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Technology Note

Synthesis of C6-Substituted Purine Nucleoside Analogues via Late-Stage Photoredox/Nickel Dual Catalytic Cross-Coupling

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ABSTRACT: Nucleoside analogues have been and continue to be extremely important compounds in drug discovery. Despite the significant effort dedicated to their synthesis, medicinal chemistry campaigns around these structures are often hampered by synthetic challenges. We describe a strategy for the functionalization of purine nucleosides via photoredox and nickel-catalyzed sp^2−sp^3 cross-coupling. The conditions described herein allow for coupling of unprotected nucleosides with readily available alkyl bromides, providing opportunities for their application to parallel medicinal chemistry.

KEYWORDS: *Purine nucleosides, photoredox, cross-electrophile, late-stage diversification*

As the basic building blocks of nucleic acids, nucleosides are of fundamental importance to biological systems and are recognized as privileged structures in the search for new drugs. Purine nucleoside analogues represent an important subset of this class and have found applications in multiple therapeutic areas including infectious diseases, oncology, and immunology[1] (e.g., aciclovir,[2] fludarabine,[3] and cladribine,[4] respectively; see Figure 1A). Recently, interest in nucleoside and nucleotide therapeutics has been reinvigorated by the urgent need for treatments to combat SARS-CoV-2, against which several of these compounds have shown promising antiviral activity.[5] This fact underscores the importance of efficient methods to rapidly synthesize new nucleoside drug candidates to aid the scientific community not only in battling the current pandemic but also in preparing for the emergence of new viral diseases in the future. Despite decades of drug discovery research dedicated to the study of these important compounds, medicinal chemistry efforts toward such structures are often hampered by synthetic challenges. Indeed, lengthy syntheses and the limited number of strategies for incorporation of novel functionality on either the sugar backbone or the nucleobase can impede the exploration of structure−activity relationships (SAR) and limit the scope of compounds that can be prepared for testing.[6]

New synthetic methods that allow for the direct installation of diverse functionality on nucleoside derivatives should decrease design−make−test cycle time and expand the scope of chemical space available to medicinal chemists. With this logic in mind, we focused our attention on the functionalization of the purine nucleobase. One of the transformations used most often for this purpose is nucleophilic aromatic

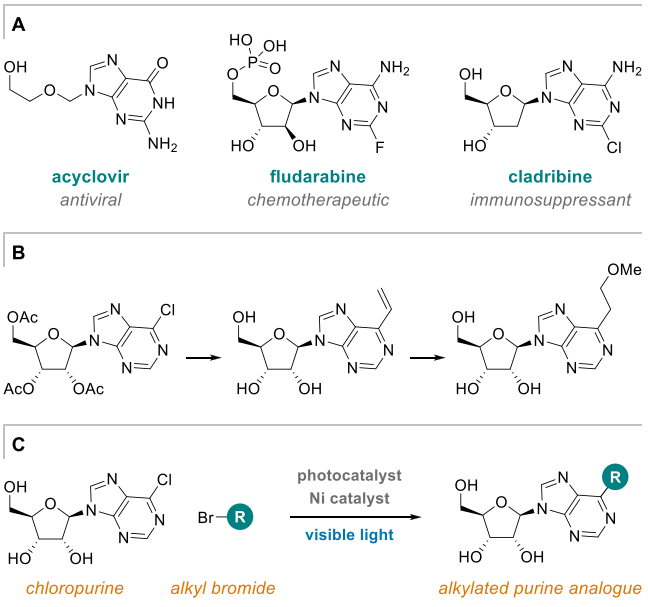

Figure 1. (A) Purine nucleoside/nucleotide analogues as pharmaceuticals. (B) Installation of alkyl substituents via multistep synthesis.[13] (C) This work: cross-coupling for direct installation of alkyl groups.

