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Synthesis of Unsymmetrically 4-Substituted 2,2'-Bipyridines.

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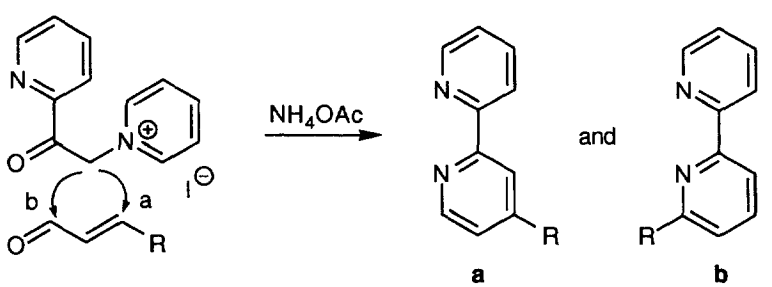
Abstract: Pyridin-2-nitrile oxide was generated *in situ* and reacted with 2-substituted but-1-ene-4-ols to give 5-substituted 5-(2-hydroxyethyl)-3-(pyrid-2-yl)-Δ^2-isoxazolines. The isoxazolines were reductively ring-opened with $LiAlH_4$ to give 2-(3-substituted-1-amino-3,5-dihydroxypentyl)-pyridines, which were subjected to Dess-Martin oxidation with concomitant dehydration to give 4-substituted 2,2'-bipyridines.

Ruthenium complexes with 2,2'-bipyridine (bipy) and 4,4'-dialkyl 2,2'-bipyridines have been studied as photosensitisers in solar energy conversion systems, improving the efficiency of hydrogen generation by visible light photocatalytic cleavage of water.[1,2] In this regard unsymmetrical 4,4'-dialkyl-2,2'-bipyridine-ruthenium(II) complexes are of particular interest.[3,4]

Several synthetic approaches to unsymmetrical 2,2'-bipyridine derivatives have been reported. The Kröhnke procedure[5] can be used to prepare 4-substituted 2,2'-bipyridines as outlined in Scheme 1, but this method suffers from several limitations such as the formation of isomeric mixtures.[6] Both 4-substituted and 6-substituted 2,2'-bipyridines may be formed, arising from initial 1,4-addition or 1,2-addition, respectively, and these isomers are often difficult to separate.[7] Furthermore, when the α,β-unsaturated carbonyl component is an aldehyde, side reactions leading to complex mixtures can result and as the size of the substituent (R, Scheme 1) increases the yield of bipyridine decreases significantly. For example when crotonaldehyde is reacted with 2-pyridacylpyridinium iodide (Scheme 1, R = CH_3) the yield of bipyridine is about 50%, however in the similar reaction with cinnamaldehyde (Scheme 1, R = Ph) the yield drops to about 30%.



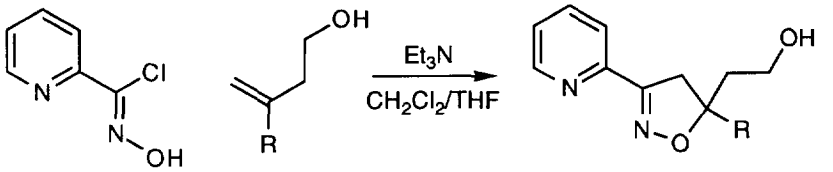
Scheme 1

Another approach is the monolithiation of 4,4'-dimethyl-2,2'-bipyridine at low temperature followed by quenching with an appropriate electrophile such as an alkyl halide,[8,9] or an aldehyde.[10] This method generally produces a mixture of unreacted 4,4'-dimethyl-2,2'-bipyridine, along with products arising from the desired monolithiation and undesired dilithiation. In many cases these mixtures are difficult to separate and purify. Other disadvantages are that neither aryl substituents nor 4-substituted-2,2'-bipyridines (where one pyridine ring is unsubstituted) are directly available by this method.

Other reported approachs include palladium catalysed coupling between a substituted pyridine and a differently substituted pyridine-*N*-oxide to give the unsymmetrical 2,2'-bipyridines directly,[11] and direct alkyllithium reactions on 2,2'-bipyridine.[12] Unfortunately both these reactions give isomeric mixtures and are thus of limited preparative use.

For spectroscopic studies we required some isomerically pure 4-substituted-2,2'-bipyridines. We herein describe a route to these compounds whereby the substituted pyridine ring is constructed using nitrile oxide cycloaddition methodology.

2-Cyanopyridine was converted to the corresponding amidoxime by heating under reflux with hydroxylamine hydrochloride and sodium carbonate in ethanol.[13] Pyridine-2-amidoxime was treated with sodium nitrite in the presence of hydrochloric acid to give pyridine-2-carbohydroximoyl chloride **1** using the method of Kočevar *et al.*[14] Pyridin-2-nitrile oxide was generated *in situ* by the treatment of pyridine-2-carbohydroximoyl chloride **1** with triethylamine in dichloromethane/THF. This was reacted with 2-methylbut-1-en-4-ol **2a** and 2-phenylbut-1-en-4-ol **2b** to give 5-methyl and 5-phenyl 5-(2-hydroxyethyl)-3-(pyrid-2-yl)-Δ^2-isoxazolines **3a,b**, respectively, in around 90% yield (Scheme 2).[15] In agreement with other reports[16] none of the regioisomeric cycloadduct was detected in either case. Importantly, there was no noticeable decrease in yield when using the more sterically demanding dipolaraphile **2b**.

