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Cyanoamidine Cyclization Approach to Remdesivir's Nucleobase

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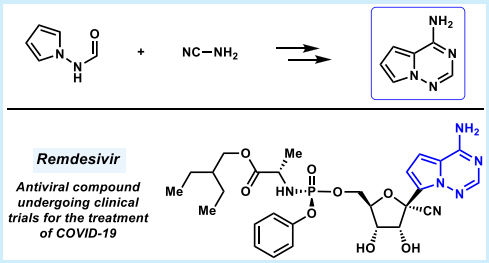
ABSTRACT: We report an alternative approach to the unnatural nucleobase fragment seen in remdesivir (Veklury). Remdesivir displays broad-spectrum antiviral activity and is currently being evaluated in Phase III clinical trials to treat patients with COVID-19. Our route relies on the formation of a cyanoamidine intermediate, which undergoes Lewis acid-mediated cyclization to yield the desired nucleobase. The approach is strategically distinct from prior routes and could further enable the synthesis of remdesivir and other small-molecule therapeutics.



The ongoing COVID-19 pandemic has prompted a remarkable response from the scientific community.[1] In roughly 6 months, numerous breakthroughs have been disclosed in testing,[2] vaccinations,[3] small-molecule therapeutics,[4,5] and other areas.[6] With respect to small-molecule therapeutic approaches to combat COVID-19, remdesivir (**1**) (Figure 1) has gained considerable attention from scientists and the general public.[4,7] This unnatural nucleotide analogue, discovered by Gilead Sciences, Inc. and now marketed as Veklury, displays broad-spectrum antiviral activity and is currently being evaluated in Phase III clinical trials to treat patients with COVID-19.[4i] The U.S. Food and Drug Administration has granted emergency use authorization for remdesivir, allowing hospitalized adult and pediatric COVID-19 patients to receive remdesivir treatments.[4a]

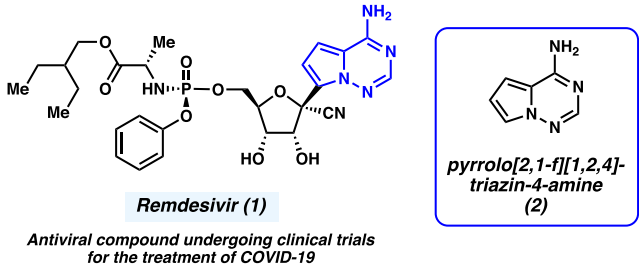


Figure 1. Antiviral drug remdesivir (**1**) and nucleobase fragment **2**.

From a synthetic perspective, **1** (Figure 1) possesses several structural features that render it a challenging target.[8] In addition to the presence of a tertiary anomeric center bearing a nitrile group, the molecule contains a phosphoramidate unit with a stereogenic phosphorus center. Moreover, the nucleobase present in **1** is the unnatural pyrrolo[2,1-*f*][1,2,4]-triazin-4-amine moiety (**2**) (Figure 1). This structural motif is present in a variety of other approved and experimental drugs, such as **3**–**6** (Figure 2).[9−12]

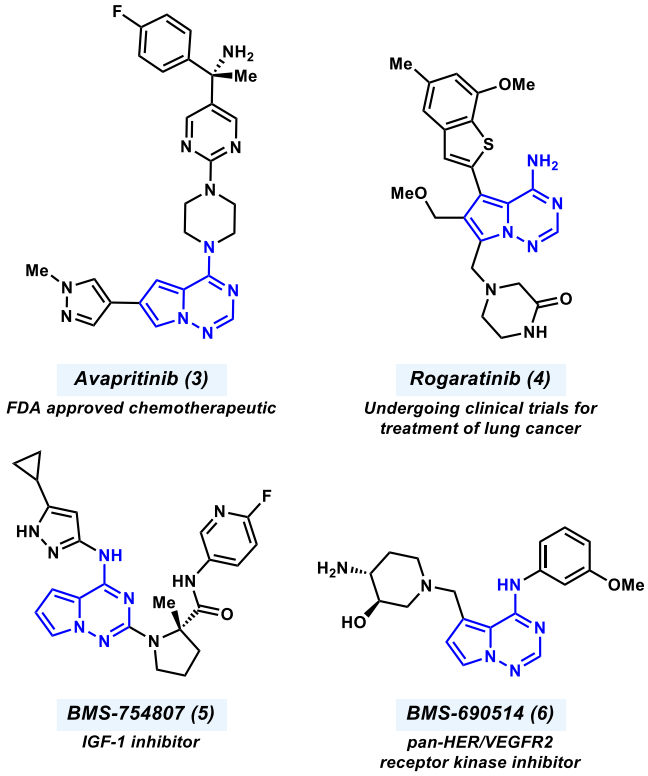


Figure 2. Selected examples of experimental and approved drugs that possess fragment **2** or a derivative thereof.

