

Selective Oxidation of a Single Primary Alcohol Function in Oligopyridine Frameworks

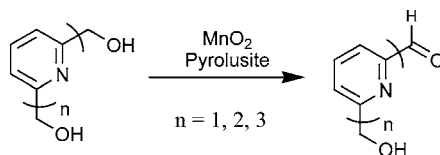
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ABSTRACT



A variety of mono-oxidized pyridine, bipyridine, terpyridine, and pyridine/pyridazine are readily prepared under mild conditions using Pyrolusite MnO₂. This phase has been characterized by means of X-ray powder diffraction and scanning electron microscopy. The oxidative activity is in keeping with the nature, morphology, and surface area of the MnO₂ reagent.

In the past decades and nowadays there has been a steady and progressive interest in convenient methods for the selective oxidation of primary alcohols to the corresponding aldehydes, and an impressive number of protocols are now available. The most popular methods for the oxidation of alcohols use activated dimethyl sulfoxide (Swern protocol),¹ pyridinium chlorochromate (Collins reagent and analogues),² *N*-chlorosuccinimide oxidation of alkoxy magnesium bromides,³ and tetraalkylammonium per-ruthenate reagent.⁴ In one case, the use of barium manganate allows the selective (85%) mono-oxidation of 2,5-diphenyl-3,4-di(hydroxymethyl)thiophene.⁵ The recent interest in the synthesis of alde-

hydes bearing donor groups has driven research into new and improved procedures leading to functionalized oligopyridines. Among these methods the use of *tert*-butoxybis(dimethylamino)methane (Bredereck's reagent) is promising.⁶

In a general sense, aldehydes are very interesting targets for the synthesis of so-called Schiff base compounds, which attract much interest in the field of coordination chemistry. The presence of a lone pair on the nitrogen atom of the imine group enables the coordination of numerous metal cations, especially when the imine function is located at the ortho position of the heterocycle such as in pyridine. Recently, various molecules found interesting applications as ligands in homogeneous catalytic reactions such as hydrosilylation, Mukaiyama aldolization and cyclopropanation,⁷ homologation of aromatic aldehydes,⁸ and ethylene polymerization.⁹ In all of these applications the synthesis of the starting

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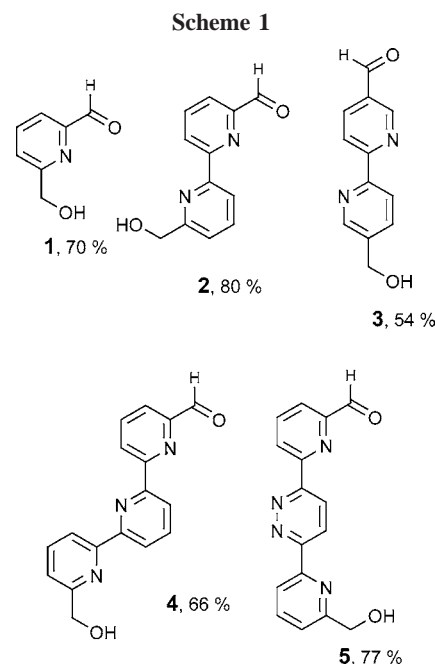
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aldehydes remains challenging and difficult. Recently, we have developed a direct and convenient synthesis of imines from bipyridine frameworks where the aldehyde function is masked in the form of a *gem*-dibromomethyl derivative.¹⁰

Interestingly, the selective oxidation of a single primary alcohol in 2,6-di(hydroxymethyl)pyridine is possible but remains difficult and feasible only under harsh conditions. Typical literature procedures utilize SeO₂ (0.5 equiv) in refluxing pyridine.¹¹ This is a major problem due to the toxicity, cost, product purity, and low isolated yields. In our hands, this was a significant issue that could not be overcome by manipulating the reaction and purification conditions. We desired conditions that would be practical, inexpensive, environmentally friendly, and amenable to large-scale synthesis and that allow for substrate generality.

The use of other metal reagents or catalysts has been developed to address this issue. Manganese dioxide has proved a valuable oxidizing agent for certain functional groups.¹² This reagent oxidizes many compounds smoothly. However, we noticed that 2,6-di(hydroxymethyl)pyridine was doubly oxidized to the bisaldehydes in acceptable yield, but at that time no characterized side products were mentioned and the exact nature of the manganese dioxide was not given.¹³ Despite these advances, there still remained a need for a general protocol that would efficiently broaden the scope of this important oxidation reaction. In this Letter, we disclose the results of using manganese dioxide for the selective mono-oxidation of oligopyridine carrying dihydroxymethyl functions.

