Catalytic Regioselective Acylation of Unprotected Nucleosides for Quick Access to Covid and Other Nucleoside Prodrugs

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KEYWORDS: pentose functionalization, regioselective, nucleosides, anti-viral drug synthesis, organocatalysis

ABSTRACT: Nucleosides have important therapeutic applications that include anti-viral activities against covid viruses. It is a common strategy to convert one or multiple of the hydroxyl (OH) units in nucleosides to the corresponding ester groups to prepare nucleoside prodrugs for better performance. Since the presence of multiple OH units in nucleosides, current protocols for access to such ester prodrugs involve multiple steps due to installation and removal of protection groups. Here we disclose a catalytic strategy that allows for regio-selective functionalization of a specific OH unit without the need of protecting other OH groups. Key step in our method is an *N*-heterocyclic carbene-catalyzed selective acylation of the pentose unit of nucleosides. We demonstrate that commercially launched covid-19 prodrugs such as Molnupiravir can be prepared in concise routes by using our strategy.

Nucleosides and nucleotides constitute basic components of life molecules that are vital in the genetics and energy supplying in living organisms.[1-8] Nucleoside analogues have played critical roles as effective therapeutics for various diseases (Fig. 1a).[9-13] For example, ribavirin is a classical broad-spectrum anti-viral drug that has been extensively used in the clinical treatment of chronic hepatitis C, influenza, and infections caused by spiratory syncytial virus and herpes simplex virus.[14-16] Adenosine is an endogenous molecule in living cells and has been used to alleviate arrhythmia, angina pectoris, myocardial infarction, and apoplexy sequela.[17-18] Cytarabine is a conventional clinical drug for therapeutic treatment of acute and chronic myeloid leukemia.[19-20] During the outbreak of Covid-19 that causes global crises, nucleotide-based molecules have given great hope in fighting these viruses. Merck and Ridgeback developed Molnupiravir as the first covid-treatment orally administrated drug approved by FDA.[21-23] Gilead Sciences launched Remdesivir that can inhibit a broad spectrum of viruses including Covid-19.[24-25] Numerous other nucleotide-based molecules are under various stages of development to treat Covid-19 and other virus infections.

Nucleosides with free OH groups on the sugar moiety have found commercial success. However, clinical applications of such molecules have frequently been limited by the low bioavailabilities, unsatisfactory pharmacokinetic properties and dangerous side effects resulted from their high doses.[6, 26-34] As a result, most nucleoside-based drugs are commercialized in their corresponding prodrug forms.[35-36] Ester formation *via* acylation on one or multiple of the OH groups of the nucleoside is the most successful strategy in developing effective nucleoside prodrugs, as indicated by the covid drug and drug candidates shown in Figure 1a. Unfortunately, since nucleoside molecules contain multiple OHs and other nucleophilic reactive groups, tedious steps involving installation and removal of protecting groups are required in order to functionalize a specific OH unit.[37-46] For example, putting an acyl group to one of the three OH groups of the ribosyl moiety in ribavirin needs the pre-protection of other OH units, and therefore leads to additional steps and side products (as illustrated in Figure 1b, see SI for details).[37-41, 43-46] Enzymatic methods allow for regioselective access to the 5'-O-acylated ribavirin derivatives without involving protection / deprotection steps, but site-selective functionalization on the other OH groups of ribavirin and its analogues (without pre-protections) has not been realized.[47-51] Overall, although enzymatic methods can give success in a few cases, there is an urgent lack of widely applicable methods (especially chemical methods) for highly regioselective installation of functional groups to specific OH site(s) of nucleosides. To the best of our knowledge, for example, direct method for selective acylation of the C3-OH group (without pre-protection of other OH groups) of ribavirin is not available, although enzymatic and transmetallic catalysis can give several 3'-O-functionalized ribosides other than ribavirin.[52-53]

