Scheme 1).

Scheme 2. Synthesis of Aldehyde **3** from Dihydroxy Pyrimidine **2**

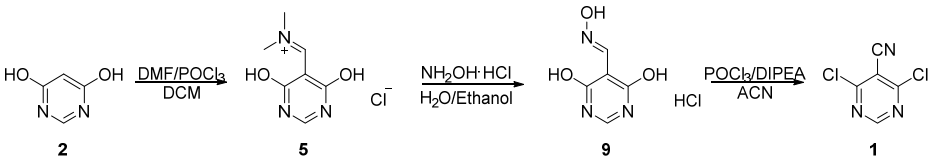


We have studied carefully the conversion from **2** to **3**[11] (Scheme 2). At lower temperature, the Vilsmeier reaction of **2** using DMF–$POCl_3$ as an electrophile yielded intermediate **5**[12, 13], which precipitated as a solid from the reaction solution. When the reaction[12,13] was heated to higher temperature, intermediate **5** was chlorinated to give the dichloride **6**. Aqueous workup of intermediate **6** gave an isolatable aldehyde **3**. DSC test report suggested compound **3** was not thermally stable above 59 °C. The intermediates **5** and **7a** were hydrolyzed to yield monohydroxy **7**[14, 15] and dihydroxy **8**[16]. The stability of aldehyde **3** in aqueous conditions was poor. We found the compound **3** was storable at -20 °C for 1 to 2 days. However, on a small scale the

quenching temperature was easily controlled. On a kilo scale to suppress the generation of by-product in aqueous conditions, it was too difficult to control an extreme exotherm.

Beside the chemical stability issue of aldehyde **3**, the oxime **4** is thermal unstable as well. Oxime **4** was tested by DSC to show an exotherm at 61~103 °C with high energy (ΔH = 501.2 J/g) indicating a violent decomposition. The suggested thermally stable temperature of oxime **4** was below -6 ^{o}C. Our vendor reported a spontaneous combustion accident, where ten kilos of oxime **4** self-ignited in the hood on a hot summer day. When the original route was scaled up in kilogram scale production there were some safety and unwanted stability issues occurred with the intermediates **3** and **4**.

Scheme 3. Alternative Scalable Route of Nitrile **1**



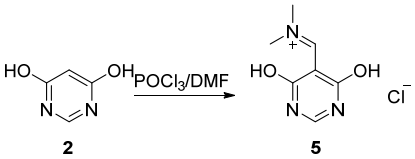
With a good understanding of the above issues in original route, we recognized that it is very necessary to develop an alternative route to prepare 4,6-dichloropyrimidine-5-carbonitrile **1**, targeting improved safety, scalability and robustness of synthesis (Scheme 3). Described herein are the results of our safety evaluation and scale-up of an improved process for the synthesis of nitrile **1**.

- RESULTS AND DISCUSSION

The stability issues of intermediates **3** and **4** revealed that the original route was clearly not a scalable one. We had an idea to re-design the synthetic route to get 4,6-

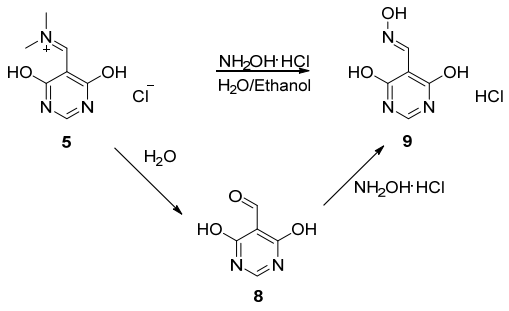
dichloropyrimidine-5-carbonitrile **1** via the intermediates, which had a similar structure with monohydroxy **7** and dihydroxy **8.** Monohydroxy **7** and dihydroxy **8** were less sensitive to moisture and much more stable than aldehyde **3**. However monohydroxy **7** was yielded always hand in hand with dihydroxy **8**, and it was not easy to separate them due to their poor solubility in most solvents.

Scheme 4. Generation of Intermediate **5** via Vilsmeier Reaction



Noteworthy to mention, intermediate **5** could be readily generated via Vilsmeier reaction (Scheme 4)[16, 17] and isolated from the reaction mixture as a good solid by simple filtration without other tedious purifications. Intermediate **5** is thermally stable toward the DSC. No decomposition was detected up to 300 °C. The intermediate **5** was successfully manufactured on 20 kg scale with 97.1% purity, 91.7% assay and 92.8% yield in pilot plant.

