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Letter

Expanding Access to Remdesivir via an Improved Pyrrolotriazine Synthesis: Supply Centered Synthesis

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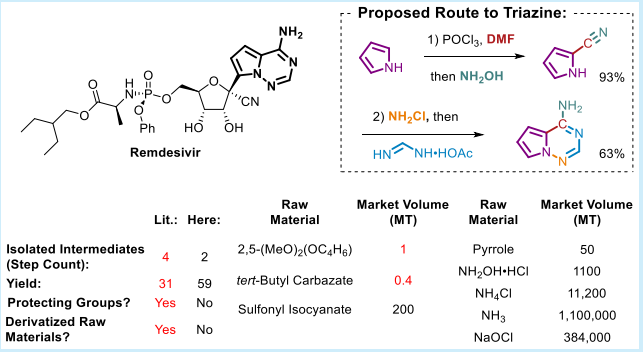
ABSTRACT: Pyrrolotriazine **1** is an important precursor to remdesivir. Initial results toward an efficient synthesis are disclosed consisting of sequential cyanation, amination, and triazine formation beginning from pyrrole. This route makes use of highly abundant, commoditized raw material inputs. The yield of triazine was doubled from 31% to 59%, and the synthetic step count was reduced from 4 to 2. These efforts help to secure the remdesivir supply chain.



	Lit.:	Here:	Raw Material	Market Volume (MT)	Raw Material	Market Volume (MT)
Isolated Intermediates (Step Count):	4	2	2,5-$(MeO)_2(OC_4H_6)$	1	Pyrrole	50
Yield:	31	59	*tert*-Butyl Carbazate	0.4	NH_2OH•HCl	1100
Protecting Groups?	Yes	No	Sulfonyl Isocyanate	200	NH_4Cl	11,200
Derivatized Raw Materials?	Yes	No			NH_3	1,100,000
					NaOCl	384,000

Introduction: The Need for Supply Chain Improvements. COVID-19's emergence has greatly elevated awareness of the pharmaceutical supply chain's importance,[1] and the desire to make remdesivir broadly available presents a case in point.[2] Initial supply is constrained after it emerged as a viable COVID-19 treatment, and Gilead subsequently donated the existing active pharmaceutical ingredient (API) stock. Production of final drug substance is a challenge and can take up to one year as a result of scarce, long lead-time raw materials and several low yielding steps.[3] Due to issues of pricing and licensing, countries are left questioning who will or will not have access to the drug.[2c] A more robust supply chain can be developed by inventing from inherently available building blocks (commodities) and increasing the route's yields and throughput. We call this "Supply Centered Synthesis" (SCS).[4]

The topic of supply chain security was examined within the construct of remdesivir's pyrrolotriazine synthesis (Figure 1). The triazine passes through several low yielding steps, and as an early raw material, large quantities are required. Possibly a preferred route could help overcome recent challenges related to supply and price. The only full route to the base triazine **1** was published by Bayer Healthcare[5,6] despite the biological importance of the pyrrolo[2,1-*f*][1,2,4]triazine framework.[7] The sequence above nicely supplied preparative quantities of triazine (50 g scale); however, some aspects of the route warrant improvement.

1. The yield is 31% over four steps. Increasing yield would decrease consumption of raw materials.

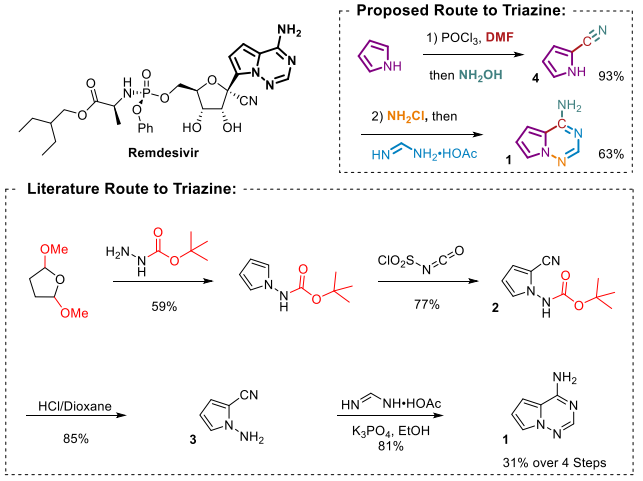


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Figure 1. An atom economic route to triazine from abundant chemicals.

