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Article

Facile and Scalable Methodology for the Pyrrolo[2,1-*f*][1,2,4]triazine of Remdesivir

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ABSTRACT: Pyrrolo[2,1-*f*][1,2,4]triazine (**1**) is an important regulatory starting material in the production of the antiviral drug remdesivir. Compound **1** was produced through a newly developed synthetic methodology utilizing simple building blocks such as pyrrole, chloramine, and formamidine acetate by examining the mechanistic pathway for the process optimization exercise. Triazine **1** was obtained in 55% overall yield in a two-vessel-operated process. This work describes the safety of the process, impurity profiles and control, and efforts toward the scale-up of triazine for the preparation of kilogram quantity.

KEYWORDS: *antiviral agents, API, remdesivir, triazine, supply centered synthesis*

INTRODUCTION

The process research community has embarked on rapid development of a practical commercial route to remdesivir since it emerged as a COVID-19 therapeutic.[1,2] We recently published a route to construct pyrrolo[2,1-*f*][1,2,4]triazine (**1**) from commodity starting materials[3] and the retrosynthetic analysis of triazine **1**, as shown in Figure 1. 2,5-Dimethoxytetrahydrofuran, *tert*-butylcarbazate, and chlorosulfonyl isocyanate were replaced with the more readily available pyrrole, dimethylformamide (DMF), hydroxylamine, ammonia, and bleach in an effort to secure supply of this important regulatory starting material **1**.[4] In addition to proceeding from low-cost raw materials, this procedure also increased overall yield from 33% to 55%, as shown in Figure 2. Triazine **1** is a key component in the synthesis of remdesivir, a COVID-19 treatment, and its use occurs at the outset of a convergent synthesis, thus necessitating a sustainable manufacturing process of compound **1**.[1]

Our recent publication highlighted the feasibility of assembling the triazine moiety from pyrrole and other commodity chemicals.[3] This work describes our process research and development program followed by scale-up and feasibility studies for larger-scale operations. Furthermore, to scale-up the process, the safety concerns, removal of impurities generated during the synthetic process development, and ability to make substantial quantities of high quality triazine **1** are addressed. To demonstrate the utility of the process, 1 kg of triazine was made via this two-reactor system.

Safety Studies: Thermochemical Analysis of Cyanation and Amination. Understanding the chemistry's safety profile was a primary objective prior to further implementation of this chemistry at a larger scale. The first reaction of the sequence contains an exothermic aromatic substitution and quench of a reactive species,[5] and the second sequence involves the use of a strong base; sodium hydride[6] in conjunction with *N*,*N*-dimethylformamide, potentially an explosive combination.[7]

To address the hazards associated with using monochloramine in this synthetic route, which can decompose to toxic and explosive trichloramine,[8] the development of a safe and robust method for on demand production of the monochloroamine and immediate consumption of this reagent was needed to minimize the potential hazards associated with this material.

Reaction calorimetry (RC-1 reactor system) was chosen to evaluate the heat profile for the generation of 2-cyanopyrrole and all the downstream processes. First, 50 g of pyrrole (**1**) was dissolved in 500 mL of DMF, and the subsequent sequence of reactions was studied in the RC-1 reactor for reaction heat flows and was evaluated by differential scanning calorimetry (DSC) to understand the thermal stability of the reaction mixtures and intermediates.

The cyanation sequence was examined incrementally at each stage of the process, including generation of the Vilsmeier reagent (**4**), addition of pyrrole, quench of phosphoryl chloride species (**5**) with water, followed by hydroxylamine addition. The dehydration of the oxime to give the nitrile was completed by treatment with acetic anhydride (Tables 1−3).

Generation of the Vilsmeier reagent (**4**) was exothermic (ΔT_{ad} 30.40 °C, Table 1), and the maximum temperature of synthesis reaction (MTSR) was low (30.40 °C). The reaction mixture was evaluated by DSC and showed an onset of decomposition at 105 °C with a mild exothermic event of

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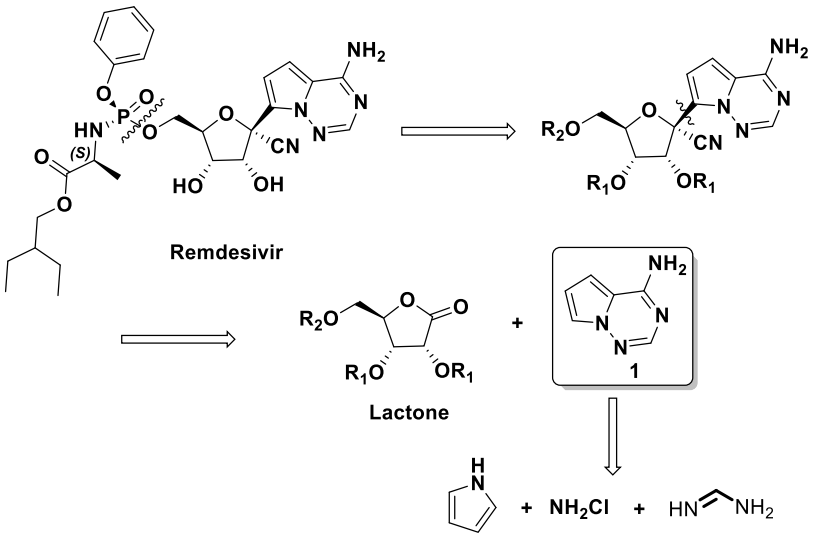

Figure 1. Retrosynthetic analysis of remdesivir from subunits lactone and triazine **1**.