Scheme 5. Synthesis of Oxime **9** via Substitution



The oxime **9** could be obtained from intermediate **5** by reacting with hydroxylamine hydrochloride in one pot (Scheme 4). When intermediate **5** was exposed to water, it was quickly and completely converted to the corresponding

aldehyde **8**, which was the major impurity in intermediate **5**. However this aldehyde impurity had no effect on next step reaction because it could react readily with hydroxylamine hydrochloride to yield oxime **9**.

Table 1. Study of Different Solvent Ratios[18]

Entry	Ratio of Ethanol/water	Assay (% w/w)[a]	Yield (%)[b]
1	0 vol./10.0 vol.	96.1	46.5
2	10 vol./4.0 vol.	90.4	79.3
3	10 vol./2.0 vol.	86.6	84.3
4	10 vol./1.0 vol.	84.6	86.2

[a]By Q-NMR. [b]Isolated yield.

Two different charging sequences had a similar conversion[19], while adding salt **5** to an aqueous solution of hydroxylamine hydrochloride was much more convenient. At the beginning, water was chosen as the solvent, but the yield was low (Table 1, Entry 1). Ethanol was then tried as co-solvent, and the composition of solvent system was screened (Table 1). More water gave lower yield, but higher assay as inorganic salt could be easily removed under this condition. A ratio of 10 vol./2.0 vol. of ethanol/water was finally selected as the solvent system, which offered a fairly good assay and yield.

Table 2. Study of Different Equivalents of $NH_2OH{\cdot}HCl$ [20]

Entry	$NH_2OH{\cdot}HCl$ (eq.)	Conv.[a] (%)	Yield (%)

1	0.8	82.6[b]	N/A
2	1.5	96.0	78.6
3	2.0	99.6	81.1
4	3.0	99.6	81.4

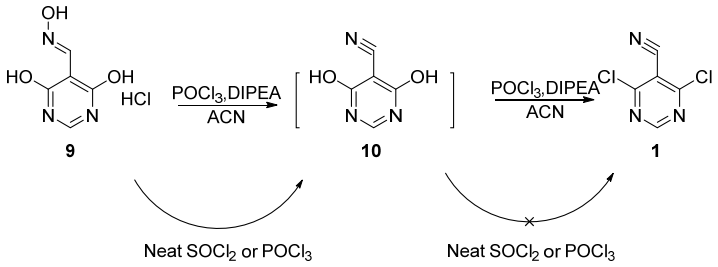
[a]Conversion after 15 h, testing by HPLC. [b]Additional 0.8 eq. of $NH_2OH{\cdot}HCl$ and 15 h improved conversion rate up to 97.7%.

Different equivalents of hydroxylamine hydrochloride were studied as shown in Table 2. Sample was taken after 15 h and analyzed by HPLC. The results indicated that about 1.5-2.0 eq. of $NH_2OH{\cdot}HCl$ was needed to push the reaction go to completion.

DSC test report of oxime **9** showed a decomposition in a broad range of 109-267 ^oC with a high energy (ΔH = 761.5 J/g). More accurate ARC testing for oxime **9** showed an exotherm at 114-303 ^oC with the energy of 1038.8 J/g. Td24 based on the ARC data was 98.7 ^oC. Adiabatic temperature rise of adding intermediate **5** to a solution of hydroxylamine hydrochloride was 4.3 ^oC by RC1 test. Analysis of the reaction completion stream by DSC showed an exotherm from 140 to 208 ^oC with the energy of 187.0 J/g. The recommended safety operation temperature was below 58 ^oC (Td24). In pilot plant this step reaction was run between 20-30 ^oC, which was lower than Td24 and allowed a moderate operating margin in carrying out the reaction. Oxime **9** was much more thermally stable and less sensitive to moisture comparing to chlorinated oxime **4.**

The process was successfully scaled up to about 30 kg with the production of oxime **9** in 99.1% purity, 85.6% assay and 80.6% yield. The chloride residue in oxime **9** was 18.1%, which was indicated oxime **9** was a hydrochloride[21].

