Toward Secure Supply of Remdesivir *via* a 2-Pot Triazine Synthesis: Supply Centered Synthesis

Paymode, Dinesh J.[†a]; Cardoso, Flavio S.P.[†a]; Agrawal, Toolika[a]; Tomlin, John W.[a]; Cook, Daniel W.[b]; Burns, Justina M.[b]; Stringham, Rodger W.[b]; Sieber, Joshua D.[a]; Gupton, B. Frank[a]; Snead, David R.*[a]

AUTHOR ADDRESS

a) Chemical Development, Medicines for All Institute, 737 N. 5th St., Box 980100, Richmond VA, 23298-0100

b) Analytical Development, Medicines for All Institute, 737 N. 5th St., Box 980100, Richmond VA, 23298-0100

Supporting Information Placeholder

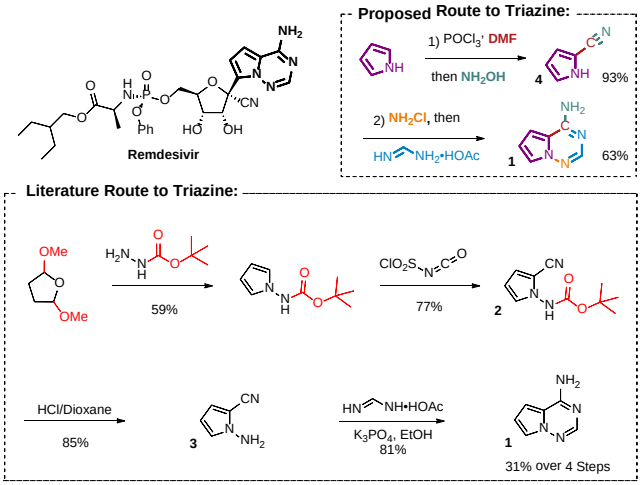
ABSTRACT: Pyrrolotriazine **1** is an important precursor to Remdesivir, and an efficient synthesis is disclosed. This route features atom economy and reduced derivatization of starting materials, by making use of highly abundant, commoditized raw material inputs. The yield of triazine was doubled from 31% to 59%, and the synthetic step count was reduced from 4 to 2. A one-pot cascade sequence was developed for direct cyanation of pyrrole. Amination and cyclization with formamidine acetate complete the synthesis. The problematic nature of typically dilute electrophilic aminations was solved with semi-continuous processing. Moreover, development of a continuous platform afforded access to the ideal yet non-commercial aminating reagent, monochloramine. These efforts help to secure the Remdesivir supply chain.

■ 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[2b-c] after it emerged as a viable COVID-19 treatment,[2a] and Gilead subsequently donated the existing API stock.[2d] 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[2b-c] and several low yielding steps.[3] Due to issues of pricing and licensing, countries are left questioning who will or won't have access to the drug.[2f] 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 recently published on this topic which we term "Supply Centered Synthesis" (SCS) of API.[4]

We examined this topic of supply chain security within the construct of Remdesivir's pyrrolotriazine synthesis (Fig. 1). The triazine passes through several low yielding steps, and as an early raw material, large quantities are required. We wondered if 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.
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 2-steps from furan.[8] *tert*-Butyl carbazate is made in 4 chemical steps from *tert*-butanol and ammonia.[9] Derivatizing commodities requires additional chemical processing and creates waste.



	Lit.:	Here:	Raw Material	Market Volume (MT)[10]	Raw Material	Market Volume (MT)[10]
Isolated Intermediates (Step Count):	4	2	$2,5\text{-}(MeO)_2(OC_4H_6)$	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

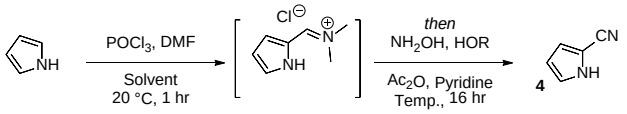
Figure 1: An atom efficient route to triazine from abundant chemicals.