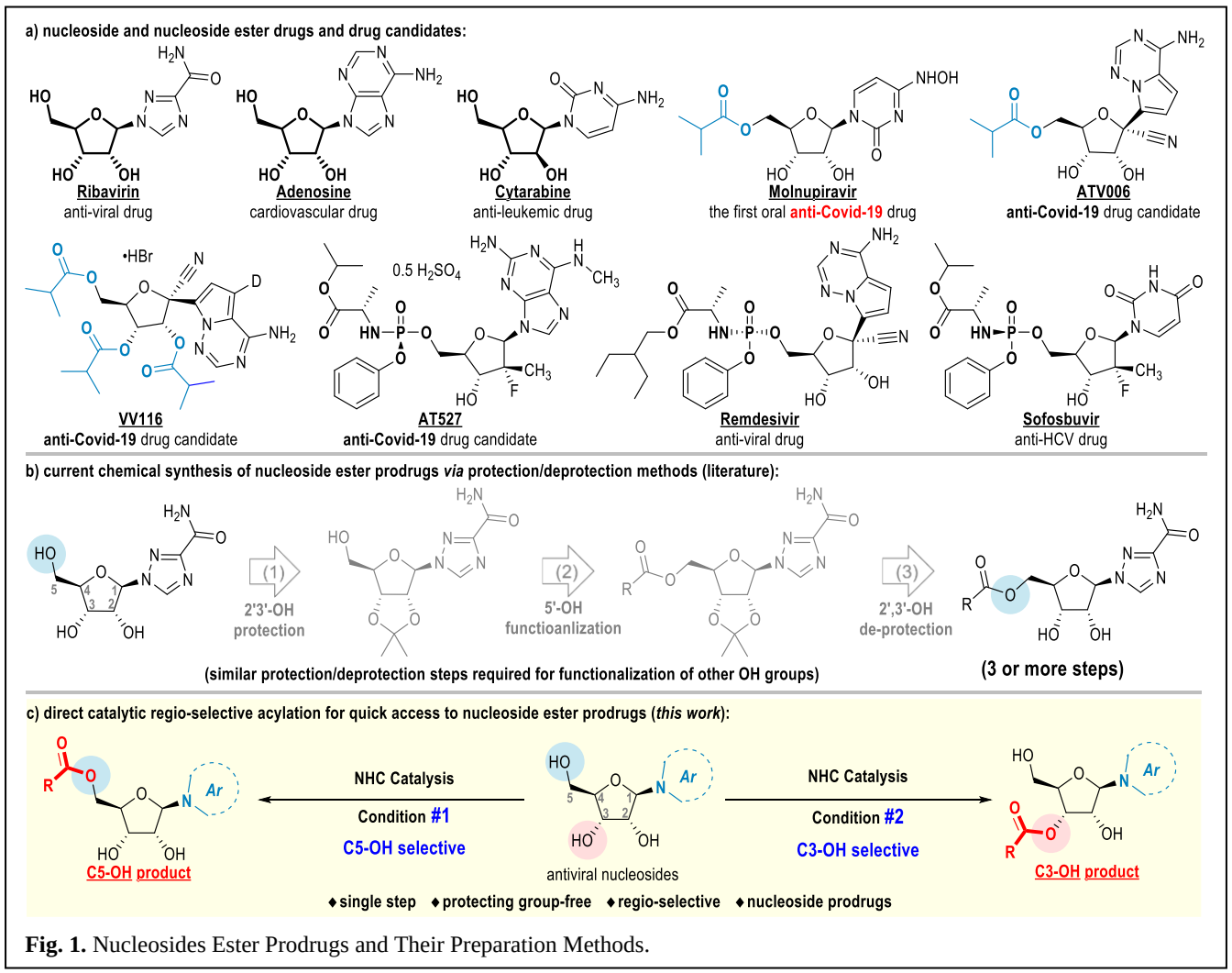


Fig. 1. Nucleosides Ester Prodrugs and Their Preparation Methods.

We are interested in developing chemo-selective strategies for direct modification of complex molecules bearing multiple reactive moieties, such as saccharides. Recently we realized site-selective reactions for monosaccharides with six carbon atoms in the chain (hexoses, such as glucosides and galactosides).[54] Many of the structure features, such as site, stereo-chemistry, neighbouring units, and ring sizes, can dramatically influence the reaction efficiency and site-selectivity for saccharides. Different strategies and protocols need to be developed for different classes of saccharides and their analogues. For example, when comparing simple hexoses and nucleosides bearing pentose moiety, the increased steric hindrance caused by the base moieties of the nucleosides has inevitably added difficulties to the regioselectivities for the nucleoside OH esterification reactions.[55-56] Here we disclose a regioselective acylation method for nucleosides bearing a pentose moiety (Figure 1c). Ribavirin, a broad-spectrum anti-viral molecule, was chosen as a representative nucleoside model molecule. We demonstrated that without any pre-protections (of the OH groups), selective acylation of the C5- or C3- OH group can be effectively realized with arylaldehydes *via* *N*-heterocyclic carbene (NHC) catalysis. Preliminary bioactivity evaluations suggest that the acylated Ribavirin showed moderate improvement on anti-viral activities against TMV and PVY. Our selective acylation method also allows for concise access to other nucleoside prodrugs and drug candidates such as Molnupiravir and **ATV006** that are being used to treat covid infections.

Ribavirin (**1**)[14-16] was chosen as a model substrate to develop our selective acylation method. Aldehyde (e.g., benzaldehyde) was used as an acylation agent under an oxidative condition (e.g., **DQ** as the oxidant) (Fig. 2). We first studied the effect of NHC catalysts without using additives or co-catalysts. NHC pre-catalysts bearing different substitution patterns were initially tested for the acylation reaction with K_2CO_3 used as the base in DMF under 30 °C (Fig. 2a). All the 3 mono-benzoate products were observed from the NHC-catalyzed ribavirin acylation reactions, but the regioselectivities of these transformations showed close relationship to both the molecular framework and the *N*-substituent of the NHC catalyst. Although the 3'-O-benzoate product **3** dominated in all the acylation reactions, the NHC catalysts bearing an electron-deficient *N*-pentafluorophenyl group showed relatively better preference to the 5'-O-benzoate product **2** (e.g., **C** and **F**).

Boric acids have been disclosed as promising reagents for effective protection of the 2',3'-OH of ribavirin through transient covalent and / or non-covalent interactions.[57-58] Therefore, we tested various boronic acids as additives in