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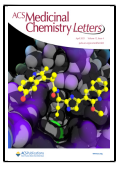


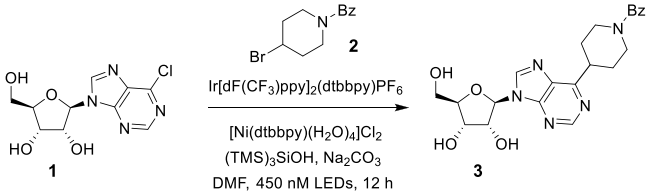
substitution, which can be effective for installation of heteroatom substituents but is not broadly useful for the formation of C−C bonds.[7,8] Advances in sp^2−sp^2 cross-coupling have facilitated the installation of aryl/heteroaryl groups,[9,10] but the installation of alkyl functionality remains challenging. Common strategies rely on the use of reactive nucleophiles that may limit functional group compatibility and reaction scope[11,12] or require multiple-step sequences to convert alkene functionality installed via sp^2−sp^2 cross-coupling into an alkyl group[13] (Figure 1B). More recently, radical-based approaches have been applied to the functionalization of purine nucleosides via the Minisci reaction.[14] In these examples, carboxylic acids serve as radical precursors for C−H alkylation, with regioselectivity governed by the electronics and substitution pattern of the heterocycle substrate.

As an alternative, we envisioned sp^2−sp^3 cross-coupling of halogenated nucleosides, which would enable direct and regiospecific installation of saturated functionality in a single step. By incorporating alkyl substituents, this transformation would provide access to novel products with increased sp^3 character, which has been correlated with higher success rates from drug discovery through approval.[15] Within this context, we felt that cross-electrophile coupling would be a particularly attractive strategy, as it would offer the advantage of drawing from a large pool of commercially building blocks such as alkyl bromides, resulting in increased structural diversity of the newly accessible products. Methods for cross-coupling of aryl halides and alkyl halides have been published using nickel,[16] palladium,[17] and cobalt[18] catalysts in conjunction with reducing metals such as zinc or manganese. In addition, photoredox catalysis and electrochemistry have recently been combined with nickel catalysis to enable aryl−alkyl cross-electrophile couplings in the absence of stoichiometric metal reductants.[19,20]

With our specific goals in mind, we chose to apply nickel/photoredox dual catalysis to the direct cross-coupling of 6-chloropurine with alkyl bromides (Figure 1C). Because of the mildness of the reaction conditions generally employed in visible light-mediated dual catalytic cross-couplings, we expected that this method would be suitable for coupling at a late stage and should thereby circumvent the need for challenging multistep syntheses to be carried out in parallel.

We began our investigations by exploring reaction conditions for sp^2−sp^3 coupling of nucleoside **1** with alkyl bromide **2** to provide the alkylated derivative **3**. We took our initial inspiration from the conditions described in the original report of photoredox and nickel-catalyzed cross-electrophile coupling from Zhang et al.[19a] As a light source, we chose an integrated photoreactor developed to improve ease of use as well as consistency of illumination.[21,22] After modifying a number of parameters, we were delighted to find conditions under which the fully unprotected nucleoside **1** could serve as a suitable substrate for cross-coupling (Table 1). This result was particularly consequential in light of our goal of designing a strategy amenable to late-stage diversification. Because protection of the nucleoside is not required, we envision that coupling could be carried out as the very last step of a synthesis using readily available alkyl bromides. As such, a single batch of the desired nucleoside core could be prepared and then broadly diversified in a single step without the need for deprotection of the resulting product library, which might comprise dozens or even hundreds of compounds.

Table 1. Reaction Conditions for Cross-Electrophile Coupling



reaction conditions[a]	yield of 3[b]
as above	53%
4CzIPN as photocatalyst	47%
$(TMS)_3SiH$ as reductant	38%
LiOH as base	4%
2,6-lutidine as base	22%
DME as solvent	13%
MeCN as solvent	8%
no nickel catalyst	3%

[a]Standard conditions: 0.07 mmol 1, 2 equiv of **2**, 2 mol % photocatalyst, 10 mol % Ni catalyst, 1 equiv of silanol, 3 equiv of base, 0.10 M. [b]Determined by ^{1}HNMR using mesitylene as internal standard.