Scheme 6. Formation of Nitrile **1** via Dehydration and Chlorination



Halogenated reagent was used to enable two transformations of oxime **9**[8, 22]: dehydrating oxime moiety into cyano group and substituting both hydroxyl groups into chlorides in one pot (Scheme 4). Neat $SOCl_2$ or $POCl_3$ was used as the halogenated reagent at first, but only dehydrating intermediate **10** was generated. The $POCl_3$/DIPEA/ACN system presented itself a highly effective dehydrating and di-chlorinating agent for the conversion of oxime **9** to the corresponding nitrile **1**. After the addition of oxime **9** portion-wise to a solution of $POCl_3$ and DIPEA in ACN, reaction heat measured by RC1 was 561.5 KJ/mol and adiabatic temperature rise was 77.1 ^{o}C without residual heat. In the pilot plant, the addition of oxime **9** was in 10-20 portions at interval of 10-15 mins to ensure that exotherm could be removed from reaction for each portion in time. In the process of heating up to 75 ^{o}C, reaction heat measured by RC1 was 28.7 KJ/mol and adiabatic temperature rise was 3.9 ^{o}C. If directly heating the reaction to 85 ^{o}C, the MTSR was 88.9 ^{o}C, which was type 3 of runaway scenarios[23, 24]. It was recommended to reduce the heating speed after the reaction was heated up to 75 ^{o}C, such as the reaction was heated to 85 ^{o}C from 75 ^{o}C over 1 h. And then MTSR was 78.9 ^{o}C. It was type 1 of runaway scenarios and had

the lowest risk. Nitrile **1** was successfully produced on 24 kg scale with 100.0% purity, 98.0% assay and 47.7% yield. There were 5.6% mass loss in active carbon cake and 14.5% in the mother liquor. The process could be further optimized in future.

Stability test suggested nitrile **1** could be stored at 0-10 ^{o}C in a sealed double LDPE bag for almost 1 year or at room temperature for 6 weeks with almost no change in purity profile, assay or appearance.

▪ CONCLUSIONS

In summary, an alternative robust, safe and scalable synthesis for nitrile **1** was developed. There was no tedious work-up or purification. The chemical and physical properties of the related intermediates **5**, **9** and final target **1** are stable at normal conditions. This efficient, expedient synthesis of nitrile **1** enabled its rapid and safe supply as a commercial starting material.

▪ EXPERIMENTAL SECTION

General Information. All commercially available reagents and solvents were used directly as received. ^{1}H NMR spectra were recorded on Varian 400 MHz and 500 MHz spectrometers. Chemical shifts (δ) are reported in parts per million and coupling constants (J values) in hertz. Spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), bs (broad singlet). LC-MS spectra were obtained on an Agilent 1260 and GC-MS were obtained on a Thermo trace E3000. Reactions were monitored by reversed-phase HPLC using a CAPCELL PAK C18-AQ column with 5 μm particle size, 250*4.6 mm. For HPLC, solvent A was a 0.1% solution of H_3PO_4 in water, and solvent B was ACN. The flow rate was 0.6 mL/min with a column temperature of 15 °C. The detection wavelength was 220 nm. DSC data were obtained on TA Q10, ARC data were obtained on HEL Phi-Tec I and RC1 data were obtained on Mettler. All DSC, ARC and RC1 reports were provided by process safety lab (PSL) of Asymchem Life Science (Tianjin) Co., Ltd.

_N_-((4,6-Dihydroxypyrimidin-5-yl)methylene)-_N_-methylmethanaminium chloride (5)[17].

$POCl_3$ (32.9 kg, 214.6 mol) was added to DCM (198.8 kg) at 10-25 °C. A solution of DMF (15.8 kg, 216.2 mol) in DCM (36.2 kg) was added to the reaction. The resulting mixture was then warmed to 15-25 °C for another 2 h. 4,6-dihydroxypyrimidine (**2**) (20 kg, 178.4 mol) was added in portions at 15-30 °C. The mixture was stirred for 28 h until the starting material **2** was ≤1.0% in the filtrate (as determined by HPLC). The reaction mixture was filtered to afford the wet cake, which was washed with DCM (53 kg) twice and dried at 40-45 °C under vacuum to give 36.8 kg of **5** as yellow solid with 97.1% purity and 91.7% assay in 92.8% yield from **2**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 (s, 1H), 8.44 (s, 1H), 3.62 (s, 3H), 3.30 (s, 3H). LC-MS: $[M\text{-}Cl]^+$, 168.

4,6-Dihydroxypyrimidine-5-carbaldehyde oxime hydrogen chloride (9).

Intermediate (**5**) (31.2 kg, 153.2 mol) was added in portions to a solution of hydroxylamine hydrochloride (23.4 kg, 336.7 mol) in ethanol (268.6 kg) and water (68.0 kg) at 20-30 °C. The mixture was stirred for 21 h at 20-30 °C and then anhydrous ethanol (19.4 kg) was charged into the above mixture at 20-30 °C to rinse the reactor wall. After that, the mixture was stirred until the starting material **5** was ≤1.0% in the filtrate (as determined by HPLC). The product was collected by filtration and washed with ethanol (54 kg) twice, dried at 40 °C under vacuum for 12 h to give 27.5 kg of **9** as yellow solid with 99.1% purity and 85.6% assay in 80.6% yield from **5**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.33 (s, 1H), 8.63 (s, 1H), 8.26 (s, 1H). LC-MS: $[M\text{-}Cl]^+$, 156.

