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Pyridone Functionalization: Regioselective Deprotonation of 6-Methylpyridin-2(1*H*)- and -4(1*H*)-one Derivatives

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In memory of Russ Bowman

Abstract: Selective functionalization at the α -methyl group of 1-substituted pyridin-2(1*H*)- and 4(1*H*)-ones (2- and 4-pyridones) can be achieved by appropriate choice of base. *n*-Butyllithium was found to effect clean 6(2)-methyl deprotonation of 1-benzyl 2- and 4-pyridone derivatives, while potassium hexamethyldisilazide (KHMDS) was the preferred reagent for methyl deprotonation of the corresponding 1-methyl 2- and 4-pyridones. Deprotonation proceeds smoothly at -78 °C and the resulting anions react readily with a wide range of electrophiles (aldehydes, ketones, alkylating reagents, and an azo compound) under precise temperature control to form usefully functionalized 2- and 4-pyridones and quinolizinones.

Introduction

1(*N*)-Substituted 2(1*H*)- and 4(1*H*)-pyridinones (commonly referred to as 2- and 4-pyridones) are widely employed in medicinal chemistry,^[1] occur as key fragments of natural products^[2] and as hydrogen bonding synthons in supramolecular chemistry.^[3] Pyridones are regarded as privileged heterocyclic scaffolds,^[4] and both synthesis and functionalization of the pyridone ring system continue as intensive areas of research.^[5]

Recently, CH activation of pyridones (Figure 1) has been highlighted employing Ni, Pd or Fe catalysis.^[6] In this communication we wish to report an alternative approach for side chain functionalization of *N*-alkyl 2- and 4-pyridones by selective deprotonation of a 6- or 2-methyl substituent, along with convenient methods for the preparation of the required *N*-alkyl 6-methyl-2- and 2-methyl-4-pyridone substrates.

Figure 1. Functionalization of pyridone scaffolds.^[6]

Methyl substituted 2- and 4-pyridones represent versatile building blocks for elaboration to side chain functionalized derivatives, and for construction of quinolizinones, bridgehead nitrogen compounds of significant recent interest as bicyclic scaffolds in medicinal chemistry.^[7] While the addition of electrophiles to lithiated methyl pyridines continues to be studied in depth,^[8] there is a lack of information on reactions of metalated 6-methyl-2- and 2-methyl-4-pyridones. Only limited examples of alkylation of 2-pyridone methyl substituents are reported in the literature,^[9] along with early pioneering work on ring and *N*-substituent lithiation.^[10] A heterocyclic methyl group represents a source of diversity for ring functionalization,^[11] while conditions to selectively effect lithiation of a pyridine ring, but leaving a methyl substituent intact, have also been developed.^[12] Metalation of a methyl substituent on the weakly aromatic pyridone system thus represents a significant challenge in synthetic carbanion chemistry. Here we report the successful methyl deprotonation of a range of 6-methylpyridin-2(1*H*)- and 2-methylpyridin-4(1*H*)-ones, and reaction with a variety of electrophiles, including aldehydes, ketones, diketones, alkylating reagents and an azo compound to form highly functionalized pyridone derivatives relevant to medicinal chemistry. Careful choice of base and temperature control allows excellent regioselectivity and clean product formation in moderate to excellent isolated yield.

Results and Discussion

Our study started with the synthesis of the required 1-substituted 6-methylpyridin-2-ones **2a-g** (Scheme 1) via direct alkylation of 2-methoxy-6-methylpyridine **1** adapting a method for 2-methoxypyridine.^[13] Reaction with alkyl bromides proceeded in good to excellent yield in the absence of solvent, despite the ring nitrogen being flanked on both sides by the methoxy and methyl substituents.

Scheme 1. Synthesis of 2-pyridone precursors

Demethylation occurred concomitantly, presumably by attack by bromide ion and loss of the volatile MeBr, generating the 1-substituted pyridones **2a-g**. We were also able to generate a 1:1 mixture of 1,6-dimethyl pyridine-2(1*H*)-one **2a** and 1-benzyl-6-methylpyridine-2(1*H*)-one **2e** by treating **1** with 0.5 equivalents of benzyl bromide. The two compounds could be separated readily by chromatography. *N*-Alkylation-*O*-dealkylation is an effective method for conversion of alkoxy pyridines to pyridones^[14] and avoids the frequent heteroatom selectivity problem associated with attempts to alkylate ambident pyridones.^[15]