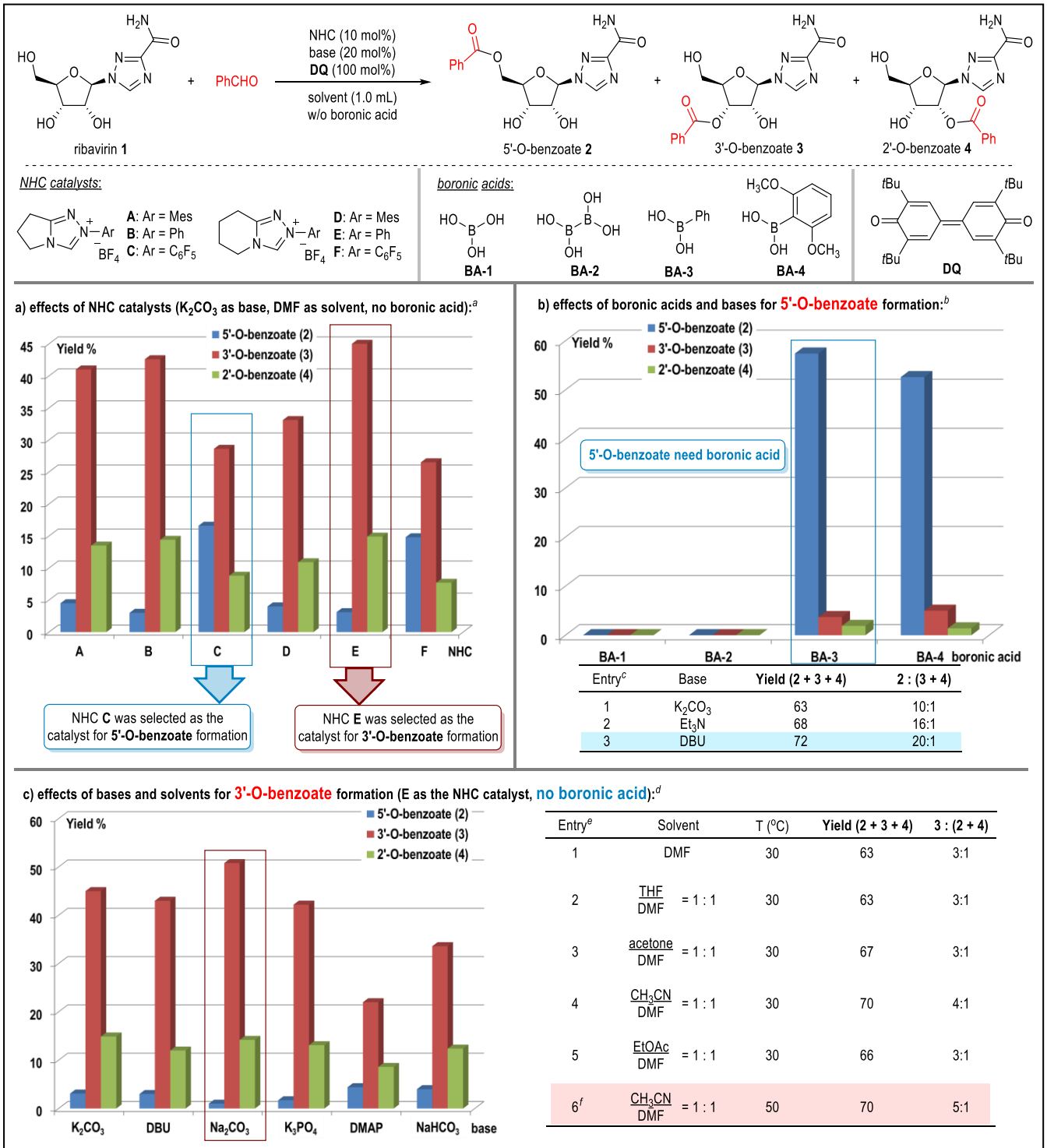


Fig. 2 Condition Optimization for the Regioselective Formation of the Ribavirin 5'- and 3'-O-Benzoates. [a] Unless otherwise specified, the reactions were carried using **1** (0.10 mmol), PhCHO (0.20 mmol), **NHC** (0.01 mmol), Base (0.02 mmol), **DQ** (0.10 mmol) and DMF (1.0 mL) at 30 °C under N_2 for 12 h. [b] with **C** as the NHC catalyst, K_2CO_3 as the base, and boronic acid (0.10 mmol). [c] with **BA-3** as the boronic acid. [d] with **E** as the NHC catalyst. [e] with Na_2CO_3 as the base, mix DMF and other solvents as solvent. [f] 50 °C for 2h.

cooperation with the NHC pre-catalyst **C** to search for promising conditions for the regioselective 5'-OH acylation reactions (Fig. 2b). The boronic acids **BA-1** and **BA-2** completely inhibited the NHC-catalyzed acylation reaction, which might be resulted from their strong acidities. To our great delight, both of the boronic acids **BA-3** and **BA-4** provided excellent regioselectivities to the 5'-OH acylation process, with the 5'-O-benzoate product **2** obtained in 63% yield with 10:1 regioselectivity from the NHC **C** / **BA-3** co-catalytic system (Fig. 2b, entry 1). Switching the base K_2CO_3 into organic bases led to additional improvements on both the product yields and regioselectivities of the 5'-O-benzoate product **2** (entries 2 to 3).

Finally, the 5'-O-benzoate product **2** could be isolated in 72% yield with an excellent 20:1 regioselectivity (entry 3).

Since all the NHC pre-catalysts we tested showed preference for the formation of the 3'-O-benzoate product **3** without boronic acid additives (Fig. 2a), we are also interested in the improvement on both the product yield and regioselectivity for the 3'-OH acylation reaction through adjusting the bases and solvents for this transformation (Fig. 2c). The NHC pre-catalyst **E** can give a higher yield and regioselectivity than the other NHC pre-catalysts we tested for the 3'-OH acylation reaction. Therefore, we examined the effects of bases with **E** used as the reaction catalyst (Fig. 2c). Both of the product yield and regioselectivity of the 3'-O-benzoate product **3** can be increased when switching the base from K_2CO_3 to Na_2CO_3. The reaction outcome could be further improved when a mixed solvent was used instead of the pure solvent of DMF. For instance, the product mixture could be isolated in 70% yield and 4:1 regioselective ratio with the 3'-O-benzoate **3** formed as the major product (Fig. 2c, entry 4). The regioselective ratio could be improved to 5:1 with retention of the product yield when the reaction was carried out at a higher temperature (entry 6).

Having identified the respectively optimized reaction conditions for the formation of the 5'-O-benzoate and 3'-O-benzoate products from the ribavirin **1**, we then sought to extend the reaction scope using both carbaldehyde and nucleoside substrates with different substitution patterns (Tables 1 and 2).