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With the overall aim of lowering the cost of manufacturing remdesivir or identifying alternative pathways for its synthesis, we considered the few known synthetic approaches to **2**.[13] As summarized in Figure 3, **2** has been generally prepared from

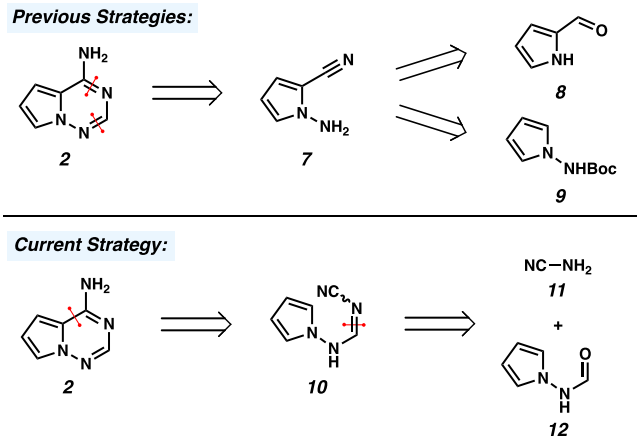


Figure 3. Prior and current strategies for the synthesis of **2**.

nitrile **7**.[14] In turn, **7** can be accessed from 2-formylpyrrole (**8**)[14a] or aminopyrrole derivative **9**.[14b−f] An exciting improvement to the synthesis of **2** via intermediate **7**, which uses pyrrole as the starting material, has recently been reported by the Medicines for All Institute.[8a] We devised a distinct, complementary approach in which **2** would be accessed from cyanoamidine **10** via electrophilic aromatic substitution. Amidine **10** would arise from condensation of cyanamide (**11**) with formamide **12**.[15] To our knowledge, this alternate strategy has not been evaluated previously. The overall conversion of **11** + **12** to **2** could theoretically proceed with water as the only byproduct, thus rendering the approach highly attractive.

We initiated our experimental efforts by preparing formamide **12** (Figure 4). Two distinct routes proved

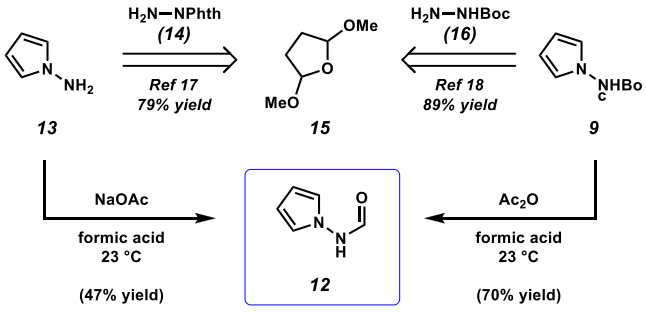
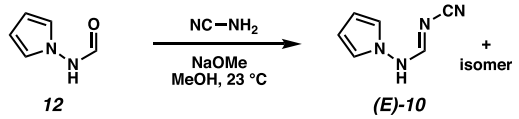


Figure 4. Synthetic routes to formamide **12** stemming from **15**.

fruitful.[16] In the first, 1-aminopyrrole (**13**), which can be prepared in two steps from 2,5-dimethoxyfuran (**15**),[17] underwent formylation to provide **12**.[18] Alternatively, Boc-protected aminopyrrole **9** could be utilized, which is notable since it is easily accessible in a single high-yielding step from **15**.[14b,f,19,20] Treatment of **9** with acetic anhydride in formic acid[21] at room temperature gave formamide **12** in 70% yield.

Table 1 provides a sampling of conditions that were examined for the next step, which is the conversion of formamide **12** to cyanoamidine **10**. Although the reaction of **12** with 2 equivalents of cyanamide and substoichiometric

Table 1. Selected Conditions for the Conversion of Formamide 12 to Cyanoamidine (*E*)-10[a]



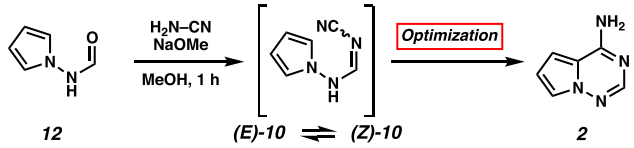
entry	equiv of H_2NCN	equiv of NaOMe	conversion[b]
1	2.0	0.5	0%
2	2.0	1.0	quantitative
3	1.0	1.0	quantitative

[a]Conditions: formamide **12** (1.0 equiv), cyanamide (1.0−2.0 equiv), sodium methoxide (0.5−1.0 equiv), and methanol (0.5 M) stirred at 23 °C for 1 h in a sealed vial under an atmosphere of N_2. [b]Conversion to (*E*)-**10** and its isomer was determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an external standard; for entries 2 and 3, the ratio of (*E*)-**10** to its isomer was observed to be 1.8 to 1.

amounts of sodium methoxide as the base did not give the desired product (entry 1), the use of stoichiometric sodium methoxide led to complete conversion, thus furnishing two isomers of cyanoamidine **10** in a ratio of 1.8 to 1 (entry 2), presumably favoring the depicted *E* isomer.[22] We also found that only 1 equivalent of cyanamide was necessary. Thus, treatment of formamide **12** with 1 equiv of cyanamide and 1 equivalent of sodium methoxide at 23 °C gave quantitative conversion to (*E*)-**10** and an isomer (entry 3). Although the cyanoamidine products displayed sensitivity to water, they could be easily isolated by filtering the crude reaction mixture over Celite and removing the volatiles under reduced pressure.