With the 2-pyridone derivatives **2a-g** in hand, we studied the deprotonation of the 6-methyl substituent to synthesize new *N*-alkyl-6-substituted 2-pyridones. Initially we focused on **2a** and **2e** as test compounds and a study of reactivity towards *n*-BuLi was undertaken (Scheme 2). 1-Benzyl-6-methyl-2-pyridone **2e** was treated with *n*-BuLi in THF at $-78\text{ °C} \rightarrow 0\text{ °C} \rightarrow -78\text{ °C}$ resulting in an intense blue solution. Quenching the mixture with D₂O at -78 °C led to clean recovery of the mono-deuterated pyridone **3a** (>98% by NMR; 87% isolated) substituted on the methyl group (C-7 position). The location of the label was established by ¹H and ¹³C NMR spectroscopy [(δ_H 2.23 (2H, bs) and δ_C 19.6 (t, $^1J_{CD} = 20\text{ Hz}$)]. Treatment of 1,6-dimethyl-2-pyridone **2a** with 1 equivalent of *n*-BuLi under the same conditions however, resulted in formation of an orange solution, and quenching with D₂O at -78 °C produced a mixture of starting material and inseparable products.

Scheme 2. Lithiation of 1-benzyl 2-pyridones

Treatment of pyridone **2a** with KHMDS as base, led to clean formation of the monodeuterated pyridone (98% by NMR; 55% isolated), with no by-product formation. In the subsequent experiments with **2a**, we thus chose to employ KHMDS as base, since *n*-BuLi appeared to attack the unhindered pyridone ring. The lithiated benzyl 2-pyridones **2e** and **2f** were then exposed to a range of electrophiles at $-78\text{ }^{\circ}\text{C}$ to produce compounds **3b-o** (Figure 2). Subsequent optimization steps demonstrated that the best yields for direct methyl alkylation of the 1-benzyl-6-methyl-2-pyridone anion occurred with 1 eq. of *n*-BuLi. Use of 1.2 $\rightarrow$ 2 eq. afforded products in which the benzylic position was also alkylated, as observed by Katritzky.^[10b,c] Pleasingly, the conditions developed operated effectively for all electrophiles tested (aldehyde, ketone, diketone, ketoester, alkylating agent, azo compound) possessing a range of functionality, proceeding in general in high yield with few exceptions. In the synthesis of pyridone **3k**, the low yield of 19% was attributed to the poor solubility of the dibromobenzil electrophile, while addition of an unsaturated aldehyde gave a 33% yield of **3d** together with a low yield of the unstable **3e** formed by conjugate addition. In an attempt to synthesize pyridone **3f**, with propionaldehyde as electrophile, a 26% yield of the ring alkylated product **4** (addition at C-3) was obtained, together with starting material, as the pyridone anion was basic enough to deprotonate the α position of the aldehyde.

Figure 2. Functionalized 1-benzyl 2-pyridones prepared.

In studying the reactivity of the 1,6-dimethylpyridin-2(1*H*)-one **2a**, deprotonation took place efficiently when KHMDS was used as base (Scheme 3). To exploit the methyl anion of the pyridone synthetically we employed aldehyde, ketone, and alkylating agents as electrophiles. The reactions, forming compounds **5a-5e**, occurred in good to excellent yield, except when 5-bromo-1-pentene was used. Due to its low reactivity, reaction at $-78\text{ }^{\circ}\text{C}$ or $-35\text{ }^{\circ}\text{C}$ returned only starting material, while reaction with 2.5 eq. of base and electrophile addition at $0\text{ }^{\circ}\text{C}$ afforded the ring alkylated (**5f**; E=1-penten-5-yl, 8%), dialkylated (**5g**; 8%) and methyl dialkylated (**5h**; 18%) pyridones. Use of 1.0 eq. of base and electrophile addition at $-10\text{ }^{\circ}\text{C}$ was required to form the desired product **5d** cleanly with isolation in a low 20% yield, as found by Sammes^[9] who obtained 6.6% yield operating at $-23\text{ }^{\circ}\text{C}$. In comparison, **5a** and **5b** were obtained in significantly lower yields of 37% and 38% respectively when *n*-BuLi was employed as base.

The next part of the study investigated methyl deprotonation of the corresponding 1-alkyl 2-methylpyridin-4(1*H*)-one derivatives. These were considered more challenging substrates due to the high polarity of the 4-pyridone system (dipole moment $\geq 7.3\text{ D}$ for *N*-alkyl derivatives^[16] compared with ~ 4.0 for 2-pyridones.^[17] 4-Pyridones are more susceptible to attack by

nucleophiles,^[18] which could compete with metalation. The higher polarity also resulted in lower isolated yields due to difficult extraction and chromatography. The substrates **9a** and **9b** were prepared by alkylation of 2-methyl-4-alkoxypyridines (Scheme 4).