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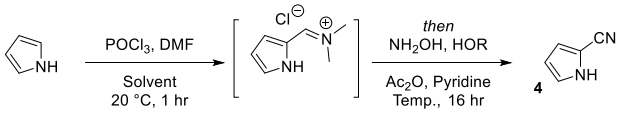
2. Hydrazine is protected as a carbazate, and then carbamate **2** must be deprotected to reveal amine **3**. This creates mass inefficiency, adds to the step-count, and decreases overall yield.
3. 2,5-Dimethoxytetrahydrofuran and *tert*-butyl carbazate are not commodity materials. 2,5-Dimethoxytetrahydrofuran is made in two steps from furan.[8] *tert*-Butyl carbazate is made in four chemical steps from *tert*-butanol and ammonia.[9] Derivatizing commodities requires additional chemical processing and creates waste.

The ideal synthesis would increase overall yield, proceed from commodity materials, and reduce step count, thus strengthening the remdesivir supply chain. This work describes investigation of the bond-forming steps to do so from pyrrole which is abundant and made commercially in one step from furan.[11] Formyl groups are easily installed in the 2-position of pyrroles,[12] and aldehydes can be oxidized to nitriles via aldoxime intermediates.[13] Moreover *N*-amination of pyrroles and indoles, though challenging, are known.[14] The hypothetical synthesis would intercept the penultimate intermediate **3** at this point, and the demonstrated literature condensation with formamidine acetate would render triazine **1**. One could foresee how these transformations could be executed with reagents having high atom economy and market availability.[15] Perhaps efficiency could be further increased by reducing the step count and thus eliminating associated workups.

Results and Discussion. I. A One-Pot Oxidative Vilsmeier Cascade. This effort began with functionalization of pyrrole (Figure 2). Perhaps isolation of the aldehyde or aldoxime



Entry	Scale (g)	Solvent (Vol)	Pyridine (Equiv.)	HOR (Vol)	Temp. (°C)	4, AY	4, IY (Purity)[c]
1[a]	0.2	DMF (10)	-	EtOH, 3	90	84	-
2[a]	0.2	DMF (10)	-	H_2O, 3	90	78	-
3	0.2	DMF (10)	5	EtOH, 3	90	93	-
4	0.2	DMF (10)	5	H_2O, 3	90	92	-
5	0.2	MeCN (10)	5	EtOH, 3	90	88	-
6	0.2	MeCN (5)	3.5	EtOH, 3	90	85	-
7	5	MeCN (10)	3.5	H_2O, 3	70	-	93 (80)
8[b]	25	MeCN (10)	5	H_2O, 3	70	-	76 (90)
9[b]	25	DMF (10)	5	H_2O, 3	90	-	90 (89)
10	100	DMF (10)	5	H_2O, 3	90	-	94 (85)

a) Ac_2O not added to reaction mixture. b) Purified by distillation. c) Measured by HPLC.

Figure 2. A simple one-pot cyanation.

intermediates is unnecessary. 2-Formyl pyrrole is a low melting solid not easily distilled or recrystallized in good yield. Moreover, waste will be generated in the process of purifying the aldehyde, aldoxime, or other intermediates. The iminium chloride salt could possibly be used to form nitrile **4** directly in a one-pot process. Residual $POCl_3$ and related species would need to be quenched due to chemical incompatibility with hydroxylamine; however, the HCl generated in the course of the quench could be used as a catalyst for the dehydration of aldoxime.[16] The $POCl_3$ quench should be monitored to ensure completion.[17] This concept was validated experimentally with surprising simplicity by adding water or ethanol prior to adding the hydroxylamine salt to give the product in >80% assay yield (AY) (entries 1−2). A recent paper nicely demonstrated use of DMPU·HCl as a key additive, but in our case, DMF as solvent worked sufficiently well.[16c] The yield was further improved to >90% AY by activating the oxime formed *in situ* with acetic anhydride and base (entries 3−6). Distillation provided pure material for downstream investigations (entries 8−9). There are very few examples of one-pot nitrile formation via strategies that make use of an oxidative Vilsmeier cascade, and this avoids the use of costly and high molecular weight iodine.[18]

II. Assessing Amination Feasibility. The conditions of Hynes Jr. were used as a starting point to explore the critical amination (Figure 3). Chloramine was made from bleach and

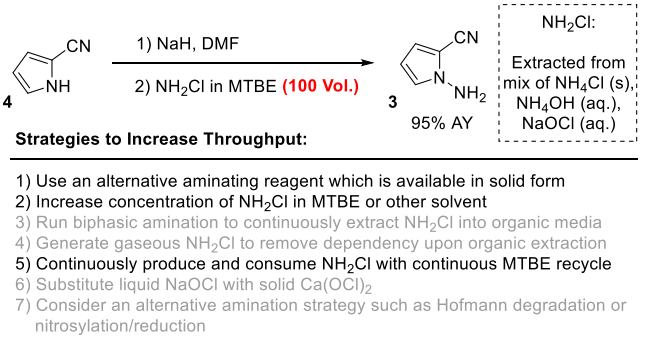


Figure 3. Clean amination of pyrrole from bleach and ammonia under highly dilute conditions.