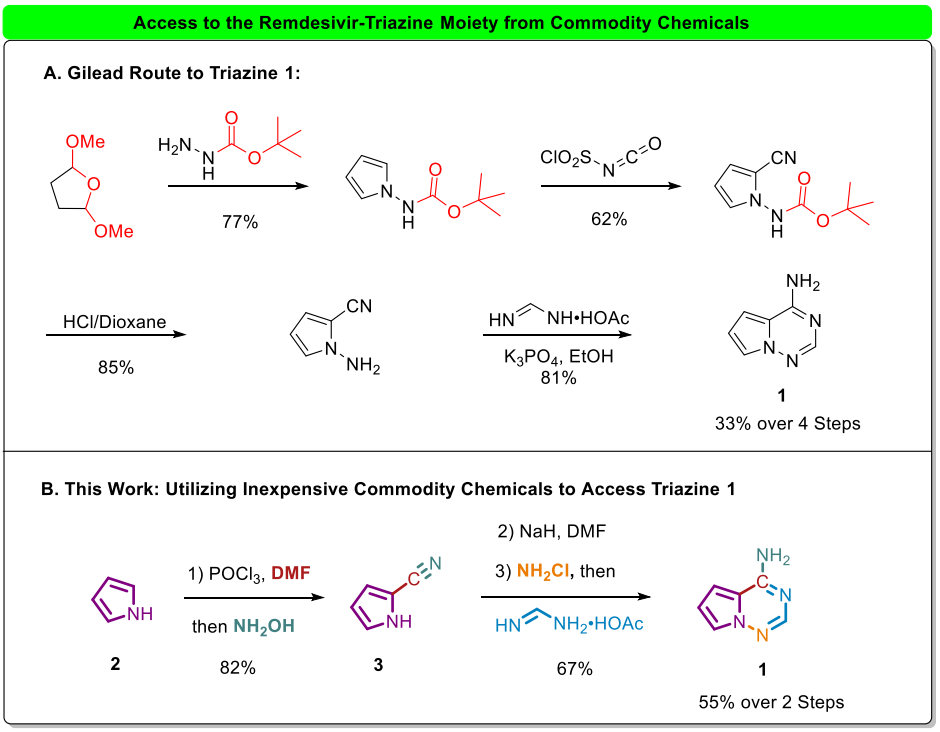

Figure 2. Current route to make triazine **1**.

127.25 J g^{-1}. Since the MTSR value is well below the MTT (boiling point of solvent), it showed low severity as per Stoessel's Rules.[9] Moreover, no thermal accumulation of heat was observed. The overall data project this to be a potentially safe process for scale-up operations.

Addition of pyrrole to the Vilsmeier reagent (**4**) showed an additional exotherm (Table 2) as ΔT_{ad} is 84 °C, and DSC showed that there were two exothermic events, one starting at 148.77 °C (with 13.9 J g^{-1}) followed by a second event at 210 °C (with 64.74 J g^{-1}). The maximum attainable temperature is 84 °C, which is below the MTT; hence, severity is low, and based on the DSC data, the amount of energy that could result from uncontrolled addition would be of low risk. The reaction was quite rapid with high conversion upon completion of the dosing (98%). By diluting the reaction from 5 volumes (ΔT_{ad} 179 °C) to 10 volumes of DMF (ΔT_{ad} 84.5 °C), the safety hazard of the reaction is controlled.

Quenching of the phosphoryl chloride species (**5**) was conducted by addition of water at 0 °C after acylating the pyrrole (Table 3). The MTSR was significantly below the MTT (46 °C *vs* 152 °C), and importantly, thermal conversion was nearly complete (very little accumulation) by the end of addition (98%), thus reducing the risk of delayed heat release from the unquenched reactive species.

Options exist for handling the sequence of Vilsmeier reagent formation, electrophilic aromatic substitution of pyrrole, and quenching of phosphoryl chloride species[10] using flow chemistry as an alternative to the batch process. This can be used to further decrease the risk associated with scaling this process.

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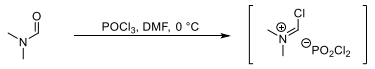
Org. Process Res. Dev. 2022, 26, 82−90

Table 1. Thermochemical Analysis of $POCl_3$ Addition to DMF at 0 °C



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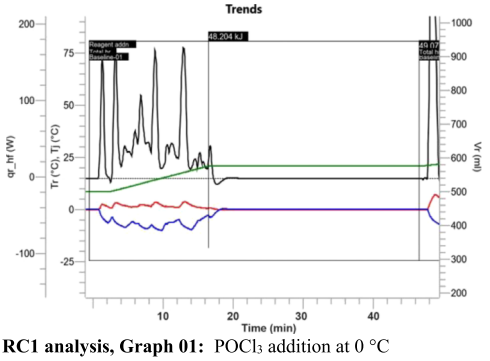
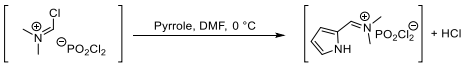
RC parameters	Results
Heat generated	49.08 kJ/50 g of pyrrole 65.88 kJ/mol of pyrrole
Adiabatic temp. rise (°C)	30.40
MTSR (°C)	30.40
MTT (°C)	152
Thermal accumulation at the end of dosing	1.80%
Thermal conversion at the end of dosing	98.20%
Specific heat before addition ($kJ \cdot kg^{-1} \cdot K^{-1}$)	2.83
Specific heat after addition ($kJ \cdot kg^{-1} \cdot K^{-1}$)	2.69