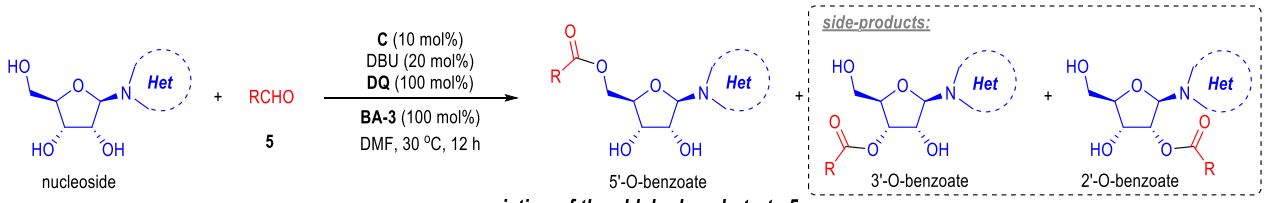
The 5'-OH group of the ribavirin **1** can be selectively acylated by the benzaldehyde under the catalysis of the NHC catalyst **C** in the presence of the boronic acid **BA-3** (Fig. 2b, entry 3). Substituents with various electronic properties are well tolerated at each position of the benzene ring of the benzaldehyde substrate, with the corresponding ribavirin 5'-O-benzoate products afforded in moderate to good yields with excellent regioselectivities (Table 1, **6** to **20**). The benzaldehyde substrate can be switched to the heteroaromatic aldehydes to give the ribavirin 5'-O-benzoate products **21**,**22** with moderate yields and regioselectivities. Cinnamaldehyde is also a suitable acylation reagent for the regioselective ribavirin functionalization process, although the product yield and regioselectivity were slightly dropped (**23**). Only trace amounts of 5'-OH acylated products can be generated when using alkyl aldehydes. To our great delight, a variety of structural fragments with proven biological activities and medicinal applications can be efficiently introduced onto the 5'-OH group of the ribavirin molecule through this NHC / boronic acid cooperative catalytic process. For instance, the isoniazid containing an isonicotinic acid structure has been extensively used for clinical treatment of tuberculosis. The ribavirin 5'-O-isonicotinat (**24**) can be afforded in 68% yield with 16:1 regioselective ratio from this approach. Similarly, the ribavirin 5'-O-acetate containing the anti-plant virus vanillin fragment (**25**), the anti-arthrolithiasis probenecid fragment (**26**), and the anti-inflammatory tolfenamic acid fragment (**27**) can be afforded in moderate to good yields with excellent regioselectivities.

Nucleosides bearing different basic groups are also amenable in the regioselective 5'-OH acylation reaction under the same reaction condition. For example, the adenosine and 8-bromoadenosine can be acylated at the 5'-OH position by the benzaldehyde to give the 5'-O-benzoate products **28** and **29** in moderate yields as almost single regio-isomers. The widely used food additive and drug precursor guanosine can react with the benzaldehyde through this approach and afford the 5'-O-benzoate **30** in 67% yield with 15:1 regioselective ratio. The bioactive cytidine, benzoylcytidine and 5-methyluridine can all give the related 5'-O-benzoate products with excellent regioselectivities, although the reaction yields are relatively lower in these cases (**31** to **33**).

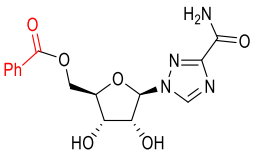
Meanwhile, the 3'-OH group of ribavirin **1** can be selectively acylated by various carbaldehyde substrates with the promotion of the NHC catalyst **E** (Fig. 2c, entry 6). Both electron-donating and electron-withdrawing substituents are well tolerated on the *p*- and *m*-positions of the phenyl ring of the benzaldehyde substrate and lead to the 3'-O-benzoate products in moderate to good yields and regioselectivities (Table 1, **34** to **43**). Both of the electronic properties and the steric hindrance of the *o*-substituents of the benzaldehyde substrates possess significant impacts on the reaction yields and regioselectivities of the ribavirin 3'-OH functionalization process (**44** to **50**). Benzaldehydes bearing either *o*-electron-donating groups (e.g., **44** to **45**) or small-sized electron-withdrawing groups (e.g., **46** and **50**) generally give the target products in moderate to good yields with moderate regioselectivities. In contrast, both of the reaction yield and the regioselectivity increase dramatically when steric bulky and electron-withdrawing substituents are installed on the *o*-positions of the benzaldehyde substrates (e.g., **47** to **49**). Gratifyingly, product **48** bearing a 2-bromo group on the phenyl ring can be afforded in 77% yield with an excellent 10:1 regioselective ratio under the current catalytic condition. An excellent regioselectivity can also be obtained when the furfural is used as the acylating reagent, although the product yield is a little bit lower (**51**). Switching the phenyl ring of the benzaldehyde substrate into a 2-thiophenyl, 2-naphthyl or a cinnamyl group can lead to the formation of the 3'-O-benzoate products in similar yields and regioselectivities (**52** to **54**). The use of alkyl aldehydes gave trace amounts of 3'-OH acylated products. Carbaldehydes derived from natural products or bioactive molecules can also be selectively introduced onto the 3'-OH group of the ribavirin **1**, although the regioselectivities in these cases are not satisfactory at this stage (e.g., **55** to **58**).

The 3'-OH groups of the nucleosides other than ribavirin can be selectively acylated by the benzaldehyde under the same catalytic condition. For instance, the 3'-O-benzoate product **59** can be obtained from the 5-methyluridine in a good yield with a moderate regioselectivity. A significant increase in regioselectivity can be obtained when adenosine is used as the reaction substrate, although the yield of product **60** is only moderate. To our delight, the 3'-OH group of the 8-bromoadenosine can be efficiently acylated under the current reaction condition and give the target product **61** in 82% yield with an excellent 8:1 regioselective ratio. It is also worth noting that the use of 2'-deoxyadenosine as the substrate showed poor regioselectivities between the 3'- and 5'-benzoae products under both reaction conditions (**62**, **63**). This is probably due to the severely decreased binding affinities to either the boronic acid additive or the NHC catalyst caused by the lack of the 2'-OH in the pentose structure.

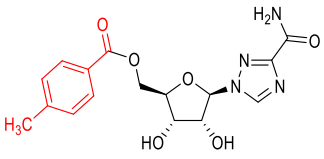
Table 1. Substrate Scope for the 5'-OH Acylation Reaction of Nucleosides[a]



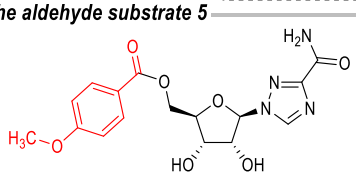
variation of the aldehyde substrate 5



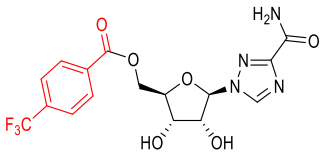
2, 72%, 20:1 r.r.