The ideal synthesis would increase overall yield, proceed from commodity materials, and reduce step-count, thus strengthening the remdesivir supply chain. This work describes efforts to do so from pyrrole which is abundant and made commercially in 1 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 transformation could be executed with reagents having high atom efficiency and market availability. 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



Entry	Scale (g)	Solvent (Vol)	Pyridine (Equiv.)	HOR (Vol)	Temp. (°C)	4, AY	4, IY (Purity)
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)

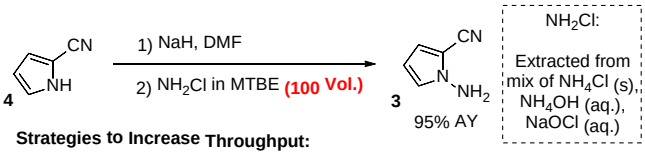
a) Ac_2O not added to reaction mixture. b) Purified by distillation.

Figure 2: A simple one-pot cyanation.

This effort began with functionalization of pyrrole (Fig. 2). We wondered whether isolation of the aldehyde or aldoxime intermediate was necessary. 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. Perhaps the iminium chloride salt could be used directly to form nitrile **4** 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 catalyst for the dehydration of aldoxime.[15] 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% 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.[15c] 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.[16] This avoids the use of costly and high molecular weight iodine.

II: Assessing Amination Feasibility

The conditions of Hynes Jr. were used as a starting point to explore the critical amination (Fig. 3). Chloramine was made from bleach and ammonia then extracted into MTBE. Pyrrole **4** converted cleanly to the *N*-amino product (95% AY) despite reports of moderate yield.[14b,17] 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, we sought strategies which would increase throughput of *N*-amino-2-cyanopyrrole. This was also the likely



Strategies to Increase Throughput:

1) Use an alternative aminating reagent which is available in solid form
2) Increase concentration of NH_2Cl in MTBE or other solvent
3) Run biphasic amination to continuously extract NH_2Cl into organic media
4) Generate gaseous NH_2Cl to remove dependency upon organic extraction
5) Continuously produce and consume NH_2Cl with continuous MTBE recycle
6) Substitute liquid NaOCl with solid $Ca(OCl)_2$
7) Consider an alternative amination strategy such as Hofmann degradation or nitrosylation/reduction

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

conclusion of Bristol Myers Squibb, whose subsequent disclosures focused on improved efficiencies *via in situ* chloramine production in a biphasic mixture[18] and production of gaseous chloramine to negate the need for dilute organic solution.[19]

We did not have success with the biphasic conditions and 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.[20] This reagent has been used at scale;[14d] however, neither aminating reagent is available at commodity levels, they are not atom efficient, and there are safety concerns with use of these reagents at increasing temperatures and concentrations.[21] We thus focused on producing solutions to complement these existing strategies.

III: Increasing Amination Space-Time Yield

The remainder of our investigation centered on use of monochloramine. It is an optimal reagent to install the nitrogen atom because atom efficiency 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. We sought better understanding of chloramine preparation and use, and produced 0.5-0.9 M NH_2Cl/MTBE solutions which were five to ten times stronger than the reported value. Our study suggested that the literature procedure added NH_2Cl in four-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 (Fig. 4). Perhaps this is due to the acidic nature of chloramine which has an estimated pKa of 14. With 1.25 equivalents 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 equivalents 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 (Fig. 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.