RC1 analysis, Graph 01: $POCl_3$ addition at 0 °C

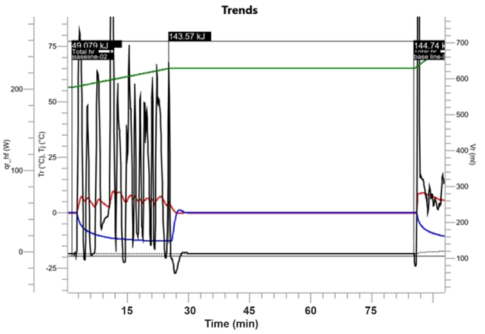
Trend	Color	Axis	Units
Tr		2	°C
Tj		2	°C
qr_hf		1	W
Vr		3	ml

Table 2. Thermochemical Analysis of Addition of Pyrrole to Vilsmeier's Reagent in DMF



4 5

RC parameters	Results
Heat generated	144.73 kJ/50 g pyrrole 194.27 kJ/mol pyrrole
Adiabatic temp. rise (°C)	84.54
MTSR (°C)	84.54
MTT (°C)	152
Thermal accumulation at the end of dosing	0.80%
Thermal conversion at the end of dosing	99.80%
Specific heat before addition ($kJ \cdot kg^{-1} \cdot K^{-1}$)	2.69
Specific heat after addition ($kJ \cdot kg^{-1} \cdot K^{-1}$)	2.63



RC1 Graph 02: 1-H-pyrrole addition at 0 °C.

Trend	Color	Axis	Units
Tr		2	°C
Tj		2	°C
qr_hf		1	W
Vr		3	ml

The last step of the acid quench and formation of the nitrile from the iminium chloride was essentially completed at the end of reagent addition, evolving 96.5% of heat of reaction as oxidation to the nitrile was not a fast reaction (Table 4). Also, this step was the least exothermic of the sequence. In order to obtain the optimal thermal profile, we have examined several quench protocols with the hydroxylamine addition process. It is important to note that the acetic anhydride quench protocol provided the optimum process parameters for the scale-up and thermal properties of this reaction.

Next, the amination was also examined calorimetrically to assess the risks associated with the combination of NaH and DMF.[6] Sodium hydride (19.13 g, 60%) was added to DMF (400 mL) at 3 °C to generate 2.87% dispersion, and a mild adiabatic temperature rise of 0.14 °C was observed (Table 5). The evaluation of the mixture by DSC showed that there was an exothermic event at 100 °C (giving off 470.75 J g^{-1}) followed by a secondary event at 329.86 °C (with 134.73 J g^{-1}). Afterward, 2-cyanopyrrole (**3**, 40 g) was added to the NaH dispersion which was immediately deprotonated by the base, generating **7** (Table 6). The adiabatic temperature rise was 55 °C, and the MTSR is 58 °C as the reaction was performed at 0 °C. MTSR was found to be less than the MTT (152 °C) and hence it was safe to handle. The same reaction mixture was evaluated by DSC, and there were no events of interest until 249 °C, although the amount of energy that was measured was not of a concern (33.11 J g^{-1}). There was nominal thermal accumulation (~6%) after the dosing of 2-cyanopyrrole (**3**). This renders the reaction a low-process safety risk for the scale-up to produce **8**. However, extra attention to details around handling of the chloroamine is required given its hazards (always review the current safety data sheet for this material).

A residual 0.1 equiv of unreacted NaH (1.04 g) was present in ~440 mL of reaction mass, which is equivalent to approximately 0.24 wt % NaH in DMF. Chloramine is acidic (pKa 14),[11] which consumes the remaining base (Table 7). Onset of exothermic events was tied to the concentration of NaH in DMF, and recent studies show that the thermal runaway occurs at 10−26 wt % of NaH in DMF.[6] In this process, the concentration was sufficiently below or negligible for the defined runaway window, although additional safeguards should be evaluated. The subsequent reaction with monochloramine was only mildly exothermic, and based on DSC data, there were no exothermic events found. Therefore, the process we defined may be suited for further scale-up operations, according to the examined parameters.

Impurity Analysis and Control. In order to ensure the production of high-quality and high-yielding triazine **1**, we undertook the identification of the impurities generated

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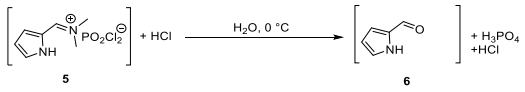
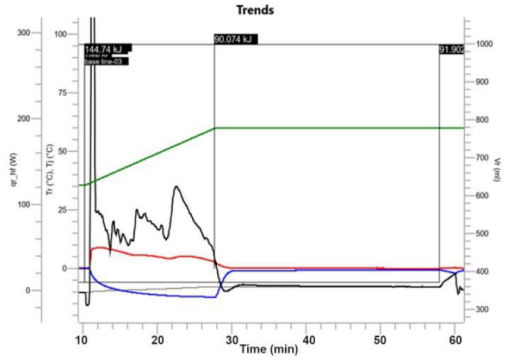
Org. Process Res. Dev. 2022, 26, 82−90