ammonia and then extracted into MTBE. Pyrrole **4** converted cleanly to the *N*-amino product (95% AY) resolving the discrepancy between moderate isolated yield and high conversion.[14b,19] This serves as a drop-in replacement for **3** and improves yield to 88% as compared to 41% by the literature route. Unfortunately the reaction conditions are highly dilute (1 wt %) as a function of extracting monochloramine from water into MTBE, thus limiting overall throughput and jeopardizing supply. For this reason, strategies which would increase throughput of *N*-amino-2-cyanopyrrole were needed. This was also the likely conclusion of Bristol Myers Squibb, whose subsequent disclosures focused on improved efficiencies *via in situ* chloramine production in a biphasic mixture[20] and production of gaseous chloramine to negate the need for dilute organic solution.[21]

Amination attempts with the biphasic conditions were unsuccessful, and we did not have access to the degree of engineering required for gaseous chloramine generation; however use of solid aminating reagents such as *O*-(4-Nitrobenzoyl)hydroxylamine provided a means to run reactions at 15−20 volumes, thus greatly increasing product throughput.[22] This reagent has been used at scale;[14d] however, neither aminating reagent is available at commodity levels, they are not atom economic, and there are safety concerns with use of these reagents at increasing temperatures and concentrations.[23] Complements to these existing strategies were thus the focal point of remaining efforts.

It is worth mentioning the safety hazards of monochloramine production. Monochloramine is a common water treatment chemical produced onsite at hospitals, food and beverage facilities, and hotels;[24] however, if reaction conditions are not carefully controlled, NCl_3 (explosive) can be coproduced.[25] Important factors to consider include pH,

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Org. Lett. 2020, 22, 7656−7661

temperature, concentration of reactants, and source of NH_3. It is desirable to keep the pH above 8, use NH_4Cl in place of NH_4SO_4, and cool the reaction during synthesis. Here, the pH is kept ≥12 at all stages of reaction. Facilities should carefully assess production prior to scaling.

III. Increasing Amination Space−Time Yield. The remainder of the investigation centered on use of monochloramine. It is an optimal reagent to install the nitrogen atom because atom economy is high, and it is made from simple ingredients which can be accessed anywhere in the world, bleach and ammonia. To render monochloramine accessible, the volumes of extraction solvent (MTBE) must be mitigated. 0.5−0.9 M NH_2Cl/MTBE solutions were produced which were five to ten times stronger than the reported value. This suggested that the literature procedure added NH_2Cl in 4-fold excess. Decreasing chloramine equivalents would greatly increase concentration by reducing MTBE consumption.

Probing the relationship between base and chloramine equivalents showed an interdependent nature, where as much chloramine as base is required (Figure 4). Perhaps this is due to the acidic nature of chloramine which has an estimated pK_a of 14. With 1.25 equiv of base and 0.5 M NH_2Cl, 25 volumes of MTBE are needed. In theory this can be decreased to a minimum of 17 volumes with a 0.9 M NH_2Cl and 1.1 equiv of NaH, which is an 80% reduction in solvent usage. Still, dilution remains at levels higher than desired.

Perhaps, an effectively high concentration "gaseous" form of chloramine can be accessed by recycling MTBE solvent (Figure 4). The reagent can be considered gaseous because at the extreme, infinite recycle of MTBE, only chloramine, a gas, is consumed. Addition of chloramine in fractional charges with subsequent evaporation and recycle of MTBE would seem to present one such option for achieving that aim. With this strategy in mind, the chloramine was added to **4** in four portions of 10 volumes with the MTBE removed and reused at the end of each addition. The effective chloramine concentration becomes 2.0 M rather than 0.5 M. Assay yields of **3** matched those of the original procedure, and the total reaction volume was limited to 15 volumes (10 MTBE, 5 DMF) with an end point of 5 volumes and 20 wt % pyrrole in DMF.

Effective cycle time for this operation can be achieved because MTBE is easily removed from reaction solution due to its low boiling point (55 °C), and because the amination of pyrrole is very rapid, occurring in less than 5 min. This presents a reasonable path toward manufacturing, and 90% of solvent was recycled. Aminated pyrrole was made in 90% assay yield, and this result was scaled 100× to 10 g without change in performance. The amination investigation was concluded with preliminary exploration of strategies which might address the hazards of NaH and DMF mixtures.[22,26] Preliminary calorimetric data to be released in a follow-up publication indicated low thermal risk; however, the hazard can be eliminated by replacing DMF with diglyme (97% AY).