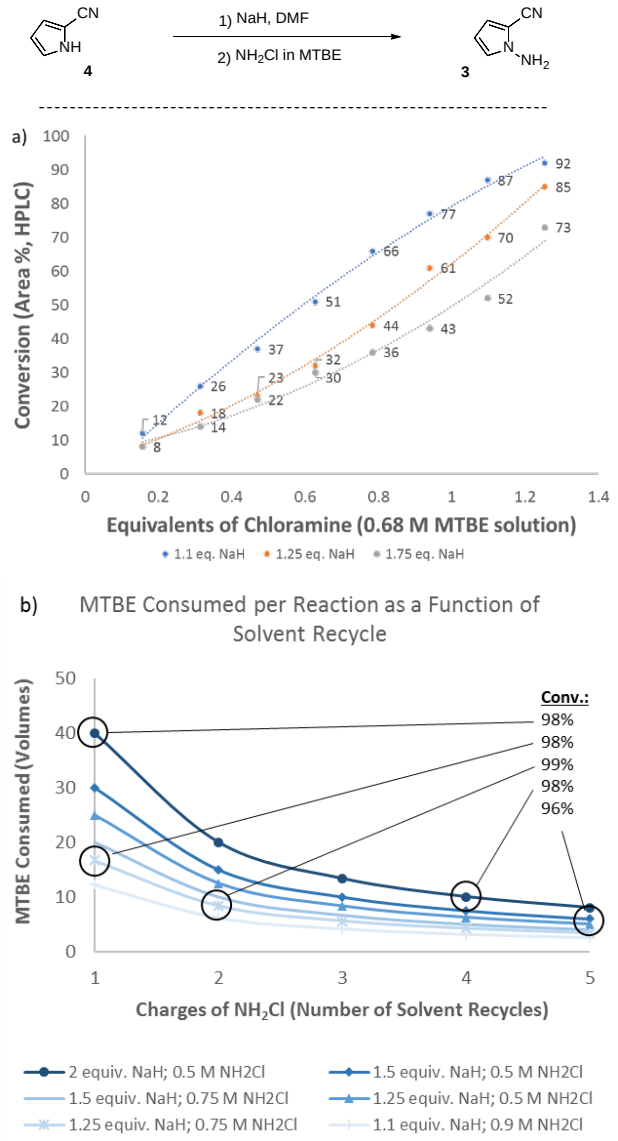


Figure 4: a) Lower equivalents of chloramine can be used at lower loadings of NaH. b) Addition of NH_2Cl in multiple charges with subsequent solvent recycle increases throughput and decreases solvent consumption.

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 minutes. 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 100x to 10 g without change in performance. We concluded our amination investigation by addressing the hazards surrounding use of NaH in conjunction with DMF.[20,23]

IV: On-Demand Chloramine

Even with a solution to the challenge of running dilute electrophilic aminations and despite the advantages of monochloramine, preparation and use of NH_2Cl at scale poses further practical challenges. The reagent needs to be made on site as it is not available for purchase. One reason for the lack of market presence is likely a result of the limited half-life of chloramine which is on the order of days,[22] and also the difficulty in controlling titer of chloramine solutions. Chloramine is a dissolved gas and has a tendency to effervesce out of solution. The need for onsite production would require a very large storage tank to hold the NH_2Cl/MTBE solution—up to 40 reaction volumes are required.

Production of a chloramine generator[24] *via* continuous processing presents a solution for on-demand production, reagent instability, and solvent recycle (Fig. 5). Creation of a captive solvent recycle loop prevents build up of large solvent volumes which can limit space time yield. Further, continuous chloramine generation fits within a semi-continuous amination motif which benefits from frequent volume reduction *via* application of vacuum. High concentration aqueous chloramine solutions have been produced for on-site water treatment and manufacturing via a continuous stirred-tank reactor (CSTR) at concentrations up to 2 M.[25] To demonstrate proof of concept, all that is needed is to modify the conditions of Hynes for continuous synthesis and separation. Chloramine was simultaneously made and extracted into MTBE in a CSTR with a 10 minute residence time. This biphasic mixture flowed into a gravity separator. Steady-state was reached within 30 minutes, and titration of the MTBE layer showed that ~0.45 M chloramine was produced as compared to 0.52 M solution as made in batch.