Table 3. Thermochemical Analysis of Addition of Water to Unquenched Phosphoryl Chloride Species



5 6

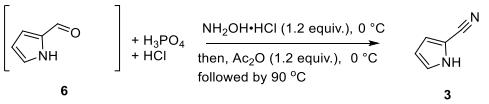
RC parameters	Results
Heat generated	91.90 kJ/50 g pyrrole 123.35 kJ/mol pyrrole
Adiabatic temp. rise (°C)	46.63
MTSR (°C)	46.63
MTT (°C)	152
Thermal accumulation at the end of dosing	1.86%
Thermal conversion at the end of dosing	98.14%
Specific heat before addition ($kJ \cdot kg^{-1} \cdot K^{-1}$)	2.63
Specific heat after addition ($kJ \cdot kg^{-1} \cdot K^{-1}$)	2.46



RC1 Graph 03: Water addition at 0 °C.

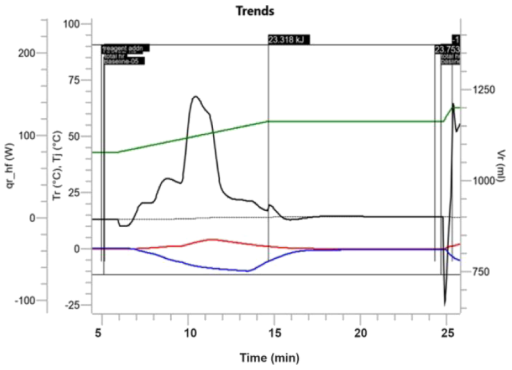
Trend	Color	Axis	Units
Tr		2	°C
Tj		2	°C
qr_hf		1	W
Vr		3	ml

Table 4. Thermochemical Analysis of Addition of Acetic Anhydride



6 3

RC parameters	Results
Heat generated	23.75 kJ/ 50 g pyrrole 31.88 kJ/mol pyrrole
Adiabatic temp. rise (°C)	9.88
MTSR (°C)	9.88
MTT (°C)	152
Thermal accumulation at the end of dosing	1.85%
Thermal conversion at the end of dosing	98.15%
Specific heat before addition ($kJ \cdot kg^{-1} \cdot K^{-1}$)	2.13
Specific heat after addition ($kJ \cdot kg^{-1} \cdot K^{-1}$)	2.03



RC1 Graph 04: Acetic Anhydride addition at 0 °C.

Trend	Color	Axis	Units
Tr		2	°C
Tj		2	°C
qr_hf		1	W
Vr		3	ml

throughout the synthetic process and optimized the reaction conditions to minimize these impurities.

Fortunately, due to the high-yielding nature and defined reaction conditions of the synthetic process, limited byproduct formation was observed. In the cyanation reaction, 1-*H*-pyrrole-2-carboxamide (**9**) was the major impurity detected, likely a byproduct formed under acidic conditions in the presence of water. To minimize the formation of 1-*H*-pyrrole-2-carboxamide (**9**), it was identified that the dilution effect was important (Table 8). Therefore, it is important to note that an increase in the dilution of the reaction (9% w/v 1-*H*-pyrrole-2-carboxamide at 5 V DMF to 2.57% w/v 1-*H*-pyrrole-2-carboxamide at 15 V DMF) reduced the formation of **9** to a minimum level.

It was observed that some polymeric material was formed during the course of this reaction.[10,12] This material appeared as dark brown to black particles in the work-up of 2-cyanopyrrole. Judicious control of the reaction conditions was critical in preventing the particles during the work-up process and is explained in detail in the experimental procedure.

The major byproduct in aminating **3** with NH_2Cl is actually reversion of *N*-amino-2-cyanopyrrole **8** back to 2-cyanopyrrole (Figure 3B). This occurs when an excess of chloramine is introduced into the system after all 2-cyanopyrrole (**3**) is converted to *N*-amino-2-cyanopyrrole **8** (Table 9). It is worth noting that such a phenomenon is precedented.[13] Moreover, *N*-amino-2-cyanopyrrole (**8**) afforded ~20% of 2-cyanopyrrole (**3**) when treated with NH_2Cl in the absence of any base. This reversal process can be controlled by monitoring the conversion to product during the last 20% of the controlled addition of chloramine to the reaction mixture. By carefully monitoring the presence of excess NH_2Cl and the basicity of the reaction mass, NH_2Cl can be introduced in small portions (continuous feeding), which in turn can control the reversal process to a minimum level (<2%, see the experimental procedure).