We then investigated the key cyclization.[23] Given the aforementioned sensitivity of the cyanoamidine intermediates to water, **12** was converted to **10** (presumed to be (*E*)-**10** and an unassigned isomer) using our optimized reaction conditions, and it was carried directly into the next step without purification (see Table 2). The crude intermediate was subjected to a variety of acid sources with the hope of obtaining **2** through cyclization of the *Z* isomer of **10**. Table 2 features a comparison of ^{1}H NMR yields obtained using 1,2-

Table 2. Selected Conditions for the Synthesis of 2[a]



entry	acid	conc. (M)	yield of **2**[b]
1	$BF_3{\cdot}OEt_2$	1.0	4%
2	$BF_3{\cdot}OEt_2$	0.5	3%
3	**$BF_3{\cdot}OEt_2$**	**0.1**	**22%**
4	HCl	0.1	0%
5	AcOH	0.1	0%
6	TMSCl	0.1	0%
7	$Zn(OTf)_2$	0.1	trace
8	$Cu(OTf)_2$	0.1	trace
9	$TiCl_4$	0.1	7%
10	**$SnCl_4$**	**0.1**	**28%**

[a]Conditions for the cyclization step: crude **10** (1.0 equiv, assuming quantitative conversion from **12**), acid (2.5 equiv), and 1,2-dichloroethane (0.1 M) heated at 90 °C for 16 h in a sealed vial under an atmosphere of N_2. [b]Yields were determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an external standard.

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dichloroethane as the solvent at 90 °C (see the Supporting Information for additional results on variation of the acid source, solvent, temperature, etc.). We were delighted to find that $BF_3{\cdot}OEt_2$ could be employed as the Lewis acid (entries 1–3), with the highest yield of **2** (22%) being observed at a concentration of 0.1 M (entry 3). Protic acids such as hydrochloric acid and acetic acid were ineffective (entries 4 and 5). Whereas chlorotrimethylsilane also failed to deliver **2** (or a silylated derivative thereof), trace amounts or low yields were obtained using zinc triflate, copper triflate, or titanium tetrachloride (entries 7–9). However, subjecting crude **10** to tin tetrachloride furnished the desired heterocycle **2** in 28% yield (entry 10).[24]

Given the urgency and importance of efforts to alleviate the COVID-19 pandemic and the currently limited research capacity at our home institutions, we opted to limit further optimization studies and instead evaluate our current protocol on a millimolar scale. Figure 5 provides an overview of the

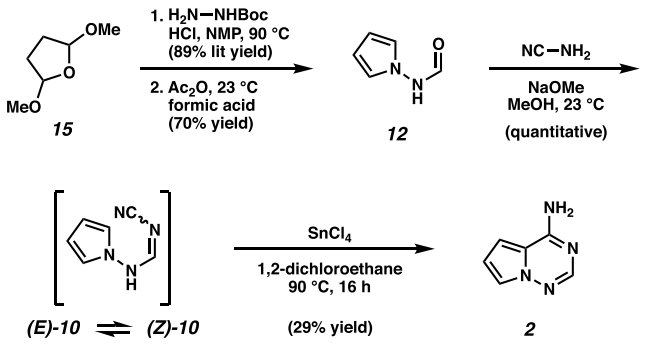

Figure 5. Synthesis of **2** on a >1 mmol scale.

synthetic sequence with isolated yields.[25] Furan **15** is converted to formamide **12** in two steps. Subsequent condensation with cyanamide furnishes intermediate **10**, which in turn undergoes cyclization through its *Z* isomer to give **2**. We are optimistic that further optimization efforts will lead to practical improvements and welcome the expertise of process chemists worldwide to help address this challenge.

In summary, we have developed an alternative strategy to synthesize nucleobase **2**, a key fragment in remdesivir and other experimental or approved small-molecule therapeutics. The route relies on intermediate formamide **12**, which is derived in two steps from 2,5-dimethoxyfuran (**15**). Condensation of **12** with cyanamide yields an intermediate cyanoamidine (i.e., **10**), which then undergoes Lewis acid-mediated cyclization to deliver **2**. Our approach to **2** is atom-economical and strategically distinct from prior routes. Further improvements in the final cyclization step can be expected in future studies. We anticipate that our synthetic route will further enable the synthesis of remdesivir and other small-molecule therapeutics that possess nucleobase **2**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03052.

Experimental details and compound characterization data (PDF)

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§R.R.K. and V.T. contributed equally to this study.

Notes

The authors declare no competing financial interest.

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