4,6-Dichloropyrimidine-5-carbonitrile (1).

To ACN (220.0 kg), $POCl_3$ (138.0 kg, 1888.1 mol) and DIPEA (93.0 kg, 719.5 mol) were charged at 20-30 ^oC, followed with the addition of oxime (**9**) (23.5 kg, 122.8 mol) in portions while stirring. The mixture was stirred at 20-30 ^oC for 2 h until oxime **9** was ≤3% (as determined by HPLC). The mixture was heated to 75 ^oC at a rate of 30-40 ^oC/h, and then carefully heated to 80-85 ^oC over 1 h. The reaction temperature was maintained at 80-85 ^oC. The reaction was monitored by HPLC analysis till area% of intermediate ≤1.0% (as determined by HPLC). The resulting mixture was concentrated below 50 ^oC under reduced pressure until the volume was about 180-195 L. The resulting residue was added portion-wise to ice (450 kg)/water (106 kg) at 0-15 ^oC over 5.5 h. After addition, the mixture was warmed to 20-25 ^oC and stirred for 6 h and then the mixture was filtered. The product was collected and washed with water (110.0 kg). The wet cake was dissolved in DCM (550 kg). Active carbon (4.2 kg) was charged into the above mixture at 20-30 ^oC and stirred for 2.5 h. The mixture was filtered. The filtrate was settled for 0.5 h and the aqueous phase was removed by phase separation. The organic phase was decolored with active carbon (4.1 kg) and then filtered. The filtrate was concentrated below 30 ^oC under reduced pressure until the volume was about 140-150 L. Ethyl acetate (16.0 kg) was charged into the residue at 20-30 ^oC and stirred for 2 h to precipitate a lot of solid. The mixture was filtered and rinsed with the solution of DCM (1.1 kg) and ethyl acetate (1.0 kg). The wet cake was dried at 40 ^oC under vacuum for 8 h to give 10.4 kg of the desired product **1** as yellow solid with 100.0% purity and 98.0% assay in 47.7% yield from **9**. ^1H NMR (400 MHz, DMSO-d_6) δ 8.96 (s, 1H). GC-MS: $[M]^+$, 173.

- LIST OF SYMBOLS AND ABBREVIATIONS

ACN, acetonitrile.

ARC, accelerated rate calorimeter.

DCM, dichloromethane.

DIPEA, *N*-ethyldiisopropylamine.

DMF, N,N-dimethylformamide.

DSC, differential scanning calorimetry.

LDPE, low density polyethylene.

MTSR, maximum temperature of a synthesis reaction (°C).

RC1, reaction calorimeter.

ΔTad, adiabatic temperature rise (°C).

Td24, the temperature where TMRad equals to 24 hours.

TMRad, the time to maximum reaction rate under adiabatic condition, it could be called time to explosion generally.

▪ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR spectra of the compounds **5**, **9** and **1**. DSC reports of the compounds **3**, **4**, **5** and the reaction completion stream of Scheme 5. DSC and ARC reports of oxime **9**. RC1 reports of Scheme 5 and Scheme 6.

▪ AUTHOR INFORMATION

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▪ ACKNOWLEDGMENTS

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18. Procedure for **Table 1**: To a solution of hydroxylamine hydrochloride (3 eq.) in the corresponding solvents, intermediate **5** (3 g, 14.7 mmol) was added in portions at 20-30 ^{o}C. And then the resulting reaction mixture was stirred for 15 h.
19. Dropping hydroxylamine hydrochloride aqueous solution to a suspension of intermediate **5** *vs.* adding intermediate **5** in portions into an aqueous solution of hydroxylamine hydrochloride.
20. Procedure for **Table 2**: To a solution of hydroxylamine hydrochloride in the solvents of ethanol/water (2 vol./10 vol.), intermediate **5** (6 g, 29.5 mmol) was added in portions at 20-30 ^{o}C. And then the resulting reaction mixture was stirred for 15 h.

21. In our supporting information the oxime **9** molecular is given as free form in DSC and RC1 reports. While the Cl residue in oxime **9** from different batch is about 18% w/w and it cannot be reduced by dring or slurry. It is suggested oxime **9** should be a hydrochloride.
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