When forming the 1,2,4 triazine **1** with formamidine acetate in the last stage of the sequence, an adduct **10** was formed by the condensation of amino pyrrole **8** with DMF. This impurity was formed up to 5% by HPLC (A %). It is important to note that this impurity can be rejected under the defined work-up and crystallization conditions. Once the reaction was completed, water was added to the reaction mixture to precipitate the product and once filtered, the crude product showed >3% of impurity **10**. The final purification with methyl

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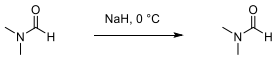
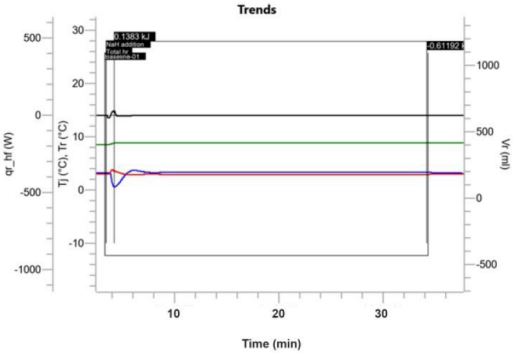
Org. Process Res. Dev. 2022, 26, 82−90

Table 5. Thermochemical Analysis of Sodium Hydride in DMF



RC parameters	Results
Heat generated	0.14 kJ/ 19.13 gof NaH 0.30 kJ/mol of NaH
Adiabatic temp. rise (°C)	0.14
MTSR (°C)	3.14
MTT (°C)	152
Thermal accumulation at the end of dosing	30%
Thermal conversion at the end of dosing	70%
Specific heat before addition ($kJ \cdot kg^{-1} \cdot K^{-1}$)	2.39
Specific heat after addition ($kJ \cdot kg^{-1} \cdot K^{-1}$)	2.39

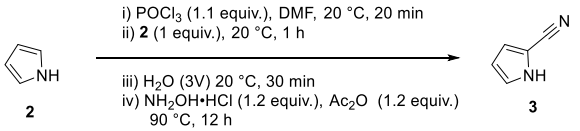


RC1 Graph 5: Sodium hydride addition at 0 °C.

Trend	Color	Axis	Units
Tr		2	°C
Tj		2	°C
qr_hf		1	W
Vr		3	ml

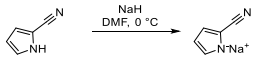
tert-butyl ether (MTBE) completely rejected **10**, and product **1** purity was found to be 99.80% (see the experimental details).[14]

Scale-Up of 2-Cyanopyrrole (3) and Triazine (1). To test the viability of the synthetic protocol, the preparation of triazine **1** was demonstrated on a 3 × 100 g scale to understand the process safety and impurity profile. It was gratifying to see that the reproducibility of the process was excellent. Next, our attention was focused on a scale to produce up to kilogram quantities of triazine **1**. First, we commenced with the production of 2-cyanopyrrole. The Vilsmeier reagent was formed by the addition of phosphorous oxychloride to DMF (10 volumes). Pyrrole was then added and allowed to react for 1 h. Reactive phosphorous species were then quenched with water. Hydroxylamine hydrochloride was added followed by acetic anhydride addition to partially neutralize the acid generated from the reaction and oxidation processes.[15]

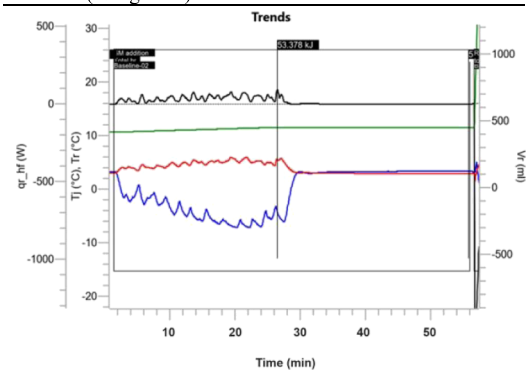


Yield = 82%, purity >99 A%

Table 6. Thermochemical Analysis of Addition of 2-Cyanopyrrole



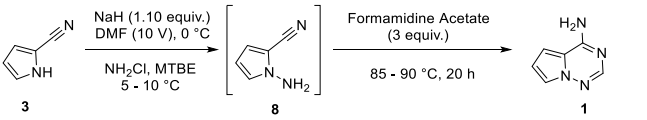
RC parameters	Results
Heat generated	57.30 kJ/ 40 g of SM 131.84 kJ/mole of SM
Adiabatic temp. rise (°C)	54.81
MTSR (°C)	57.81 (3 + 54.81)
MTT (°C)	152
Thermal accumulation at the end of dosing	5.64%
Thermal conversion at the end of dosing	94.36%
Specific heat before addition ($kJ \cdot kg^{-1} \cdot K^{-1}$)	2.39
Specific heat after addition ($kJ \cdot kg^{-1} \cdot K^{-1}$)	2.38



RC1 Graph 6: 2-cyano pyrrole addition at 3 °C

Trend	Color	Axis	Units
Tr		2	°C
Tj		2	°C
qr_hf		1	W
Vr		3	ml

Results from the amination and reaction of the resultant amine with formamidine acetate to form the triazine translated well from 25 to 500 g scale. Yields were typically between 65 and 75% over the two steps. The number of equivalents of sodium hydride was examined, and 1.1 equivalent was found to be the optimal condition in this process. Recrystallization of the mixture afforded high-quality triazine (99.90 area %, 98.4 wt %) in good recovery (87.5%).