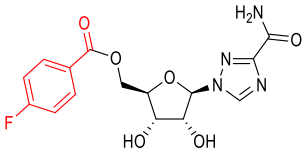
6, 68%, 19:1 r.r.



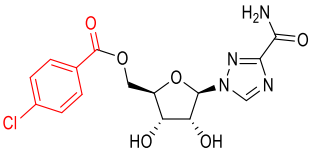
7, 72%, 19:1 r.r.



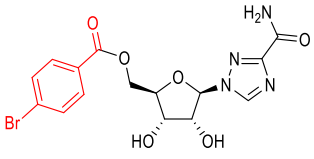
8, 61%, > 20:1 r.r.



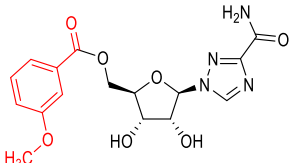
9, 68%, 13:1 r.r.



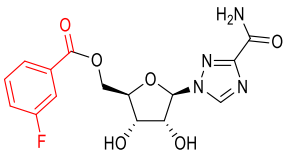
10, 69%, 16:1 r.r.



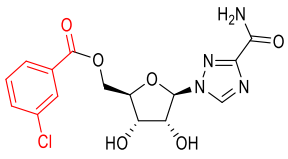
11, 68%, 17:1 r.r.



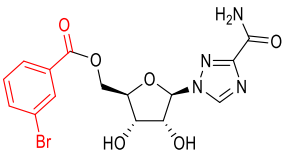
12, 68%, 11:1 r.r.



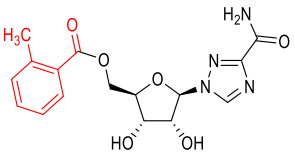
13, 71%, 20:1 r.r.



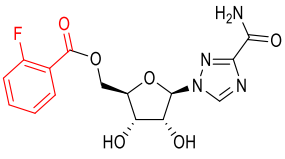
14, 64%, > 20:1 r.r.



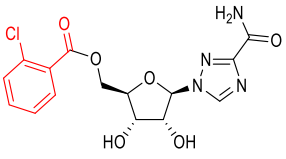
15, 62%, 20:1 r.r.



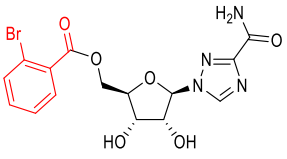
16, 60%, 20:1 r.r.



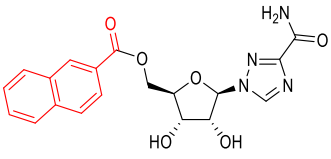
17, 67%, > 20:1 r.r.



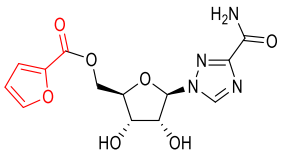
18, 67%, > 20:1 r.r.



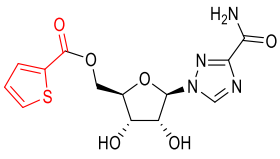
19, 57%, 20:1 r.r.



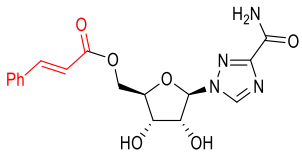
20, 78%, 15:1 r.r.



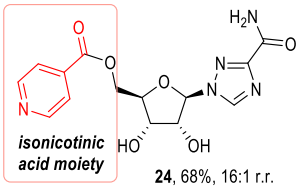
21, 61%, 8:1 r.r.



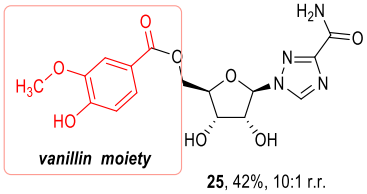
22, 63%, 17:1 r.r.



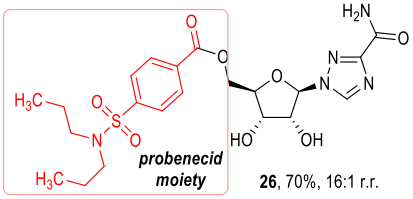
23, 62%, 12:1 r.r.



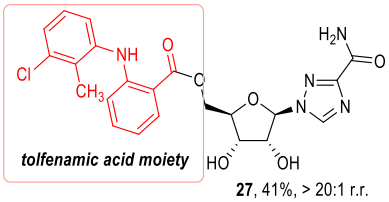
24, 68%, 16:1 r.r.



25, 42%, 10:1 r.r.

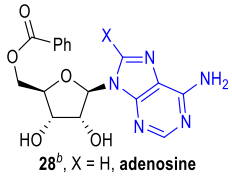


26, 70%, 16:1 r.r.

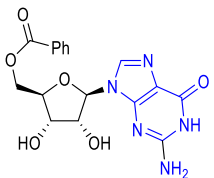


27, 41%, > 20:1 r.r.

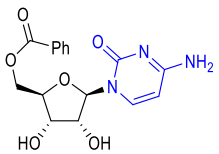
variation of the nucleoside substrate



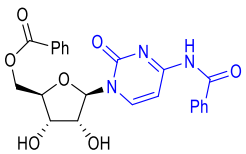
28[b], X = H, **adenosine**
65%, > 20:1 r.r.
29[b], X = Br, **8-bromoadenosine**
58%, > 20:1 r.r.



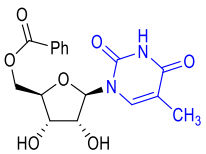
30[b], **guanosine**
67%, 15:1 r.r.



31[b], **cytidine**
54%, 19:1 r.r.



