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Regioselective Alkylation of Pyridinium Riboses

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Abstract

The nucleophilic addition of alkyl, benzyl, and allyl organozinc reagents to protected pyridinium riboses proceeds under mild conditions and with yields of >90% in several cases and complete regioselectivity for the 4-position.

Graphical Abstract

Keywords

Alkylation; Allylation; Nitrogen heterocycles; Nucleophilic addition; Synthetic methods

Introduction

Nicotinamide riboses and their reduced dihydropyridine (DHP) analogs have a range of biological activities. As a result of being subunits of NADH and NAD⁺, there are a number of binding sites for nicotinamide analogs that can be exploited for drug discovery. One example is the old but highly effective tuberculosis drug isoniazid, which is a prodrug and forms a NAD⁺ conjugate containing the 4-functionalized dihydropyridine ribose unit, which in turn are strong inhibitors of InhA^[1] and MbaA.^[2] Truncated analogs of these adducts, such as **1**, have been studied extensively as antimycobacterial agents.^[3] Similarly, other 4-alkyl derivatives of nicotinamide ribose have been synthesized and studied for a variety of biomedical applications such as mitochondria-related diseases or cardioprotective properties.^[4] Finally, the facile reoxidation of DHP is of interest because it gives access to a variety of 4-substituted NAD⁺ analogs and a variety of photoredox catalyzed reactions provide access to crosscoupling products.^[5] DHP analogs are therefore of broad interest in organic and medicinal chemistry.

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Conceptually, the synthesis of 4-substituted dihydropyridines can be accomplished by nucleophilic addition of a variety of organometallic reagents to activated pyridinium salts and has been investigated extensively. *N*-acyl pyridinium salts were found to be more reactive due to increased activation of the π -system. As shown in Scheme 1, the Buchwald group^[6] reported the *in situ* generation of a chiral copper hydride (CuH) complex for the 1,4-dearomatization of pyridine for constructing chiral 1,4-DHP derivatives. The highly diastereoselective addition of organoboronates to activated pyridine complexes was reported by the Aggarwal group in 2014.^[7] They hypothesized that strong cation– π interactions between the electron-rich boronate and the electron-deficient pyridinium were responsible for the high diastereoselectivity. The Knochel^[8] group reported the regioselective addition of alkyl and aryl Grignard reagents or alkyl zinc reagents through *in situ* activation of the pyridine using BF_3 for the synthesis of 1,4-DHP. Enantioselective organozinc addition to *N*-acyl-pyridinium salts was performed by the Feringa group using copper and a phosphoramidite ligand as the catalyst.^[9] This complex provided mainly 1,2-nucleophilic addition to the pyridinium. They applied this method to the formal synthesis of (R)-coniine with good yield and high enantioselectivity. Other applications of this approach include a reoxidation of the dihydropyridine to yield substituted pyridines.

Nucleophilic addition to *N*-substituted pyridinium salts can lead to either 1,2-dihydropyridines or 1,4-dihydropyridines, indicating that regioselectivity is a concern in these reactions.^[10] It is also not clear whether the nucleophilic addition to pyridinium ions shown in Scheme 1 can be applied to the synthesis of nicotinamide ribose derivatives where

the activating electron withdrawing group on the nitrogen is replaced by the glycosidic center of a ribose, which is expected to be labile upon Lewis acid catalysis. Finally, the presence of additional functional groups, including several Lewis-basic sites in the ribose, could pose additional selectivity problems that could require very mild reaction conditions to avoid nucleophilic substitution on the glycosidic center and highly selective reagents for addition to the 4-position of the pyridinium ring. Here, we report the results of a focused study of the nucleophilic addition of organometallic reagents to nicotinic ester riboses to investigate whether these reactivity and selectivity problems can satisfactorily be addressed.

Results and Discussion

As model systems for this study, we selected benzoyl protected 3-carboxyethyl pyridinium ribose triflate **2** and 3-bromo pyridinium ribose triflate **3**. There have been surprisingly few reports of these potentially versatile intermediates in the literature.^[11] We found that they are easily accessible in good yields and on a gram scale from commercially available β -D-ribofuranose 1-acetate 2,3,5-tribenzoate, activated by trimethylsilyl trifluoromethanesulfonate, and the corresponding pyridine derivative as shown in Scheme 2.

The reaction of different types of organometallic reagents including organolithium, organomagnesium, and organozinc reagents with benzoyl protected nicotinic ester ribose **2** was investigated as shown in Table 1. The addition of *t*-BuLi and *t*-BuMgCl both gave complex mixtures of products (entries 1, 2), highlighting again the selectivity problems discussed above. Benzyl and allyl magnesium chloride addition provided the desired products with low yields (entries 3, 4) while the mass balance was again a complex mixture of products. This outcome can be rationalized by the high reactivity of these reagents toward nucleophilic replacement of the pyridinium moiety or nucleophilic attack on the ester functionality. The addition of benzyl and allyl magnesium chloride is in line with the higher reactivity of these reagents due to higher ionic character of the carbon-Mg bond compared to other classes of Grignard reagents.^[12]

There are previous reports in the literature that the addition of LiCl to Grignard reagents^[13] improves their selectivity and functional group tolerance.^[12a, 14] Using the commercially available mixture of 1 eq LiCl as an additive to isopropyl magnesium chloride ("Turbo Grignard"), selected to exclude a possible steric influence in the case of the *tert*-butyl magnesium chloride, provides the desired compound in high yield. Finally, we evaluated the use of organozinc reagents, which are expected to have less reactive than allylic magnesium chloride but more selective, thus leading higher functional group compatibility and selectivity.^[8–9] Organozinc reagents yielded the desired product even at higher temperature, 0° C vs –40° C, compared to Grignard reagents, entry 6. The C(4) alkyl addition led to a nearly equal mixture of diastereomers.