67% overall yield
99.9 A%, 98.4 Wt%

CONCLUSIONS

In conclusion, we have described the process research, scale appropriate process safety, and development parameters for the robust process for the scale-up of triazine **1**. In addition, we demonstrated that the cyanation/amination/condensation sequence can be used to make kilogram quantities of **1** for remdesivir. Furthermore, calorimetric safety studies indicate

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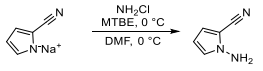
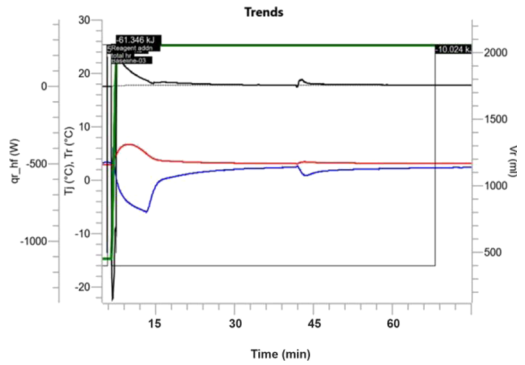
Org. Process Res. Dev. 2022, 26, 82−90

Table 7. Thermochemical Analysis of Addition of NH_2Cl in methyl *tert*-butyl ether (MTBE) Solution



7 8

RC parameters	Results
Heat generated	51.32 kJ/ 40 g of SM 118.08 kJ/mole of SM
Adiabatic temp. rise (°C)	12.04
MTSR (°C)	15.04 (3 + 12.04)
MTT (°C)	152
Thermal accumulation at the end of dosing	100%
Thermal conversion at the end of dosing	0%
Specific heat before addition ($kJ \cdot kg^{-1} \cdot K^{-1}$)	2.38
Specific heat after addition ($kJ \cdot kg^{-1} \cdot K^{-1}$)	2.09



RC1 Graph 07: NH_2Cl in MTBE Solution addition at 0 °C.

Trend	Color	Axis	Units
Tr		2	°C
Tj		2	°C
qr_hf		1	W
Vr		3	ml

that the reactions are potentially safe for additional scale-up operations along with appropriate risk analysis or process hazard analysis given the reaction parameters studied. A number of impurities generated in the synthetic process were identified, and controlled and purification procedures were developed to purge the undesired compounds. Future efforts will be directed toward on-demand production of chloramine via continuous flow chemistry, addressing the dilution effect in the amination step to improve the overall throughput and yield with high quality. This would include additional safety tests on all process steps (accelerated reaction calorimeter) to ensure proper vent sizing and testing of waste streams of the process as a part of the scale-up.

EXPERIMENTAL SECTION

General. Commercially available solvents and reagents were used as received without further purification. All NMR data were recorded using a Bruker 400 MHz instrument. Reaction calorimetric data were collected using a Mettler Toledo RC1 instrument and a Metter Toledo differential scanning calorimeter. HPLC data were collected on Waters Alliance HPLC instruments with detection by UV. HPLC conditions were as follows: for 2-cyanopyrrole: Shimpack solar C18, 250 × 4.6 mm, 5 μm, 95−40% gradient of water (0.1% perchloric acid): acetonitrile (0.1% perchloric acid), flow rate 1.0 mL/min; acquisition time, 45 min; UV at 245 nm. For pyrrolo[2,1-*f*][1,2,4]triazin-4-amine: Shimpack solar C18, 250 × 4.6 mm, 5 μm, 95−40% gradient of water (0.1% perchloric acid): acetonitrile (0.1% perchloric acid), flow rate 1.0 mL/min; acquisition time, 45 min; UV at 230 nm. Purity was calculated through % area normalization. Monochloramine solution was assayed by titration using the following procedure:

Assay by titration (NH_2Cl) (% w/w):

Solution A: 6.20 g of thiosulfate pentahydrate was added to 250 mL of deionized water and stirred until dissolved.

Solution B: 0.500 g of pure starch was added to 50 mL of deionized water and heated to 70 °C for 1 h.

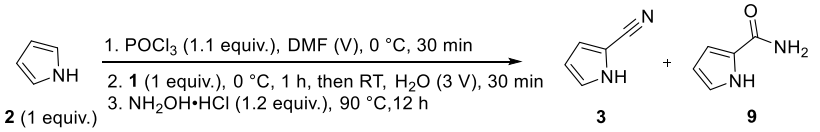
Solution C: To 200 mL of water, 10 mL of glacial acetic acid, 10 mL of solution B, and 0.8 g of potassium iodide were added.

$$\text{Assay (\% w/w)} = \frac{(\text{mL of } Na_2S_2O_3 \times 0.1\text{ N} \times 5.148)}{\text{Sample weight (g)} \times 2}$$

In a conical flask, 20.0 mL of solution B and 1.0 mL of sample were added. Under vigorous stirring, solution A was added until the solution turned colorless.

Preparation of 2-Cyanopyrrole (3). Phosphorus oxychloride (1.544 L, 16.56 mol) was added slowly into well-stirred and cooled (0−5 °C) anhydrous DMF (10 L) over 3 h, maintaining the reaction temperature at 0−5 °C. The reaction mass was allowed to attain a temperature between 15 and 20 °C and stirred for 30 min at this temperature. Reaction mass was cooled again to 0−5 °C, and pyrrole (1 kg, 14.90 mol) was added slowly to the cooled mixture over 1.5 h, maintaining the reaction temperature below 15 °C. The reaction mass was stirred for another 1 h at 15−20 °C and cooled further to 0−5 °C. Process water (3 L) was added slowly to the cooled reaction mass over 3 h, maintaining the internal temperature of the mixture below 15 °C. The mixture was stirred at 15 °C for 10 min, and then solid hydroxylamine hydrochloride (1.139 kg,

Table 8. Reaction Dilutions *vs* Amide 9 Formation



entry	DMF (V, mL)	yield (A %)	amide 9 (A %)
1	5	87	9
2	10	95	3.5
3	15	96	2.7

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Org. Process Res. Dev. 2022, 26, 82−90