Scheme 3. Functionalization of pyridinone **2a**

Figure 3. X-ray crystal structure of **5e**^[19]

The 4-benzyloxy derivative **7** was easily prepared by S_NAr reaction of 4-chloropyridine **6**, using NaH in DMSO.

Scheme 4. Synthesis of 4-pyridones.

Base catalyzed hydrolysis (NaOH/H₂O/THF) of the resulting *N*-methyl and *N*-benzyl pyridinium salts was found a convenient method of conversion to the pyridones, as the salts were easily isolated by precipitation, and did not undergo dealkylation as had occurred in the 2-pyridone series under solvent-free conditions.

The 1-benzyl 4-pyridone **9b** was investigated first, and found to behave well using the lithiation conditions developed for benzyl 2-pyridones (Scheme 5). Clean reaction was observed using *n*-BuLi, although isolated yields were only moderate. The methyl-lithiated **9b** reacted successfully with aldehyde, diketone, allyl halide and azo electrophiles forming **10a-d**.

Scheme 5. Functionalization of 4-pyridinone derivatives

Attempts to mono-metalate the 1,2-dimethylpyridin-4(1*H*)-one analogue **9a** met initially with less success. Different reaction conditions were therefore systematically investigated in order to find a set of conditions that would favour mono-alkylation. The standard conditions of 1 eq. of KHMDS at -78°C , warming to 0°C , and quenching with the electrophile at -78°C , unfortunately gave no alkylated pyridone. Screening the quantity of base from 1 to 2.5 equiv. was studied, while the temperature of the electrophile addition (-78°C) and reaction time of 2 h were held constant, but again only a high recovery of starting material was obtained. Only by adding 2.5 equiv. of base to the pyridone at -78°C , equilibrating to 0°C , and electrophile addition at 0°C (2 h) could alkylated products be obtained with a limited range of electrophiles. Reaction with pivaldehyde was found to proceed well giving pyridone **11a** in a moderate 15% yield. Isolation of the unsaturated product **11b** (17%) formed by elimination, indicated a greater degree of alkylation. Use of allyl bromide gave a low yield (10%) of alkylated pyridone **11c**, but the reaction was

complicated by the subsequent deprotonation of the product, leading to further alkylation, delivering the dialkylated compound **11d** in 39% yield. Although the yields were modest, we have demonstrated it is possible to successfully manipulate the sensitive 4-pyridone anion in a synthetically useful way.

Finally, we investigated the metalation reaction as a method to form quinolizinone derivatives, compounds of interest as bicyclic drug scaffolds.^[7] As shown in Scheme 6, we were able to generate this ring system using the chemistry developed giving bicyclic heterocycles in modest yield. Treatment of pyridone **2c** with KHMDS and reaction with 4,4'-dimethylbenzil gave **12** (10%) in which the ester group was lost. Addition of 1 eq. of *n*-BuLi, and adding the electrophile at -78°C , gave **13** showing the *N*-substituent was alkylated prior to the methyl. Use of LDA to deprotonate benzyl pyridone **2e** gave **14** in low yield together with **15**, also indicating lithiation of the *N*-alkyl group occurs first with this base.^[10b]

Scheme 6. Formation of quinolizinone scaffolds.

Quenching the reaction at low temperature allowed isolation of the diol **16**. Treatment of the preformed keto-alcohols **3i,j,l** with 2 eq. of *n*-BuLi gave modest yields of the quinolizinones **16-18**. Dehydration to the fully unsaturated ring system did not occur under the reaction conditions, but **16** and **17** could be converted to quinolizinone **19** and the 6,7-dihydro compound **20** on heating with pTSA.

Conclusions

In conclusion we have optimised deprotonation conditions for the selective methyl activation of 6-methylpyridin-2(1*H*)-ones and 2-methylpyridin-4(1*H*)-ones, and demonstrated these intermediates can be manipulated in a synthetically useful way to prepare side-chain functionalized pyridones and quinolizinones, important scaffolds in medicinal chemistry. *n*-BuLi is a suitable base for *N*-benzyl substituted pyridones, while KHMDS is preferable for *N*-methyl analogues.

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Keywords: heterocycles • pyridone • quinolizinone • scaffold • side chain metalation

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- [19] CCDC 1482299 contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.