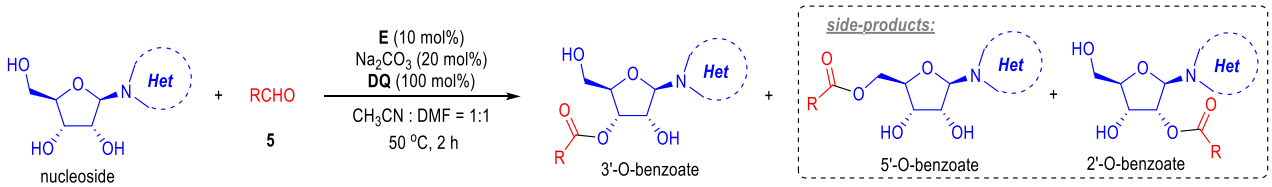
32[b], **benzoylcytidine**
46%, > 20:1 r.r.



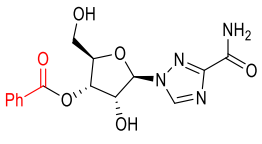
33[b], **5-methyluridine**
51%, > 20:1 r.r.

[a] Unless otherwise specified, the reactions were carried using nucleoside (0.10 mmol), **5** (0.20 mmol), **C** (0.01 mmol), DBU (0.02 mmol), **DQ** (0.10 mmol), **BA-3** (0.10 mmol) and DMF (1.0 mL) at 30 °C under N_2 for 12 h. [b] The reaction was carried out for 18 h under otherwise the same conditions. The isolated yield of 5'-O-benzoate+3'-O-benzoate+2'-O-benzoate. The ratio of 5'-O-benzoate and other benzoate. r.r. = regioselective ratio.

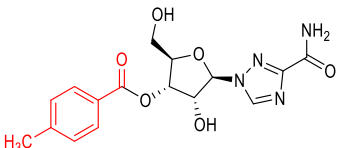
Table 2. Substrate Scope for the 3'-OH Acylation Reaction of Nucleosides[a]



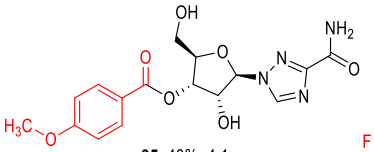
variation of the aldehyde substrate 5



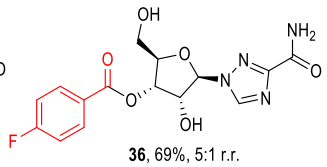
3, 70%, 5:1 r.r.



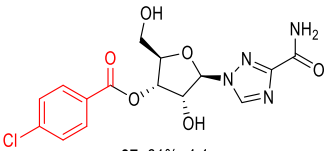
34, 66%, 4:1 r.r.



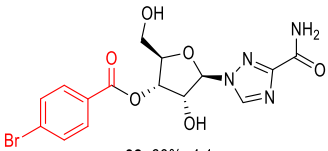
35, 40%, 4:1 r.r.



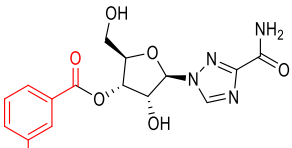
36, 69%, 5:1 r.r.



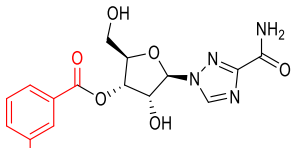
37, 61%, 4:1 r.r.



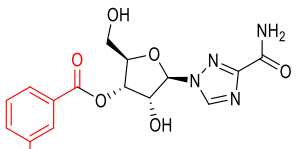
38, 60%, 4:1 r.r.



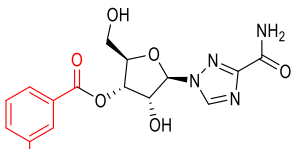
39, 71%, 4:1 r.r.



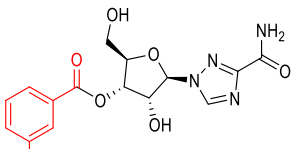
40, 70%, 4:1 r.r.



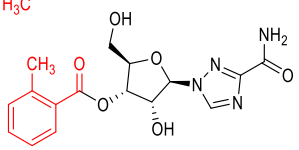
41, 75%, 5:1 r.r.



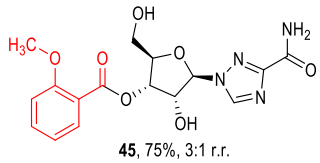
42, 66%, 5:1 r.r.



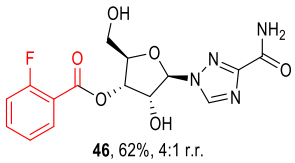
43, 63%, 5:1 r.r.



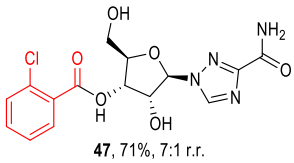
44, 46%, 4:1 r.r.



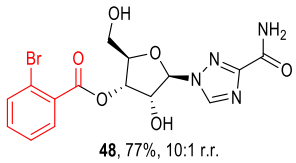
45, 75%, 3:1 r.r.



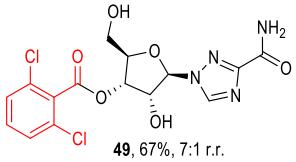
46, 62%, 4:1 r.r.



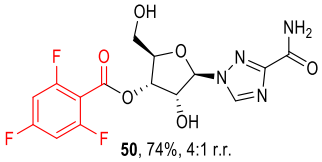
47, 71%, 7:1 r.r.



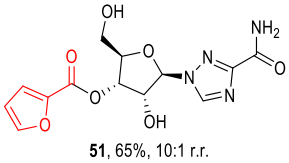
48, 77%, 10:1 r.r.



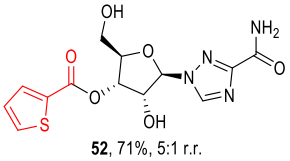
49, 67%, 7:1 r.r.



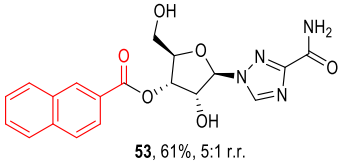
50, 74%, 4:1 r.r.