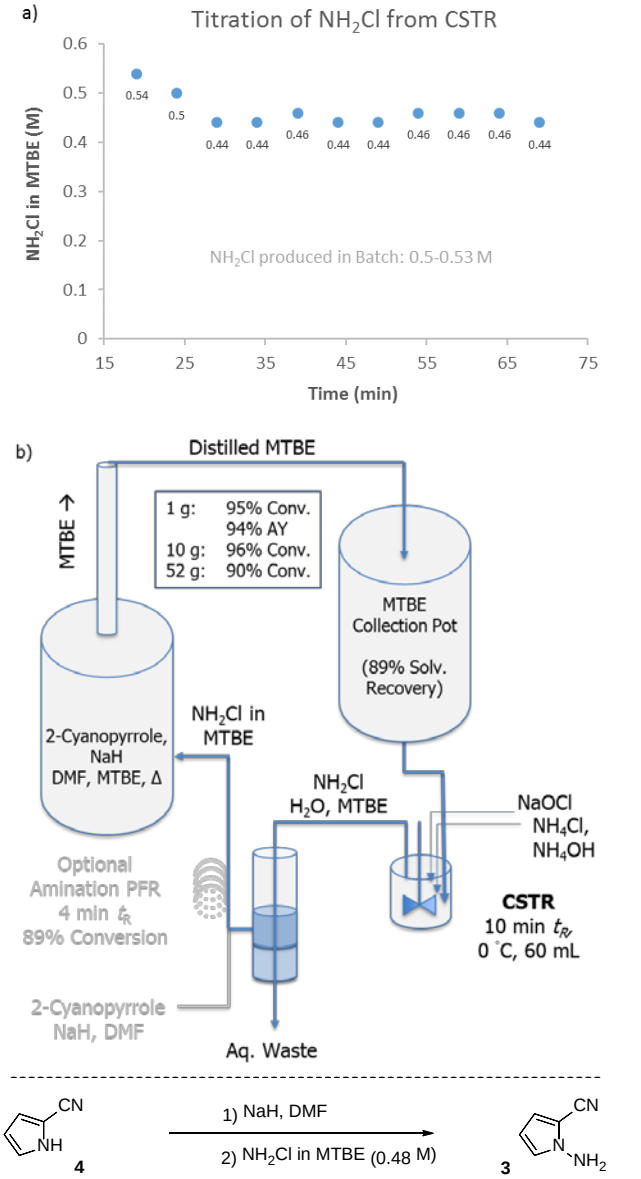
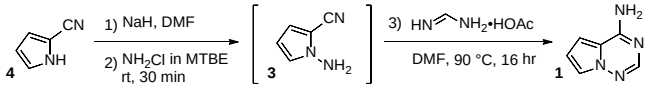


Figure 5: Steady state operation of chloramine CSTR and schematic for chloramine generator.

The on-demand NH_2Cl solution was flowed into a pot containing a solution of deprotonated pyrrole **4** in DMF. The system was placed under occasional vacuum to keep the 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 we elected to telescope the synthesis through to the triazine rather than isolate at this stage (Fig. 6). Our prior experience with hydroxypropyl adenine (HPA) suggested that DMF might be a good solvent for the condensation reaction of the amino nitrile with formamidinium acetate.[26] Formamidine acetate was added to the amination reaction mixture and heated to form the triazine with this thought in mind. This provided material in 75% AY over two steps. A quick solubility study suggested that water or MTBE would be appropriate antisolvents. *In situ* concentration of reaction mixture followed by addition of water afforded the desired triazine in 60% IY over two steps.



Entry	Scale (g)	1, AY (%)	1, IY (%)	1,Purity (%)
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.

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

■ 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 objectives 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. The chemical solution involves a novel one-pot cascade for nitrile formation, avoiding generation and isolation of aldehyde as an intermediate. Further, the work presents a solution to the challenge of limited space time yield posed by highly dilute electrophilic amination conditions and enables access to non-commercial monochloramine, an atom efficient and desirable reagent.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimentals (PDF)
Compound characterization (PDF)

AUTHOR INFORMATION

Corresponding Author

David R. Snead
737 N. 5th St.
Box 980100
Richmond, Virginia 23298-0100
email: drsnead@vcu.edu

Author Contributions

†These authors contributed equally.

Notes

The authors declare no competing financial interests.

