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Structural and electronic modifications of pyridones and pyrones via regioselective bromination and trifluoromethylation

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ABSTRACT

We report regioselective functionalization of pyridones and pyrones via electrophilic bromination (Br_2) or radical trifluoromethylation ($NaSO_2CF_3$/^tBuOOH) at the 3-position. Counter-intuitively, the 3-position EW groups decreased the carbonyl stretching energy by 6–23 cm^{-1}; however, 3,5-dibromination increased the C=O frequency by 10–22 cm^{-1} compared to the 3-Br pyridones. X-ray crystallography revealed pyridone tautomers with contracted C=O bond metrics. pK_a values and ^1H NMR shifts for the series 3-H→Br→CF_3 revealed the expected trend of increasing acidity (pK_a = 8.85 → 8.33→6.78, MeOH) and increasing chemical shifts (10.97 → 11.42→11.71 DMSO-d_6). We conclude that the paradoxical decrease in CO stretching frequencies by the 3-positoin EW groups is explained by an 'assistive' electron-withdrawing effect, whereby the 3-position EW group assists the electronegative oxygen atom in recruiting more electron density, and – as a result – attaining more oxyanion character (decreased the C=O bond strength).

1. Introduction

The 2-pyridone is an azaheterocyclic compound containing an amide moiety, the structure of which is widely found in natural products,[1] biological systems,[2] and sensor molecules.[3] Pyridone derivatives are essential precursors of biologically active compounds and medicinal chemicals,[4,5] and thus their high level of utility demands further functionalization.[6–8]

In the context of our research, the active site of the enzyme mono-iron hydrogenase (Hmd) contains a novel pyridone cofactor (Chart 1). The pyridone *N*-donor coordinates a low-spin Fe(II) ion, which is essential moiety in the active site. The enzyme's iron coordination site is postulated to be the origination point of the dihydrogen (H_2) activation and hydride transfer reactions.[9] From a mechanistic perspective, it is thought that the Lewis basic pyrid-2-one oxygen and Lewis acidic sites (Fe, methenyl-H_4MPT^+) are cooperatively involved in H_2 activation.[10] Thus, the role of the pyridone cofactor has received synthetic chemical attention regarding its capability to stabilize the active site resting state, as well to facilitate the key 'proton-relay' step.[11–14]

Furthermore, the utility of pyridone-containing ligands has been demonstrated in many coordination complexes.[16] For example, Szymczak et al. designed a tripodal pyridone ligand for coordinating a copper ion.[17] The ligand showed the carbonyl IR stretch as an evidence of the dominant pyridone tautomer, but upon metallation, the 2-hydroxypyridine forms to stabilize the Cu(Cl) center while presenting a hydrogen bond in the O–H···Cl moiety. In another case, a hydroxypyridine ligand attracted special interest due to its cooperative hydrogen transfer ability. Britovsek et al. synthesized a Rh-DHBP (6,6'-dihyroxy-2,2'-bipyridine) complex to catalyze carbonylation of methyl acetate to acetic acid.[18] Papish et al. used the DHBP ligand to coordinate Ru ion, and the hydroxy group was essential to perform the aqueous transfer hydrogenation of ketones with hydride sources.[19] Fujita and Yamaguchi devised an Ir pyridone complex to catalyze dehydrogenative oxidation of alcohols to ketones, where the pyridone/pyridinol conversion promoted addition of alcohol and protonolysis of Ir–H.[20] Hull, Himeda, and Fujita utilized the proton-relaying hydroxypyridine ligand with Ir center for the CO_2/HCO_2H conversion as a reversible H_2 storage method.[21] Thus, understanding the fundamental acid/base and electronic modifications of pyridone to modulate its basicity is of key interest to researchers in this field.

We are interested to install electron withdrawing substituents onto pyridone rings for several reasons. First, there is a need to

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generate electronic pyridone variants for biomimetic studies, since site mutagenesis studies are not applicable due to the nearly complete lack of amino acid ligation in the mono [Fe]-hydrogenase active site (Cys176 is the only protein-based ligand to Fe).[15] Thus, the chemical diversity for studying structure-electronic-activity relationships in the organic cofactor and active site must emanate from chemical synthesis. Related to this, a recent report by Hu and Shima demonstrated incorporation of a synthetic analog of the pyridone-Fe active site (a pyridinol-containing artificial cofactor) into the apo-protein to prepare an artificially modified enzyme; it demonstrated functional (albeit diminished) catalytic efficiency.[22] Second, we recognize the prevalence of the trifluoromethyl group as a pharmacophore in medicinal chemistry, thus, the electron withdrawing yet hydrophobic $-CF_3$ group is of particular interest to the synthetic community.[23]

And while numerous synthetic procedures are reported for pyridones,[24–28] there is a lack of facile methods for selective *meta* functionalization. Methods have been reported to functionalize pyridones at the meta position *provided* the pre-existence of a halide (Br, I)[29–31] or hydroxide group.[32] Also, several examples of the trifluoromethylation[30] or alkylation[33,34] of halide-functionalized pyrones are known. However, direct C–H trifluoromethylation or alkylation of pyridones and pyrones – and related carbonyl-containing heterocycles (e.g., pyrimidine-dione)[35] – is less studied. The *meta* functionalization is advantageous to broaden the scope of pyridone incorporation in drug targets, as well to investigate electronic effects by electron withdrawing/donating substituents. Pyridone derivatives are commonly synthesized by Guareschi-Thorpe condensation,[36] cyclization of enamine-dioxinones,[28] amination of pyrones,[4] and other methods.[37] There are also existing methods to utilize metal ions to prepare *N*-protected pyridones, e.g. the Rh(III),[38] Ru(II)[39]-catalyzed oxidative annulations of acrylamide and alkyne; cycloisomerization of *N*-alkenyl alkynylamides by Au(I).[40] Herein, we prepared bromo-pyridone/pyrone derivatives by simple reaction with Br_2 and several examples of trifluoromethyl-pyridone/pyrone to investigate its electronic effects on the heterocycles. The electronic modulation is determined by IR spectroscopy, pK_a measurement, ^{1}H NMR spectroscopy and X-ray crystallography. The carbonyl IR stretch is a sensitive method to analyze electronic properties of ligands and coordination complexes,[17,18] and – importantly – X-ray crystallography can differentiate the presence of pyridone or pyridinol tautomers.[17]