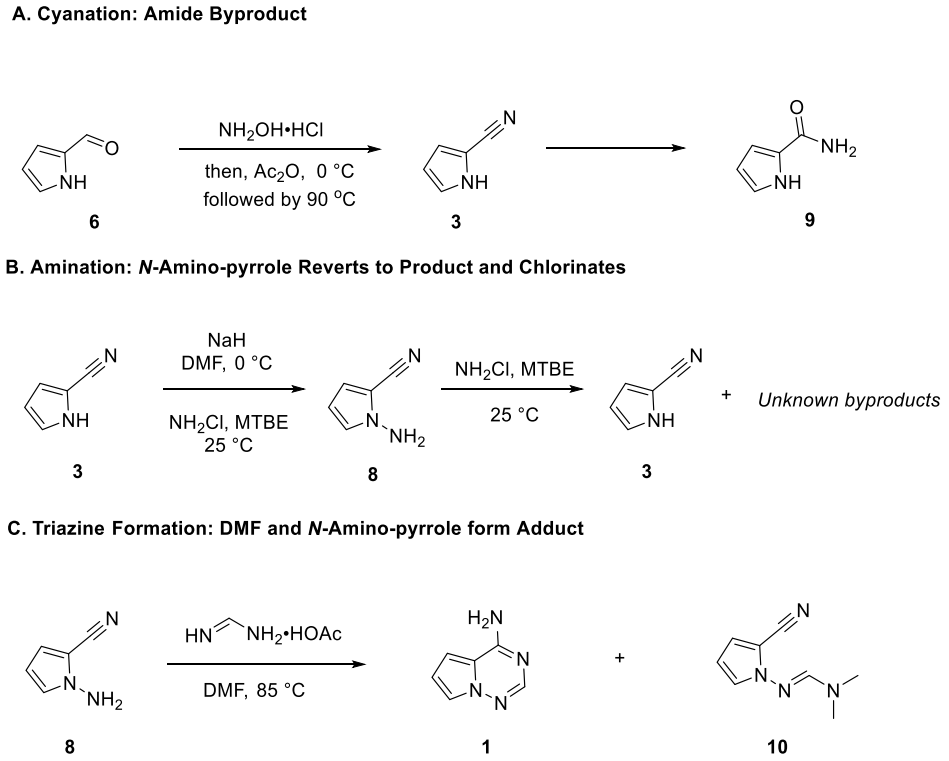
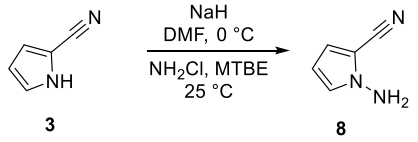


Figure 3. (A–C) Products and impurities.

Table 9. Dependency of the Reaction Outcome on the Chloramine Concentration



(1.2 equiv) NH_2Cl in MTBE (volumes)	3 (A %)	8 (A %)	impurities (A %)	3 + 8 (A %)
17	64	30		94
27	17	74		91
37	15	81		96
47	53	15	18, 5	68

16.41 mol) was added into the mixture, followed by addition of acetic anhydride (1.548 L, 16.48 mol), maintaining the internal reaction temperature below 15 °C. The reaction mass was then heated to 90 °C and stirred for 12–16 h at this temperature. Reaction progress was monitored by HPLC, and the heating was stopped when the quantity of unreacted intermediate aldehyde was found to be <2 A % by HPLC. The reaction mass was cooled to 25–30 °C, and chilled (10–15 °C) water (10 L) was added into it and stirred for 10 min, followed by addition of MTBE (10 L) with stirring for another 10 min. Stirring was stopped, and the layers were allowed to separate. The aqueous layer was further extracted with MTBE (2 × 10 L), and the combined organic extracts were washed successively with 2 N HCl solution (10 L), 10% aqueous sodium bicarbonate solution (2 × 10 L), and dried over anhydrous sodium sulfate (1 kg). The mixture was filtered, and the solution was concentrated under reduced pressure at 40–50 °C to get the crude compound as a dark brown liquid. The crude material was then purified by fractional distillation at 100–140 °C under high vacuum pressure (2–4 mm Hg) to obtain the following fractions with different assay percentages for the desired compound (2-cyanopyrrole): first fraction (containing mostly DMF and volatile impurities) (50–70 °C/2–4 mm Hg): 144.0 g (HPLC area %: 99.15%; assay: 18.20%); second fraction (95–100 °C/2–4 mm Hg): 348.0 g (HPLC area %: 99.54%; assay: 92.25%); and third fraction (100–125 °C/2–4 mm Hg): 870.0 g (HPLC area %: 99.38%; assay: 89.2%). Overall assay-based yield: 81.8%, chemical purity: >99% (excluding DMF).

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.27 (br s, 1H), 7.13 (s, 1H), 6.94–6.89 (m, 1H), 6.21 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 124.62, 119.37, 114.86, 109.50, 99.58. GCMS (m/z): 92.1.