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REFERENCES

1) a) Mullin, R. "COVID-19 is reshaping the pharmaceutical supply chain", *Chem. Eng. News*, **2020**, *98*. b) Mullin, R. "Bringing drug production back to the US", *Chem. Eng. News*, **2020**, *98*. c) Woodcock, J.; Safeguarding Pharmaceutical Supply Chains in a Global Economy, U.S. Food and Drug Administration. https://www.fda.gov/news-events/congressional-testimony/safeguarding-pharmaceutical-supply-chains-global-economy-10302019 (Accessed July 10, 2020).

2) a) An Open Letter from our Chairman & CEO, Gilead Sciences, Inc. https://stories.gilead.com/articles/an-open-letter-from-our-chairman-and-ceo-april-29 (Accessed July 1, 2020). b) Working to Supply Remdesivir for COVID-19, Gilead Sciences, Inc. https://www.gilead.com/purpose/advancing-global-health/covid-19/working-to-supply-remdesivir-for-covid-19 (Accessed July 1, 2020). c) Gilead Sciences Statement on Expanding Global Supply of Investigational Antiviral Remdesivir, Gilead Sciences, Inc. https://www.gilead.com/news-and-press/company-statements/gilead-sciences-statement-on-remdesivir-global-supply (Accessed July 1, 2020). d) An Update on COVID-19 from our Chairman & CEO, Gilead Sciences, Inc. https://stories.gilead.com//articles/an-update-on-covid-19-from-our-chairman-and-ceo (Accessed July 1, 2020). e) An Open Letter from Daniel O'Day, Chairman & CEO, Gilead Sciences, Gilead Sciences, Inc. https://www.gilead.com/news-and-press/press-room/press-releases/2020/6/an-open-letter-from-daniel-oday-chairman--ceo-gilead-sciences (Accessed July 1, 2020). f) Trump Administration Secures New Supplies of Remdesivir for the United States, U.S. Department of Health and Human Services. https://www.hhs.gov/about/news/2020/06/29/trump-administration-secures-new-supplies-remdesivir-united-states.html (Accessed July 10, 2020).

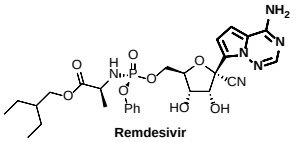
3) a)Siegel, D.; Hui, H.C.; Doerffler, E.; Clarke, M.O.; Chun, K.; Zhang, L.; Neville, S.; Carra, E.; Lew, W.; Ross, B.; Wang, Q.; Wolfe, L.; Jordan, R.; Soloveva, V.; Knox, J.; Perry, J.; Perron, M.; Stray, K.M.; Barauskas, O.; Feng, J.Y.; Xu, Y.; Lee, G.; Rheingold, A.L.; Ray, A.S.; Bannister, R.; Strickley, R.; Swaminathan, S.; Lee, W.A.; Bavari, S.; Cihlar, T.; Lo, M.K.; Warren, T.K.; Mackman, R.L. *J. Med. Chem.*, **2017**, *60*, 1648-1661. b) De Savi, C.; Hughes, D.L.; Kvaerno, L. *Org. Process Res. Dev.*, **2020**, *24*, 940-976. c) Vieira, T.; Stevens, A.C.; Chtchemelinine, A.; Gao, D.; Badalov, P.; Heumann, L. *Org. Process Res. Dev.*, **2020**, ASAP.

4) a) Snead, D.R.; McQuade, D.T.; Ahmad, S.; Krack, R.; Stringham, R.W.; Burns, J.M.; Abdiaj, I.; Gopalsamuthiram, V.; Nelson, R.C.;

Gupton, B.F. *Org. Process Res. Des.*, **2020**, *24*, 1194-1198. b) Kashinath, K.; Snead, D.R.; Burns, J.M.; Stringham, R.W.; Gupton, B.F.; McQuade, D.T.M. *Org. Process Res. Dev.*, **2020**, ASAP.