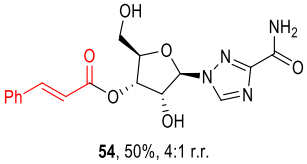
51, 65%, 10:1 r.r.



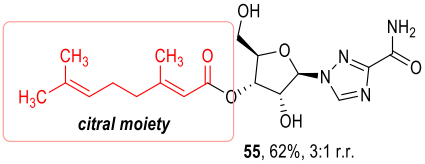
52, 71%, 5:1 r.r.



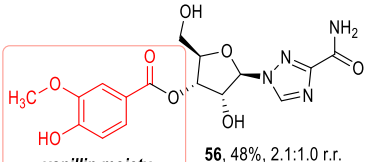
53, 61%, 5:1 r.r.



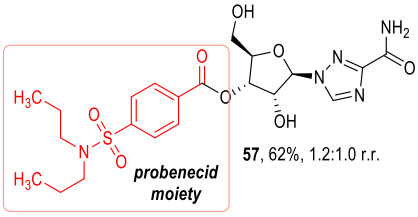
54, 50%, 4:1 r.r.



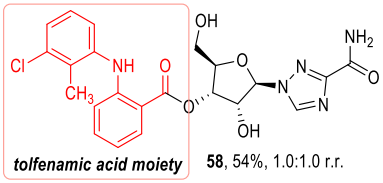
55, 62%, 3:1 r.r.



56, 48%, 2.1:1.0 r.r.

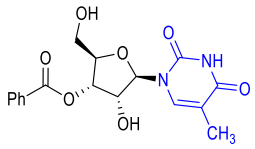


57, 62%, 1.2:1.0 r.r.

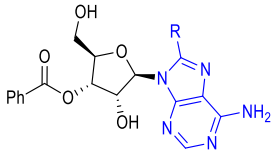


58, 54%, 1.0:1.0 r.r.

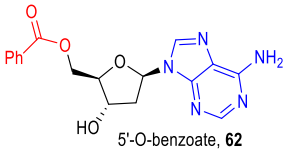
variation of the nucleoside substrate



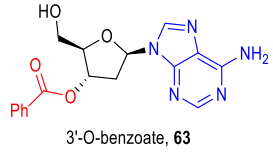
59[b], **5-methyluridine**
78%, 3:1 r.r.



60[b], R = H, **adenosine**, 44%, 8:1 r.r.
61[b], R = Br, **8-bromo adenosine**, 82%, 8:1 r.r.



5'-O-benzoate, **62**



3'-O-benzoate, **63**

62 (40% yield) : **63** (25% yield) = 1.6:1.0[c]
62 (37% yield) : **63** (29% yield) = 1.3:1.0[d]

[a] Unless otherwise specified, the reactions were carried using nucleoside (0.10 mmol), **5** (0.20 mmol), **E** (0.01 mmol), Na_2CO_3 (0.02 mmol), **DQ** (0.10 mmol) and CH_3CN:DMF=1:1 (1.0 mL) at 50 °C under N_2 for 2 h. [b] The reaction was carried out for 3 h under otherwise the same conditions. The isolated yield of 5'-O-benzoate + 3'-O-benzoate + 2'-O-benzoate. The ratio of 3'-O-benzoate and other benzoate. r.r. = regioselective ratio. [c] Conditions as stated in Figure 2b, entry 3, 18 h. [d] Conditions as stated in Figure 2c, entry 6, 3 h.

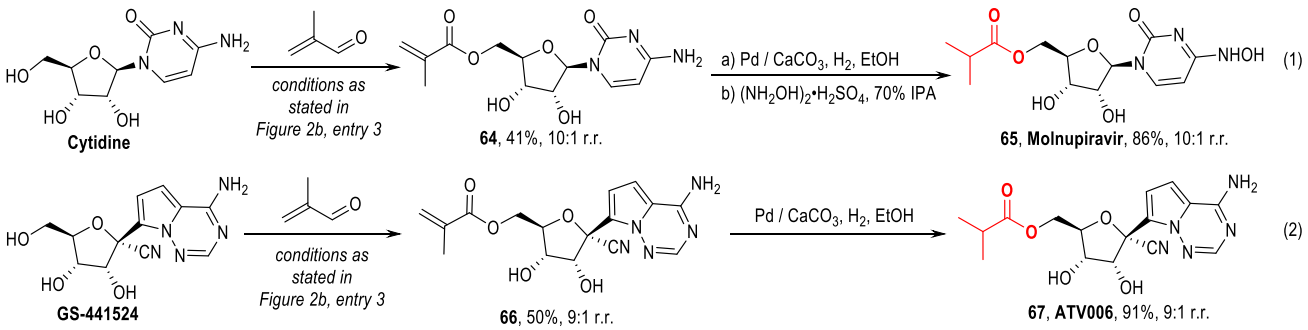


Fig. 3. Concise Access to Covid-19 Drugs and Drug Candidates.

Table 3. Inhibitive Activities of the mono-Esterified Nucleosides against TMV and PVY *in vivo*[a]

Compounds	TMV inhibition rate (%)		PVY inhibition rate (%)	
	Curative activity	Protective activity	Curative activity	Protective activity
9	**60.51 ± 3.94**	**64.61 ± 1.55**	**60.79 ± 4.83**	**58.79 ± 4.53**
36	51.63 ± 4.62	58.77 ± 3.29	59.17 ± 2.71	54.57 ± 1.74
17	45.75 ± 4.94	49.58 ± 4.30	45.89 ± 4.48	41.54 ± 5.72
46	**62.11 ± 5.23**	**66.81 ± 2.90**	**62.99 ± 4.53**	**48.21 ± 1.63**
28	**59.12 ± 4.94**	**65.56 ± 4.38**	**59.34 ± 4.29**	**48.76 ± 3.79**
60	52.95 ± 4.49	55.88 ± 4.82	60.40 ± 3.03	49.75 ± 4.12
29	**60.46 ± 4.10**	**66.27 ± 2.34**	**60.33 ± 4.21**	**56.12 ± 1.37**
61	56.95 ± 3.59	57.55 ± 3.07	55.92 ± 4.22	53.15 ± 4.80
Ribavirin	51.65 ± 3.43	54.06 ± 3.03	52.74 ± 3.04	48.19 ± 3.79
Ningnanmycin	56.56 ± 3.24	64.39 ± 2.20	60.90 ± 3.20	57.02 ± 4.30

[a]All data were average data of three replicates, those compounds at 500 μg/mL.