IV. On-Demand Chloramine. Despite the advantages of monochloramine, use of NH_2Cl at scale poses practical challenges. This includes hazards associated with monochloramine accumulation, storage of large reagent quantities (up to 40 Vol), and instability of reagent (half-life of 50−100 h).[24] Perhaps for these reasons, monochloramine is typically made on site.

Application of a chloramine generator[27] presents a solution (Figure 5). Continuous synthesis and use of monochloramine

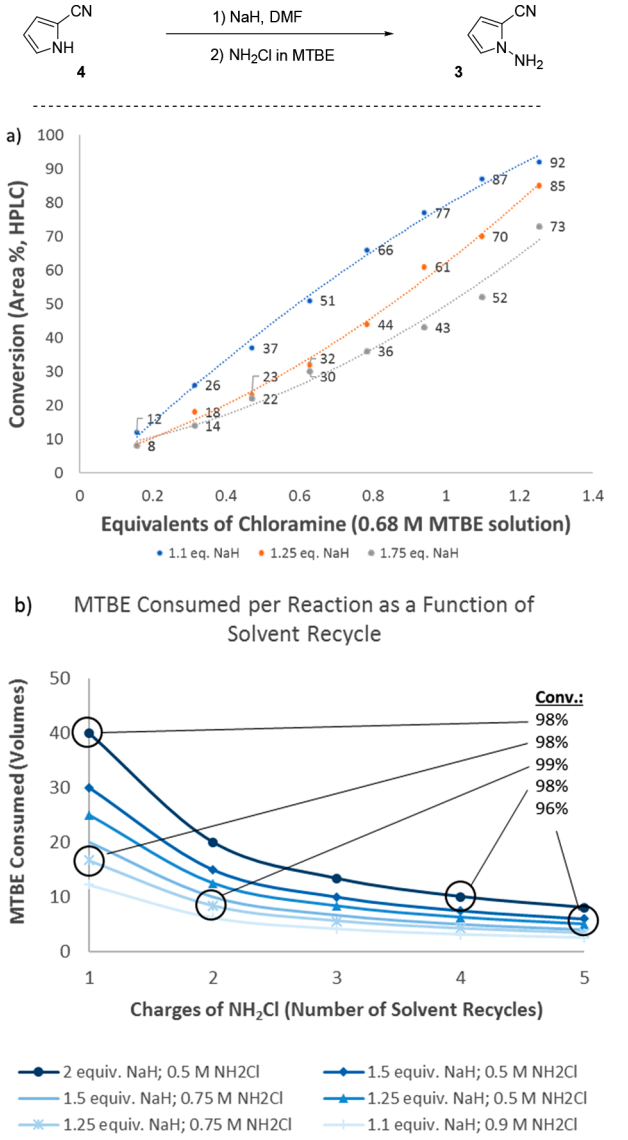

Figure 4. (a) Lower equivalents of chloramine can be used at lower loadings of NaH. (b) Addition of NH_2Cl in multiple charges with subsequent solvent recycle increases throughput and decreases solvent consumption.

would prevent NH_2Cl accumulation (amination complete within 5 min) and eliminate requirement for large volume reagent storage. Further, the concept of on-demand chloramine fits perfectly within a scheme designed to capture and recycle solvent, thus limiting waste and improving throughput. High concentration aqueous chlora mine solutions have been produced for on-site water treatment and manufacturing via a continuous stirred-tank reactor (CSTR) at concentrations up to 2 M.[28] The conditions of Hynes were modified for continuous synthesis and separation to demonstrate proof of concept. Chloramine was simultaneously made and extracted into MTBE in a CSTR with a 10 min residence time. This biphasic mixture flowed into a gravity separator. Steady state was reached within 30 min, and titration of the MTBE layer showed that ∼0.45 M chloramine was produced as compared to a 0.52 M solution made in batch.