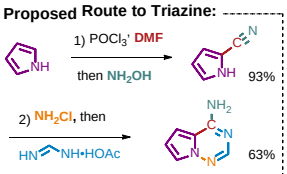
5) a) Dixon, J.A.; Phillips, B.; Achebe, F.; Kluender, H.C.E.; Newcom, J.; Parcella, K.; Magnuson, S.; Hong, Z.; Zhang, Z.; Liu, Z.; Khire, U.; Wang, L.; Michels, M.; Chandler, B.; O'Connor, S. US8143393, **2006**. b) O'Connor, S.; Dumas, J.; Lee, W.; Dixon, J.; Cantin, D.; Gunn, D.; Burke, J.; Phillips, B.; Lowe, D.; Shelekhin, T.; Wang, G.; Ma, X.; Ying, S.; McClure, A.; Achebe, F.; Lobell, M.; Ehrgott, F.; Iwuagwu, C.; Parcella, K. US8431695, **2006**.
6) Private correspondence with generic manufacturers confirmed that this route is used to supply material for remdesivir.
7) a) Yu'Ning, S.; Peng, Z.; Qingzhu, A.; Xinyong, L. *Curr. Pharm. Des.*, **2013**, *19*, 1528-1548. b) Cascioferro, S.; Parrino, B.; Spano, V.; Carbone, A.; Montalbano, A.; Barraja, P.; Diana, P.; Cirrincione, G. *Eur. J. Med. Chem.*, **2017**, *142*, 328-375.
8) Hoydonckx, H.E.; Van Rhijn, W.M.; Van Rhijn, W.; DeVos, D.E.; Jacobs, P.E. "*Furfural and Derivatives*", in Ullmann's Encyclopedia of Industrial Chemistry, Weinham, Germany: Wiley-VCH Verlag GmbH & Co. KGaA, **2000**.
9) a) Tamura, M.; Yamada, N.; Ohta, M.; Yahata, T. EP0256559, **1987**. b) Schirmann, J.-P.; Bourdauducq, P. "*Hydrazine*", in Ullmann's Encyclopedia of Industrial Chemistry, Weinham, Germany: Wiley-VCH Verlag GmbH & Co. KGaA, **2000**.
10) Market volumes taken from Indian import records.
11) Harreus, A.L. "*Pyrrole*", in Ullmann's Encyclopedia of Industrial Chemistry, Weinham, Germany: Wiley-VCH Verlag GmbH & Co. KGaA, **2000**.
12) a) Silverstein, R.M.; Ryskiewicz, E.E.; Willard, C.; Koehler, R.C. *J. Org. Chem.*, **1955**, *20*, 668-672. b) ban den Broek, S.A.M.W.; Leliveld, J.R.; Becker, R.; Delville, M.M.E.; Nieuwland, P.J.; Koch, K.; Rutjes, F.P.J.T. *Org. Process Res. Dev.*, **2012**, *16*, 934-938.
13) a) Capdevielle, P.; Lavigne, A.; Maumy, M. *Synthesis*, **1989**, *6*, 451-452. b) Wang, E.-C.; Lin, G.-J. *Tetrahedron Letters*, **1998**, *39*, 4047-4050. c) Dugar, S.; Chakravarty, S.; Conte, A.; Axon, J.; McEnroe, G.; Murphy, A. US7223766, **2004**. d) Hwu, J.R.; Wong, F.F. *Eur. J. Org. Chem.*, **2006**, *11*, 2513-2516. e) Aydin, A.E.; Yuksekdanaci, S. *Tetrahedron: Asymmetry*, **2013**, *24*, 14-22. f) Nandi, G.C.; Laali, K.K. *Tetrahedron Letters*, **2013**, *54*, 2177-2179. g) An, X.-D.; Yu, S. *Org. Lett.*, **2015**, *17*, 5064-5067.