It is exciting to find that several commercial human drugs for anti-Covid-19 therapies can be accessed with the currently developed regioselective nucleoside mono-esterification reactions (Fig. 3). For instance, the oral anti-Covid-19 drug Molnupiravir[59-64] developed by Merck and Ridgeback can be efficiently obtained *via* a 2-step process from the unprotected nucleoside Cytidine in a total yield of 35% (Fig. 3, eq. 1). The NHC / boronic acid co-catalyzed mono-esterification on the Cytidine 5'-OH group can provide the key intermediate **64** with an excellent regioselectivity. The final product of the Molnupiravir **65** can be facilely achieved from **64** through a cascade reduction / substitution process in a single-pot operation. In contrast, the reported synthetic approach for Molnupiravir gives only a total yield of 17% through over five steps from uridine. Similarly, the oral anti-Covid-19 drug candidate **ATV006**[65] can also be quickly accessed *via* a 2-step process from the commercially available intermediate **GS-441524** (Fig. 3, eq. 2). The mono-5'-OH esterification of the **GS-441524** can be successfully achieved through our strategy and the key intermediate **66** was given with excellent regioselectivity. The final product **ATV006** can then be generated from **66** through a facile reduction in an excellent yield with retention of the regioselectivity ratio.

Since most of the nucleoside reaction substrates we tested in the current study are excellent anti-viral lead structures in both medicinal and pesticide development, we were extremely interested in the anti-viral activities of the mono-esterified products obtained through our catalytic approach. Our laboratory has been committed to the exploration and development of new and efficient anti-viral drugs for plant protection. Therefore, two of the most significant plant viruses, tobacco mosaic virus (TMV) and potato virus Y (PVY), were selected as the targets for the anti-viral evaluations of the nucleoside-derived mono-ester products (Table 3).[66-69] It is pleasingly to find that many of the mono-esterified nucleoside molecules exhibited increased anti-viral activities against either TMV or PVY (For complete anti-viral evaluation results, see Supporting Information). Among the active anti-viral structures, 4 pairs of the mono-esterified nucleoside products exhibited increased and regioselective-dependent anti-viral activities against both TMV and PVY. For example, the 5'-O-esters of **9**, **28** and **29** exhibited increased anti-viral activities against TMV and PVY, which were much better than their regio-isomers of **36**, **60**, **61** and the positive control of Ribavirin. The 3'-O-ester of **46** showed better anti-viral activities than its 5'-O-ester isomer **17** and Ribavirin, which was comparable to the commercial anti-viral pesticide of Ningnanmycin. These nucleoside-derived mono-esters are valuable in the future development of anti-viral pesticides in our laboratory.

In summary, we have developed a new strategy for concise chemical synthesis of nucleoside esters *via* catalytic regio-selective acylation of the pentose unit of nucleosides. Through the influence of NHC catalysts (and in the presence of boronic acids in certain cases), the 5'- or 3'-OH group of nucleosides can be selectively acylated with arylaldehydes. No protection and de-protection steps are required during all the operations. Our method allows for concise access to many nucleoside ester prodrugs (and drug candidates) with profound impact on global health issues such as covid-19 pandemic. We expect our studies to encourage further explorations on selective functionalization/edition of mother bioactive molecules bearing multiple OH units displaced on various scaffolds. Broad bioactivity evaluations of nucleoside ester prodrugs and their analogues are also in progress in our laboratories.

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Notes

The authors declare no competing financial interests.

ASSOCIATED CONTENT

Supporting Information

General information; Traditional approaches for selective mono-functionalization of nucleosides; Determine the regio-isomers of acylated nucleosides; Condition optimization; General procedure for the catalytic reactions; The reaction results of 2'-deoxyadenosine in the catalytic systems; Synthesis of anti-Covid-19 drug Molnupiravir; Synthesis of anti-Covid-19 candidate drug ATV006; Antiviral activity evaluation; Characterization of substrates and products; ^{1}H NMR, ^{13}C NMR, ^{19}F NMR spectra

ACKNOWLEDGMENT

We acknowledge funding supports from the National Natural Science Foundation of China (21732002, 21961006, 32172459, 22061007, 22071036). Frontiers Science Center for Asymmetric Synthesis and Medicinal Molecules, Department of Education, Guizhou Province [Qianjiaohe KY number (2020)004]. The Science and Technology Department of Guizhou Province (Qiankehejichu-ZK[2021]Key033). Program of Introducing Talents of Discipline to Universities of China (111 Program, D20023) at Guizhou University. Singapore National Research Foundation under its NRF Investigatorship (NRF-NRFI2016-06) and Competitive Research Program (NRF-CRP22-2019-0002); the Singapore Ministry of Education under its MOE AcRF Tier 1 Award (RG7/20, RG5/19), MOE AcRF Tier 2 Award (MOE2019-T2-2-117), and MOE AcRF Tier 3 Award (MOE2018-T3-1-003); Nanyang Technological University.

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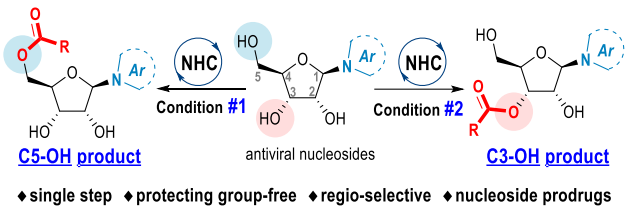

Catalytic Regioselective Acylation of Unprotected Nucleosides for Quick Access to Covid and Other Nucleoside Prodrugs