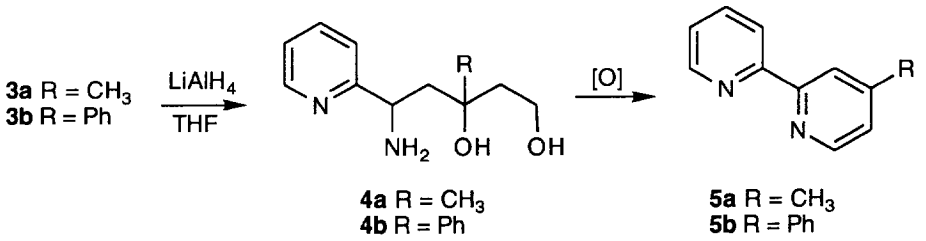


1 **2a** R = CH_3 **2b** R = Ph **3a** R = CH_3 **3b** R = Ph

Scheme 2

In order to convert the isoxazolines **3a,b** to bipyridines the isoxazoline ring must be opened and the resulting functionalised carbon skeleton converted to a pyridine ring. The nitrogen-oxygen bond of isoxazoline rings has been cleaved in a variety of ways.[17] The most common of these is catalytic hydrogenolysis on Raney nickel in the presence of boric acids,[18] leading in one case to alicyclic precursors that could be cyclized to pyridine derivatives.[19] In our hands treatment of the isoxazolines **3a,b** under these conditions led to a complex mixture of products, presumably due to undesired complexation of the metal catalyst with the substrate.[20] The isoxazolines **3a,b** were reductively cleaved with $LiAlH_4$ to give 2-(3-substituted-1-amino-3,5-dihydroxypentyl)-pyridines **4a,b** in over 70% yield (Scheme 3).[21]

The amino alcohols **4a,b** could be oxidised under Swern conditions, with concomitant cyclisation and water elimination, to give a low yield (*ca.* 15%) of the corresponding 2,2'-bipyridines **5a,b**. Other methods of oxidation using metal based oxidants (eg. manganese, nickel, or chromium oxides) were less successful. In these cases the product bipyridines, if formed, may have formed complexes with the metals making recovery difficult. The Dess-Martin periodinane[22] was found to achieve this transformation in a satisfactory 42% yield.[23]



Scheme 3

The 4-substituted-2,2'-bipyridines prepared in this way were uncontaminated by positional isomers. The key nitrile oxide cycloaddition does not appear to be greatly affected by steric requirements and we would therefore expect this method to be general.

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15. Typical procedure: To a stirred solution of pyridine-2-carbohydroximoyl chloride **1** (1.56 g, 10 mmol) and 2-methylbut-1-en-4-ol (1.29 g, 15 mmol) in dichloromethane (20 ml) and THF (20 ml) at 0°C was added triethylamine (1.5 g, 15 mmol). The solution was allowed to come to room temperature and

stirred for 1 hr. The solvent was removed under reduced pressure and the residue taken up in dichloromethane (30 ml). The solution was washed with water (3 x 20 ml), dried ($MgSO_4$) and concentrated under reduced pressure to give a light brown oil which was purified by radial chromatography to afford 5-(2-hydroxyethyl)-5-methyl-3-(pyrid-2-yl)-Δ^2-isoxazoline **3a** (1.7 g, 87%).

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20. Note: GC-MS analysis of these mixtures showed evidence of 2,2'-bipyridine formation however this was not supported by the n.m.r. spectral data. It is probable that the open-chain intermediates were cyclising to pyridine compounds in the injector block of the GC.
21. Typical procedure: Lithium aluminium hydride (0.77 g, 20 mmol) was suspended in THF (15 ml), cooled to 0°C, and to this was added dropwise 5-(2-hydroxyethyl)-5-methyl-3-(pyrid-2-yl)-Δ^2-isoxazoline **3a** (1.05 g, 5.1 mmol) in THF (15 ml). The reaction mixture was stirred for 4 hr at 0°C and then allowed to stand overnight at –15°C. Saturated sodium sulphate solution (1.5 ml) was added and the suspension was filtered. The precipitate was washed with dichloromethane (50 ml) and the combined filtrates were dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil. The crude product was purified by column chromatography on silica using methanol as eluent to give 2-(1-amino-3,5-dihydroxy-3-methylpentyl)-pyridine **4a** as a pale yellow oil (0.78 g, 74%).
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23. Typical procedure: The Dess-Martin reagent 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (3.9 g, 9.2 mmol) in dichloromethane (15 ml) was added to a solution of 2-(3-methyl-1-amino-3,5-dihydroxypentyl)-pyridine **4a** (0.48 g, 2.3 mmol) and camphorsulfonic acid (0.53 g, 2.3 mmol) in dichloromethane (10 ml) at 0°C. The mixture was stirred for 1 hr then 1.3 M sodium hydroxide solution (20 ml) and diethyl ether (60 ml) were added. The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 x 20 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give 4-methyl-2,2'-bipyridine **5a** (0.17 g, 42%).

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