After having suitable conditions in hand, we investigated the scope of commercially available organometallic reagents for the nucleophilic addition (Scheme 3). First, the scope of reagents with sp^3 centers were investigated. The addition of isopropylzinc bromide and *sec*-butylmagnesium chloride lithium chloride solutions provided the desired 4-addition products **2a** and **2b** in excellent yields. As mentioned earlier, these 4-alkyl dihydropyridine riboses can in turn serve as precursors of the corresponding alkyl pyridinium salts, as was demonstrated by oxidation of **2a** with chloranil to give **4** (not shown), albeit in modest yield of 41% due to partial decomposition. The high regioselectivity for these 4-addition reactions can be explained by a directing group effect of the ester functionality. The addition of *tert*-butylzinc bromide solution led to complete conversion of the starting material, but only a trace amount of the desired product **2c** was detected along with a complex mixture, suggesting that the formation of a sterically crowded quaternary alkyl center is not feasible with this approach.

Next, the addition of more reactive reagents including benzyl and allyl zinc bromides was investigated. We found that addition of prenylzinc bromide gave **2d** in 96% yield by reaction at the more highly substituted position of the allylic group, which is in contrast to the low reactivity of the alkylation reaction that proceeded only in trace yields for **2c**. Reaction with benzyl zinc bromide gave the 4-benzyl adduct **2e**, which provides the scaffold for the antimycobacterial agent **1**, in 92% yield. Comparison of these results with the low yields resulting from the reaction of the Grignard counterparts (Table 1, entries 3 and 4) indicates the high regio- and chemoselectivity of the organozinc reagents. We hypothesize that the origin of the high reactivity of the organozinc reagents is due to the coordination to the ester group that increases the activation of the pyridinium moiety towards nucleophilic attack. The conformational preferences of this complex could then rationalize the high regioselectivity towards attack in the 4-position (Scheme 4).

To explore the applicability of the reaction to other activating groups on the pyridinium ring, we investigated the reactivity of the 3-bromo derivative **3**. Upon reaction with isopropylmagnesium chloride lithium chloride solution, we observed the preferential addition of nucleophile at the 4-position but with a slightly lower yield of 76% at complete conversion. This is due to the formation of the debromination product (pyridinium ribose) as a side product, which indicated possible magnesium-halogen exchange, which upon quenching provides the debrominated product. This substrate was therefore not explored further.

Finally, we investigated the expansion of the scope towards organozinc reagents containing sp^2 rather than sp^3 nucleophilic carbons. For this purpose, phenyl and an alkenylzinc bromide were examined. Addition of these reagents gave rise to complex mixtures with no detectable amounts of the desired products.

Conclusions

In summary, this focused study shows that the alkylation, allylation, and benzylation of pyridinium riboses can be accomplished in excellent yields and complete regioselectivity for the 4-position using organozinc reagents under mild conditions. We anticipate that the products of these reactions can serve as valuable precursors for further elaboration, *e.g.* to NAD^+ and $NADH$ analogs.

Experimental Section

General procedure for pyridinium ribose triflates

β -D-Ribofuranose 1-acetate 2,3,5-tribenzoate (1.4 g, 4.4 mmol) and pyridine derivative (0.9 mL, 6.6 mmol) were dissolved in DCM (50 mL), and then to the resulting solution trimethylsilyl trifluoromethanesulfonate (1.039 g, 4.4 mmol) was added gradually over 10 min. The mixture was heated at reflux for 10–14 h and checked with TLC (DCM/MeOH, 1:1) to show complete disappearance of the substrate. Next, solvent was evaporated under reduced pressure, and the resulting oil was purified with MPLC using a 120-g cartridge (silica gel) with DCM: MeOH

General procedure for addition of organometallic reagents to pyridinium ribose triflate

To the pyridinium ribose salt (**2** or **3**) (0.15 g, 0.2 mmol) in THF (1 mL) under Ar, commercially available organometallic reagents (0.24 mmol, 0.5 M in THF) were added at 0°C. The resulting solution was stirred for 30 min and checked with LCMS and TLC to show formation of the product. The solvent was evaporated, and the resulting residue was purified with MPLC using a 4-g cartridge (silica gel) with DCM: MeOH (95:5).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.

Previously reported alkylation of pyridinium salts by organometallic reagents

Scheme 2.
Synthesis of pyridinium ribose triflates.

Scheme 3.

Scope of nucleophilic addition of organozinc reagents to protected pyridinium ribose triflates.

Scheme 4.
Hypothesis for origin of regioselectivity

Table 1.

Optimization of Reaction Conditions

	Reagent	Temp [°C]	Time [min]	Yield [%]
1	^t BuLi	−40	30	-
2	^t BuMgCl	−40	30	-
3	BnMgCl	−40	60	24
4	AllylMgCl	−40	60	<10
5	ⁱ PrMgCl . LiCl	−40	30	90
6	ⁱ PrZnBr	0	30	97