Our studies revealed DMF as the optimal solvent and sodium carbonate as the base of choice. For convenience and consistency of the ligand-to-metal-ratio, we employed the preligated complex $[Ni(dtbbpy)(H_2O)_4]Cl_2$ reported by Molander and co-workers as our source of nickel.[23] In addition, while we expected that a large excess of the alkyl halide might provide improved yields, we chose to limit the loading of this coupling partner to 2 equiv in anticipation of cases where the reagent might be custom-synthesized and quite precious. Using the ubiquitous photocatalyst $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ and tris(trimethylsilyl)silane, a promising 38% NMR yield of the desired product was observed. During the course of the reaction, deleterious debromination side products resulting from the reduction of **2** were often observed. Replacing tris(trimethylsilyl)silane with the increasingly common reagent tris(trimethylsilyl)silanol[24] suppressed this unproductive pathway and increased the observed assay yield to 53%. We were also pleased to find that the organic photocatalyst 4CzIPN provided comparable yields to the optimal iridium catalyst. However, subsequent time studies indicated that the rate of reaction using 4CzIPN was significantly lower, and we therefore chose to proceed with $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ for further investigation.

During the course of our studies, we recognized the potential for this reaction to proceed through a homolytic aromatic substitution mechanism instead of the dual-catalytic cross-coupling pathway originally proposed by MacMillan and co-workers,[19a] given that direct radical substitution reactions are known for related heterocyclic substrates.[25] The dual-catalytic mechanism would require nickel to undergo oxidative addition and reductive elimination steps in order to effect the desired coupling. By contrast, homolytic aromatic substitution would proceed through direct addition of an alkyl radical to the aryl chloride, followed by single-electron reduction and elimination steps to provide the desired product. No nickel catalyst would be required for the latter reaction pathway to proceed. In order to test whether a direct-addition mechanism might be operative, we performed a reaction under the newly defined standard reaction conditions, but omitted the nickel

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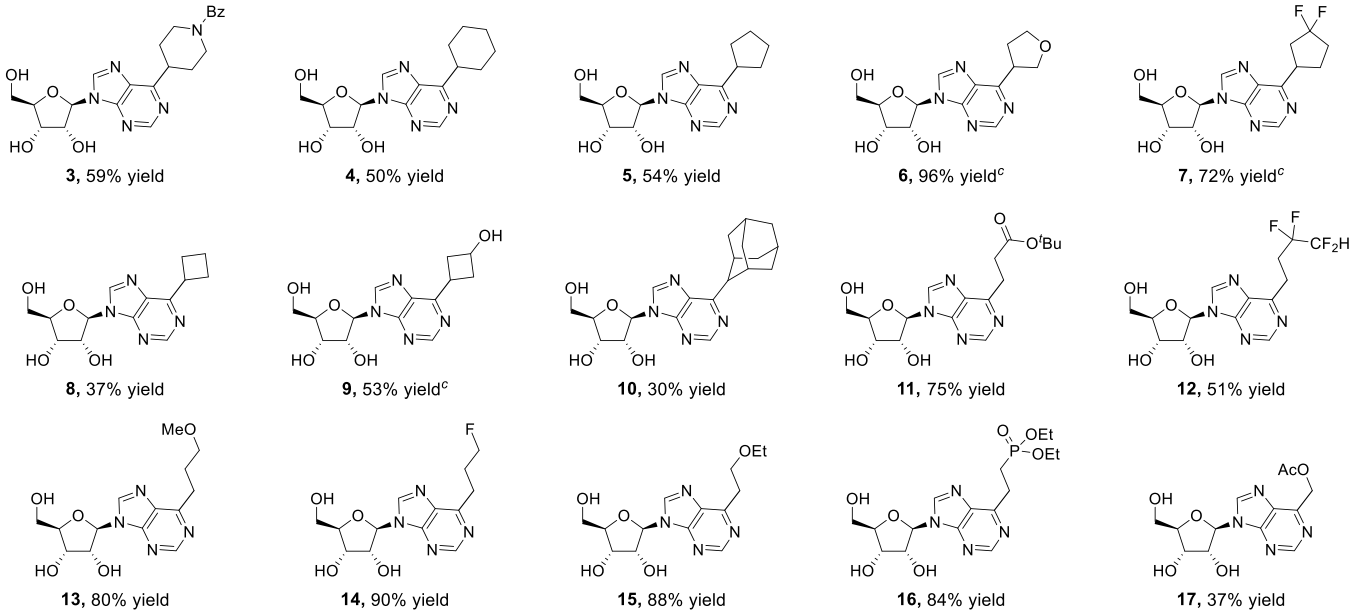
Table 2. Alkyl Bromide Scope in Cross-Electrophile Coupling of Chloropurines[a,b]