Initial results revealed that a sample of MnO₂(P) from Rhône Poulenc (Prolabo no. 25 259.296) in a stoichiometric ratio with the starting material was weakly active and only provided the monooxidized derivative **1** in CHCl₃ at 60 °C. However, a sample of MnO₂(M) from Merck (no. 805958) was very active and provided solely the di-oxidized compounds. After some experimentation, we were pleased to find that we could isolate compound **1** in 70% using a large excess of MnO₂(P) and extend the protocol to a family of oligopyridine derivatives as depicted in Scheme 1. The best solvent is CHCl₃, which gives a correct balance between the solubility of the products, the kinetics of the reaction, and the selectivity. In all cases the formation of the bisaldehydes is negligible (<5%) and the unreacted compounds could be easily recycled. The presence of oxygen is not mandatory for the oxidation, and lower temperatures provide lower yields for the oxidation. We also noticed that the use of other solvents such as dichloromethane, pyridine, or acetone and ultrasonic irradiation do not significantly improved the yields.



Next, we chose to better characterize the MnO₂ by determining the specific surface, the nature of the phase (by X-ray powder diffraction), and the morphology. First, we were pleased to discover that the MnO₂(P) sample has a low surface area of 3.8 m²/g and a much better resolved diffraction pattern when compared to MnO₂(M) (46.7 m²/g). The first sample, MnO₂(P), exhibits some sharp diffraction lines that can be attributed unambiguously to the Pyrolusite phase¹⁴ (SI). The second sample, MnO₂(M), exhibits weak and broad diffraction peaks emerging from the background that are attributed to a ϵ -MnO₂ Akhtenskite phase (SI). Furthermore, the morphology of the two manganese oxide samples has been characterized using scanning electron microscopy. For MnO₂(P), platelet-like crystallites with sizes larger than tens of microns are observed (Figure 1, top), whereas the second sample [MnO₂(M)] is composed of aggregates of a mixture of irregular shaped grains and needles of a few nanometers (Figure 1, bottom).

There is a close relation between the morphology of the crystallites, the specific surface area, and the activity of the material. The larger crystals have a lower surface area and better resolved diffraction patterns but also a weaker oxidation capability, leading specifically to the mono-oxidized compounds. The more dispersed MnO₂(M) material is less crystallized, more dispersed, and consequently more active toward primary alcohol oxidation, and in this case double oxidation is always evidenced with 2,6-di(hydroxymethyl)pyridine. Preparation of the active MnO₂ Pyrolusite phase could be achieved according to literature procedures.¹⁵

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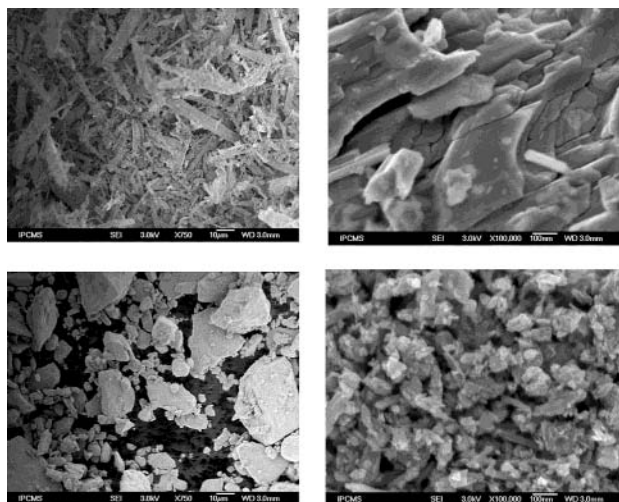
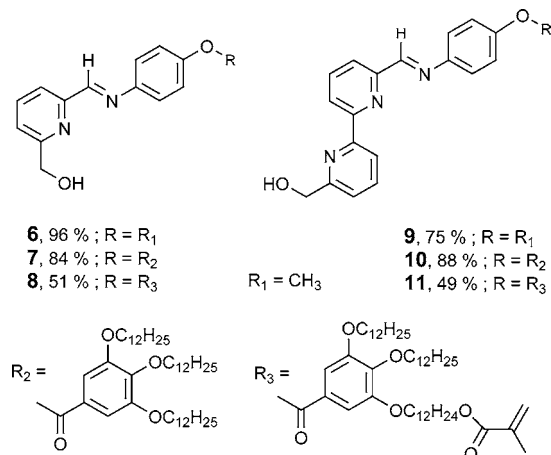


Figure 1. SEM micrographs recorded for the two MnO₂ samples: (top) MnO₂(P) Pyrolusite phase, and (bottom) ε-MnO₂ Akhtenskite phase.