2. Results and discussion

2.1. Preparation of pyridone and pyrone derivatives

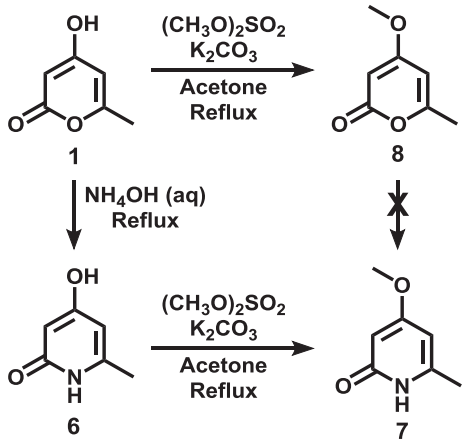
The pyridone derivatives used here are prepared either by amination of *p*-hydroxypyrones or cyclization of Guareschi imides. The compounds **4**[41], **6**[4], **17**[42], and **22**[43] were synthesized following the literature procedures. We synthesized an *N*-methoxy protected pyridone **2** by reacting **1** with NH_2OCH_3 at 100 °C (34% yield) [$NH_2OCH_3 \cdot HCl$ was neutralized by $NaHCO_{3(aq)}$ prior to use]. The *N*-protection of dissociable pyridone N–*H* is sometimes imperative for further synthetic procedures, and *N*-substituted pyridones has importance as a pharmacophore in medicinal chemicals. The other dissociable *p*-OH in pyridone can be protected by methylation using dimethyl sulfate [$(CH_3O)_2SO_2$] in hot acetone with K_2CO_3. The *p*-OH group of the pyridone **2** was protected to **3** (79%), and another *N*-Bn-pyridone **4** (Bn = benzyl) was methylated to **5** (71% yield). Amination of *p*-OH pyrone **1** with $NH_4OH_{(aq)}$ readily generates **6**[4]; however, attempts to convert *p*-OMe pyrone **8** (OMe = methoxy) to **7** did not afford the desired product by either aqueous or gaseous ammonia. The conversion of **1** to **7** was achieved only through the methylation of **6** (36% yield) after amination of **1** to **6** (Scheme 1).

While the methylation of **6** primarily yielded the *O*-methylated pyridone **7**, this reaction also afforded small quantity of *N,O*-dimethylated **9**; the *N*-only methylated pyridone has never been detected. This indicates preferential *p*-OH methylation, and the greater acidity of –OH than the –NH group renders the *p*-OH site more reactive under basic conditions. The product mixture of **7** and **9** was conveniently separated by solubility difference in organic solvent: the pyridone **9** (and several minor impurities) were extracted with ethyl acetate (EA) from the crude mixture leaving the pure product **7**; the collected EA solution was purified by silica gel column chromatography to isolate **9**. As expected, excess use of dimethyl sulfate by over two equivalents resulted only in the fully methylated **9**. The synthesized *N*- or *O*-protected pyridones are tabulated in Table 1.

2.2. Bromination of pyridones and IR characterization

Bromination provides electronic variants of pyridone compounds. Additionally, the bromo site serves as a convenient cross-coupling or lithiation site (*N,O*-di-protected only), which is important for the extension of pyridone compounds, or appending pyridone moieties to existing pharmaceutical scaffolds. From these electronic and synthetic interests, we prepared various bromopyridones by the known, simple Br_2 reactions in dichloromethane (DCM). In this work, rather than exploring new synthetic methods, we focus on the electronic variation of pyridones, and try to understand the electronic/structural relations in the variety of pyridones.

We began bromination of a 3,5-*H*-pyridone **6** (Scheme 2). A dilute Br_2 solution (1 equivalent) was dropwise added into **6** in dichloromethane (DCM) at 0 °C, forming a yellow precipitate. From the ^{1}H NMR spectrum, the product showed only one proton resonance at 5.79 ppm in the deuterated dimethyl sulfoxide (DMSO-d_6) (later determined as a 5-*H* by the NOE measurement), whereas the parent 3,5-*H* pyridone (**6**) has two aromatic protons at 5.31 and 5.58 ppm (this upfield shift of the aromatic proton is common in pyridone). Additional inspection of the bromination product by IR spectroscopy revealed the carbonyl frequency shift from 1631 cm^{-1} to 1615 cm^{-1} and the peak became broader and more intense. The weaker carbonyl stretch and peak broadness are due to formation of pyridinol·HBr salt during the reaction. The electrophilic bromination generates free HBr, which protonates the pyridone product. Due to the tautomerism, it is reasonable to consider two structures of the *O*-bound HBr in pyridone and the *N*-bound HBr in pyridinol.



Scheme 1. Synthesis of pyridone **7** starting from pyrone **1**.