The on-demand NH_2Cl solution flowed into a pot containing a solution of deprotonated pyrrole **4** in DMF. The system was placed under occasional vacuum to keep the

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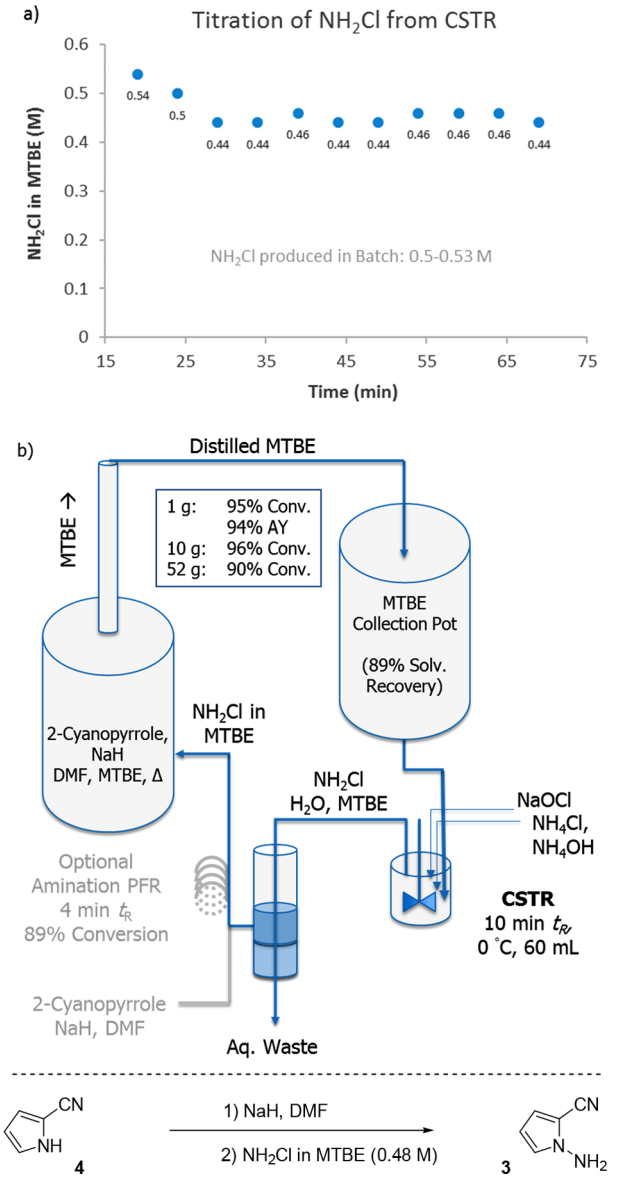
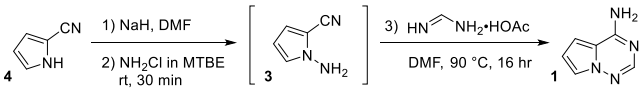


Figure 5. Steady state operation of chloramine CSTR and schematic for chloramine generator.

reaction volume at a minimal level by splitting the charge of chloramine into four portions. The MTBE was collected by condensation in a separate pot and then recycled to extract more chloramine. The total recycle rate of MTBE was 80–89%, and pyrrole **4** was aminated in 94% AY (1 g, 10 g scales). Optionally, the amination can also be conducted in flow. This demonstrates proof of concept for a chloramine generator which helps overcome throughput issues related to dilute aminations.

VI. Amination and Triazine Formation in One Pot. For efficiency's sake the synthesis was telescoped through to the triazine rather than isolate at this stage (Figure 6). Prior experience with hydroxypropyl adenine (HPA) suggested that DMF might be a good solvent for the condensation reaction of the aminonitrile with formamidinium acetate.[29] Formamidine acetate was added to the amination reaction mixture and heated to form the triazine. This provided **1** in 75% AY over two steps. A quick solubility study suggested that water or MTBE would be appropriate antisolvents. *In situ* concentration



Entry	Scale (g)	1, AY (%)	1, IY (%)	1,Purity (%)[b]
1	2.8	74	62	82
2	10	76	64	78
3[a]	10	-	63	98
4[a]	10	75	60	99

a) 2nd Stage purification by trituration with MTBE. See SI for details. b) Measured by HPLC.

Figure 6. One-pot triazine synthesis from cyanopyrrole **4**.

of reaction mixture followed by addition of water afforded the desired triazine in >60% IY over two steps.

Conclusions. This work describes an efficient means to produce the aminotriazine required for manufacturing remdesivir. Importantly, the synthesis makes use of highly abundant materials to bolster supply chain security. It is expected that these common materials will decrease costs associated with chemical inputs, an important objective given concerns around remdesivir supply and price. The synthesis has high atom economy and avoids derivatization and protecting groups. Yield is approximately doubled over the prior procedure described for the triazine while step count is cut in half. This should facilitate improved throughput of this important API intermediate. Moreover, development of a continuous platform afforded access to a noncommercial aminating reagent, monochloramine, while simultaneously preventing buildup of reagent to mitigate potential safety concerns.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02848.

Experimentals and compound characterization (PDF)

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Notes

The authors declare no competing financial interest.

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