[a]Standard conditions: 0.17 mmol **1**, 2 equiv of alkyl bromide, 2 mol % $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$, 10 mol % $[Ni(dtbbpy)(H_2O)_4]Cl_2$, 1 equiv of $(TMS)_3SiOH$, 3 equiv of Na_2CO_3, DMF (0.10 M). [b]Isolated yields. [c]For alkyl bromides with the potential to form new diastereomers after coupling, one major diastereomer was isolated, sometimes containing a small amount of the minor diastereomer.

catalyst. Under these conditions, trace amounts of product were observed (3% NMR yield), suggesting that a direct homolytic aromatic substitution mechanism is unlikely to contribute significantly to the overall reaction pathway.

Having determined useful reaction conditions, we began to explore the scope of nucleoside functionalization with respect to the alkyl coupling partner (Table 2). Upon isolation, we were pleased to find that the model substrate **2** coupled as expected based on our screening experiments, providing 59% yield of the desired product **3**. Encouraged by this result, we tested a number of other secondary alkyl bromides. Simple cycloalkanes furnished nucleosides functionalized with rings of various sizes (**4**, **5**, and **8**, 37−54% yield). Products **5** and **8** have demonstrated substrate activity with *E. coli* purine nucleoside phosphorylase, suggesting the potential utility of additional analogues.[11] The coupling of additional functionalized cyclic bromides provided good to excellent yields under the standard reaction conditions (**6**, **7**, and **9**, 53−96% yield). We were especially pleased with the 53% yield achieved for **9** resulting from the coupling of 3-bromocyclobutanol, which not only incorporates a strained ring but also another free alcohol. In addition, we found that the sterically encumbered 2-bromoadamantane could be employed to incorporate an adamantyl group in a moderate but useful 30% yield (**10**), providing straightforward access to a motif that is known to be valuable in drug design.[26]

Primary alkyl halides were generally very good substrates for alkylation of chloropurine **1** (**12**−**16**, 50−90% yield). Within this class, we were delighted to find that even the potentially sensitive bromomethyl acetate was a competent substrate, yielding acetoxymethyl nucleoside **17** in 37% yield. In contrast to their primary and secondary counterparts, tertiary alkyl bromides provided messy reactions and only traces of the desired products. Nonetheless, these conditions provide straightforward access to a diverse array of products bearing a range of functionality. Oxygen- and nitrogen-containing alkyl bromides were well-tolerated and allow for the incorporation of polarity in varying positions (**3**, **6**, **9**, **11**, **13**, and **15**−**17**). Bromides bearing fluorinated alkyl substituents were also readily coupled and can be useful for modulating lipophilicity, building new interactions, and/or blocking metabolism (**7**, **12**, and **14**).[27] In addition, compounds incorporating free or masked reactivity provide opportunities for further functionalization through handles including amines, alcohols, carboxylic acids, and phosphonates (**3**, **9**, **11**, **16**, and **17**).

In conclusion, we have demonstrated a strategy for the synthesis of C6-alkylated purine analogues via photoredox and nickel-catalyzed sp^2-sp^3 cross-electrophile coupling. The application of this dual catalytic method allows for the direct coupling of chloropurine with a wide range of readily available primary and secondary alkyl bromides. Importantly, under the optimized reaction conditions, unprotected nucleosides can be functionalized efficiently, such that diversification can be carried out at the final stage of synthesis if desired. Given this fact and the large starting material pool offered by alkyl bromides as coupling partners, we expect that this strategy will facilitate SAR exploration in drug discovery and should find particular utility in parallel medicinal chemistry efforts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmedchemlett.0c00673.

General procedures for cross-coupling, ^1H and ^{13}C NMR spectra, and other characterization data for all compounds prepared (PDF)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

DMF, *N*,*N*-dimethylformamide; DME, 1,2-dimethoxyethane; LED, light-emitting diode; 4CzIPN, 2,4,5,6-tetra(9*H*-carbazol-9-yl)isophthalonitrile

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