Preparation of Pyrrolo[2,1-*f*][1,2,4]triazin-4-amine (1). *Preparation of Monochloramine in MTBE.* To a cooled (−8 ± 2 °C) and stirred mixture of MTBE (36.0 L) and NH_4Cl (2.7 kg, 50.47 mol) in a reactor (fitted with an internal temperature probe, an addition flask, and a nitrogen line) was added aqueous ammonia solution (25%, 4.21 L), maintaining the internal temperature at −8 ± 2 °C. Then, pre-cooled (below 5 °C) sodium hypochlorite solution (chlorine content: 8–10%, 47.4 L) was added into the reaction mixture via an addition flask over 50–80 min, keeping the internal temperature at −8 ± 2 °C. The reaction mass was stirred for 30 min at −8 ± 2 °C, and then, the aqueous and organic layers were allowed to separate for a period of 30–60 min at −8 ± 2 °C. The organic layer was separated, washed with pre-cooled (0–5 °C) brine solution (12 L), and dried over anhydrous $CaCl_2$ (1.2 kg) at 0–5 °C. The dried sample was checked for the monochloramine content (~2.2%). The dried solution was kept in the reactor at −5 to 0 °C for use in the reaction for the preparation of triazine compound, as described below.

Preparation of Pyrrolo[2,1-f][1,2,4]triazin-4-amine. Sodium hydride (60% dispersion in mineral oil, 0.29 kg, 7.17

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Org. Process Res. Dev. 2022, 26, 82–90

mol) was added into stirred anhydrous DMF (6.0 L) at 0−5 °C, and the mixture was stirred further at 0−5 °C for 20−30 min under a N_2 atmosphere. Then, 2-cyanopyrrole (0.60 kg, 6.52 mol) was added into the reaction mixture at 0−5 °C under a N_2 atmosphere (gas evolution occurs), maintaining the internal temperature between 5 and 10 °C and stirred for 30−40 min at this temperature. The monochloramine solution in MTBE (2.2%) (30 V, 18 L) was added into the reaction mixture while maintaining the internal temperature between 0 and 5 °C (reaction mass becomes yellowish to brown color during addition). Reaction progress was monitored by HPLC analysis. Unreacted pyrrole-2-carbonitrile was ∼6%, the KI-starch strip showed the absence of monochloramine, and pH of the reaction showed >10 by the pH strip. Next, another 10 V of monochloramine solution in MTBE [2.2%, 6 L i.e., total 24 L (40 V), density 0.768 kg/m^3, 7.87 mol, 1.2 equiv] was added to the reaction mixture, and the reaction proceeded for 1 h to afford *N*-amino-2-cyanopyrrole **7** with 1.8% of unreacted pyrrole-2-carbonitrile. Formamidine acetate (2.04 kg, 19.56 mol, 3 equiv) was added into the reaction mixture at 0−5 °C, and the reaction mixture was then heated to 85−90 °C. Simultaneously, the MTBE was distilled from the reaction mixture at atmospheric pressure until the internal temperature reached 85−90 °C. The reaction mixture was stirred at 85−90 °C for 20 h, and after that the sample of the reaction mixture was analyzed by HPLC analysis to check the consumption of the intermediate (*N*-amino-2-cyanopyrrole **8**) (∼0.14 A %). The reaction mixture was cooled to 25−30 °C and then filtered. The filter cake was washed with DMF (0.6 L), and the combined filtrate was concentrated to ∼4 V, keeping the temperature below 70 °C under reduced pressure. The residual mass was cooled to 25−30 °C, and water (2.4 L) was added slowly into the cooled mass with stirring for 1 h at 25−30 °C. The mixture was then cooled further to 5−10 °C and stirred for 2 h at this temperature. The stirring was stopped, and the solids were isolated by filtration. The cake was washed with water (0.6 L) under applied vacuum to dry. The cake was then washed with MTBE (1.2 L, 2 V). The wet cake was dried under vacuum at 50−55 °C for 5−6 h until constant weight was obtained. The yield of pyrrolo[2,1-*f*][1,2,4] triazin-4-amine (crystalline material, **1**) was 0.69 kg (67%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.78 (s, 1H), 7.68 (br s, 2H), 7.59−7.58 (m, 1H), 6.86−6.84 (m, 1H), 6.60−6.58 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.5, 147.9, 118.1, 114.3, 110.0, 101.2. GC−MS (*m*/*z*): 134.1. HPLC purity: (230.0 nm): 99.9 A %, 98.4 wt %.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.1c00071.

General information, procedure for RC1 of pyrrole to 2-cyanopyrrole formation, procedure for RC1 of 2-cyanopyrrole to *N*-amino-2-cyanopyrrole formation, characterization of compound-10, ^{1}H NMR spectra of compound-10, compound-3, and compound-1; ^{13}C NMR and LCMS spectra of compound-10 and compound-1; ^{13}C NMR spectra of compound-3; HPLC spectra of compound-1; DSC data for formation of compound-3, compound-4, and compound-5; DSC data for the addition of sodium hydride to DMF; DSC data for the formation of the sodium salt of pyrrole 2-carbonitrile; DSC data for stability of compound-8; and Advanced Reactive System Screening Tool data for NaH and DMF (PDF)

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Notes

The authors declare no competing financial interest.

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(15) Impurity **9** data: ^{1}HNMR (400 MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.21 (bs, 1H), 6.76 (m, 1H), 6.1 (t, J = 3.76 Hz, 1H), 2.94 (s, 3H), 2.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.96, 122.01, 116.87, 113.84, 106.94, 101.83, 40.90, 35.90; LCMS (M + H) = 163.

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Org. Process Res. Dev. 2022, 26, 82−90