14) a) Somei, M.; Matsubara, M.; Kanda, Y.; Natsume, M. *Chem. Pharm. Bull.*, **1978**, *26*, 2522-2534. b) Hynes, J.; Doubleday, W.W.; Dyckman, A.J.; Godfrey, J.D.; Grosso, J.A.; Kiau, S.; Leftheris, K. *J. Org. Chem.*, **2004**, *69*, 1368-1371. c) Weiberth, F.J.; Hanna, R.G.; Lee, G.E.; Polverine, Y.; Klein, J.T. *Org. Process Res. Dev.*, **2011**, *15*, 704-709. d) Shi, Z.; Kiau, S.; Lobben, P.; Hynes Jr., J.; Wu, H.; Parlanti, L.; Discordia, R.; Doubleday, W.W.; Leftheris, K.; Dyckman, A.J.; Wrobleski, S.T.; Dambalas, K.; Tummala, S.; Leung, S.; Lo, E. *Org. Process. Res. Dev.*, **2012**, *16*, 1618-1625.
15) a) Liebscher, J.; Neumann, B.; Hartmann, H. *J. Prakt. Chem.*, **1983**, *325*, 915-918. b) Kumar, H.M.S.; Reddy, B.V.S.; Reddy, P.T.; Yadav, J.S. *Synthesis*, **1999**, *4*, 586-587. c) Mudshinge, S.R.; Potnis, C.S.; Xu, B.; Hammond, G.B. *Green Chem.*, **2020**, *22*, 4161-4164.
16) Ushijima, S.; Moriyama, K.; Togo, H. *Tetrahedron*, **2012**, *68*, 4588-4595.
17) a) Patil, S.A.; Otter, B.A.; Klein, R.S. *J. Het. Chem.*, **1994**, *31*, 781-786. b) Simmen, K.A.; Lin, T.-I.; Lenz, O.; Surleraux, D.L.N.G.; Raboisson, P. J.-M.B. WO2006035061, **2006**. c) Xin,M.; Zhang, L.; Tang, F.; Tu, C.; Wen, J.; Zhao, X.; Liu, Z.; Cheng, L.; Shen, H. *Bioorg. Med. Chem.*, **2014**, *22*, 1429-1440. d) Ning, X.; Li, M.; Hu, H.; Dai, W.; Li, X.; Wang, T.; Wu, Y. WO2016190847, **2015**.
18) Bhattacharya, A.; Patel, N.C.; Plata, E.; Peddicord, M.; Ye, Q.; Parlanti, L.; Palaniswamy, V.A.; Grosso, J.A. *Tetrahedron Letters*, **2006**, *47*, 5341-5343.
19) Tummala, S.; Leung, S.W.; Lo, E.T.; Alvarez, M.M. US7070751, **2003**.
20) See Supporting Information for more details.
21) Tran, T.P.; Fisher, E.L.; Wright, A.S.; Yang, J. *Org. Process Res. Dev.*, **2018**, *22*, 166-172.
22) a) Ura, Y.; Sakata, G. *"Chloramines"*, in Ullmann's Encyclopedia of Industrial Chemistry, Weinham, Germany: Wiley-VCH Verlag GmbH & Co. KGaA, **2000**. b) Lutze, H.V. *"Water, 6. Treatment by Oxidation Processes"* in Ullmann's Encyclopedia of Industrial Chemistry, Weinham, Germany: Wiley-VCH Verlag GmbH & Co. KGaA, **2000**.
23) Yang, Q.; Sheng, M.; Henkelis, J.J.; Tu, S.; Wiensch, E.; Zhang, H.; Zhang, Y.; Tucker, C.; Ejeh, D.E. *Org. Process Res. Dev.*, **2019**, *23*, 2210-2217.
24) For examples of chemical generators see: Dallinger, D.; Gutmann, B.; Kappe, C.O. *Acc. Chem. Res.*, **2020**, *53*, 1330-1341.
25) Delalu, H.; Peyrot, L.; Elkhatib, M.; Counioux, J.-J.; Cohen, A. US6222071, **2000**.
26) Derstine, B.P.; Tomlin, J.W.; Peck, C.L.; Dietz, J.-P.; Herrera, B.T.; Cardoso, F.S.P.; Paymode, D.J.; Yue, A.C.; Arduengo, A.J.; Opatz, T.; Snead, D.R.; Stringham, R.W.; McQuade, D.T.M.; Gupton, B.F. *Org. Process Res. Dev.*, **2020**, ASAP.

Graphical Abstract



Remdesivir

Proposed Route to Triazine:



	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