One of the objectives of the selective mono-oxidation of diols was to transform the resulting aldehyde function to a Schiff base and to evaluate them in coordination chemistry and material science. The remaining hydroxy group will act as an organizing vector in the solid state in order to stabilize tridimensional structures via hydrogen bonds. By analogy to our previous work,¹⁶ and also stimulated by our involvement in a program devoted to the engineering of mesomorphic nanostructures, we condensed 2-formyl-6-(hydroxymethyl)pyridine with aniline derivatives bearing in the *para* position an additional phenyl-ester dipole and carrying at their peripheries three paraffin chains. In one case, one of these alkyl chains is substituted by an acrylate function, a potential module for controlled polymerization reactions (Scheme 2).¹⁷ After some experimentation, we were pleased to find that these condensations can effectively be performed under mild conditions and with fair yields in the presence

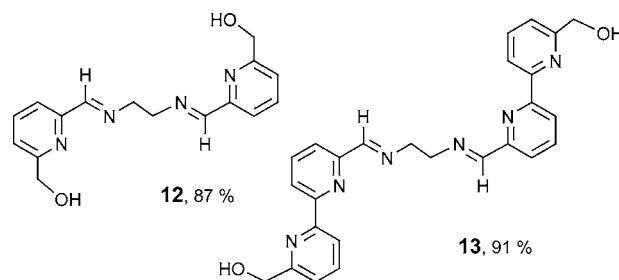
Scheme 2



of trace amounts of acid (CH₃COOH for R = CH₃ and *p*-TsOH for R = R₂ and R₃). To avoid the trans esterification byproduct with the free hydroxymethyl function and to achieve a better yield in the imine formation, *p*-TsOH was preferred instead of acetic acid.

Encouraged by the successful preparation of the imino derivatives, we moved to the more ambitious goal of expanding the methodology to the use of aliphatic diamino compounds in order to produce ditopic ligands for metal complexation. Ligands **12** and **13** were successfully prepared in good yields, by condensation of 2 equiv of 2-formyl-6-(hydroxymethyl)pyridine with ethylenediamine in the presence of trace amounts of acetic acid (Scheme 3).

Scheme 3



To test the coordination abilities of such ligands toward transition metal and to generate simple metal-induced self-organized structures, ligand **12** was allowed to react under stoichiometric and anaerobic conditions with [Cu(CH₃CN)₄](BF₄) salts.

Immediately after mixing the ligand with the metal salt, a deep-red color, characteristic of Cu-imino derivatives, developed in the solution. This coloration is indicative of a Cu(I) cation surrounded by four nitrogen donor atoms.¹⁸ FT-IR studies in solution and in the solid state of the resulting complex showed a 21 cm⁻¹ shift of the imino stretching vibration, confirming that no free imino function at ν_{C=N} 1650 cm⁻¹ was present. Furthermore, the proton NMR spectrum of the Cu-complex in CD₃CN solution revealed the presence of an AB system (exo-H: 4.57 ppm, *J* = 15.3 Hz. endo-H: 3.77 ppm, *J* = 15.3 Hz), whereas in the free ligand a singlet was found at 4.89 ppm. This prochirality of the methylene protons is consistent with the imino-pyridine fragments becoming more rigid as a result of coordination to the metal center.¹⁹ ES-MS revealed the presence of an intense molecular peak at 809.2 [M – BF₄]⁺ and 361.1 [M – 2BF₄]²⁺ typical of a dinuclear species.

Interestingly, because of intermolecular hydrogen-bonding interactions, no ν_{OH} peak for a free OH group (around 3600

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cm^{-1}) could be detected for the solid samples (anhydrous KBr) of the copper(I) complex. The ν_{OH} stretching vibrations are broader and appeared around 3445 cm^{-1} .²⁰ In the free ligand **12**, this ν_{OH} peak is shifted to 3220 cm^{-1} owing to the presence of hydrogen bond accepting groups.²¹ To further characterize the molecular structure of the binuclear complex and the plausible hydrogen bonding network we have undertaken an X-ray molecular structure determination (Figure 2).

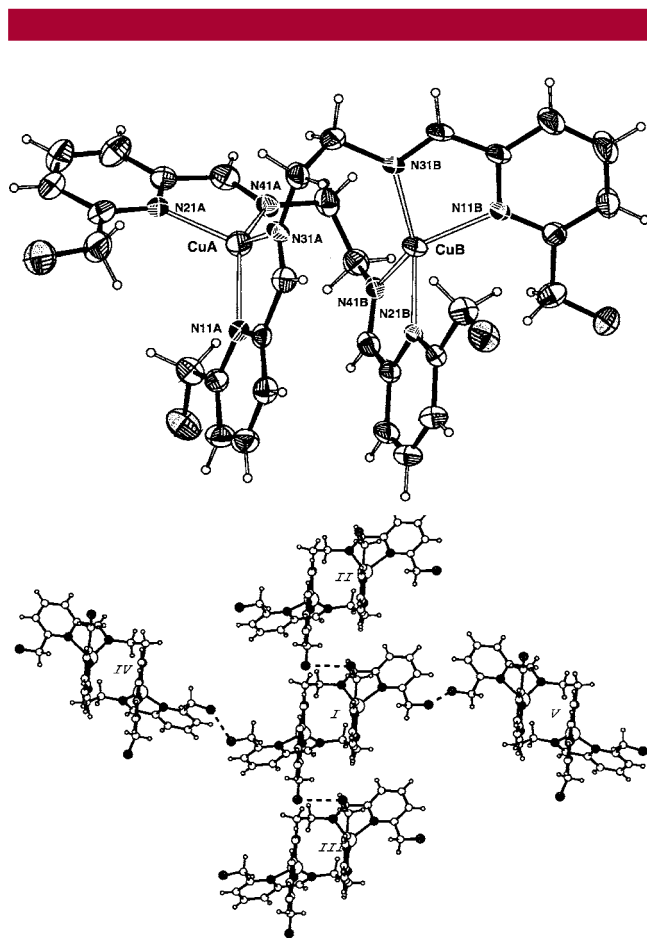


Figure 2. (Top) ORTEP drawing of the $[\text{Cu}_2(\mathbf{12})_2]^{2+}$ helicate showing the 30% probability thermal ellipsoids. The hydrogen atoms are drawn as small spheres of arbitrary radii. (Bottom) The interlinked hydrogen-bonded network.

The crystal structure confirms the formation of a binuclear metallo-helicate with the two copper(I) centers being separated by a distance of 3.902 \AA . The ligands wrap around the

two metal centers to give a double strand helicate. Each ligand chelates the two imino/pyridine fragments with two Cu(I) centers, providing a distorted tetrahedral arrangement with bite angles of $77.5(2)^\circ$ to $82.4(2)^\circ$. The Cu(I)–N_{pyr} bonds lie in the $2.053(5)$ – $2.081(5)\text{ \AA}$ range, whereas the Cu(I)–N_{im} lengths are in the $2.009(5)$ – $2.034(5)\text{ \AA}$ range. As might be expected, a certain degree of flexibility of the ligands is required to allow the helicate formation. It should be noticed that if the pyridine rings are roughly perpendicular two by two about the metal center, the whole dinuclear complex reveals a pronounced dissymmetry. Two pyridine rings N11A and N21B are parallel [deviation of only $2.5(1)^\circ$], and the two other rings N21A and N11B are perpendicular [$81.2(2)^\circ$].

Consequently, the molecular structure is extended to 12.4 \AA along the axis *a* and reveals a pronounced π – π stacking (of about 3.8 \AA) between the pyridine rings N11A and N11B. This π stacking interaction contributes to the stability of the complex. Furthermore, the crystal structure is stabilized by hydrogen bond interactions involving the four alcohol functions and forms a tight 3D H-bonded network. Two different hydrogen bonds interlink the dimeric structure. Representative distances are: O18A [*x,y,z*]...O28B [*x*,*1+y*,*z*] *d* = $2.874(9)\text{ \AA}$ and O28B [*x,y,z*]...O18A [*x*,*–1+y*,*z*] *d* = $2.874(9)\text{ \AA}$, interlinking two complexes translated along the *c* axis: O18B [*x,y,z*]...O28A [*x*,*1–y*,*–0.5+z*] *d* = $2.944(11)\text{ \AA}$ and O28A [*x,y,z*]...O18B [*x*,*1–y*,*0.5+z*] *d* = $2.944(11)\text{ \AA}$. Recently, similar polymeric arrays self-assembled by hydrogen-bond aggregation have been evidenced.²²

In conclusion, we have developed an expedient and synthetically useful, operationally simple, and general method for the preparation of monoformyl/monohydroxymethyl pyridine based molecules. This synthesis uses a Pyrolusite phase of MnO₂ that has been properly characterized by X-ray diffraction. The oxidative activity is related to this phase but also to the morphology and surface area of the reagent. Formation of a multitopic ligand was found to occur smoothly between the formyl and the target amines, in the presence of specific amounts of acids and without significant side reactions such as trans esterification. In addition, some of these ligands form dinuclear complexes with Cu(I) salts, which makes these compounds an attractive and available template for coordination and material chemistry.

Supporting Information Available: Experimental procedures and characterization for all compounds, X-ray powder diffraction of the MnO₂ samples, and CIF file for the Cu complex. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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