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Synthesis of mono-substituted 2,2′-bipyridines†

Joseph G. Cordaro,[a] James K. McCusker*[b] and Robert G. Bergman*[a]

[a] *Department of Chemistry, University of California, Berkeley, California 94720-1460, USA. E-mail: bergman@cchem.berkeley.edu; Fax: 1-510-642-7714; Tel: 1-510-642-2156*

[b] *Department of Chemistry, Michigan State University, East Lansing, Michigan 48824-1322, USA. E-mail: mccusker@cem.msu.edu; Fax: 1-517-353-1793; Tel: 1-517-355-9715, ext. 106*

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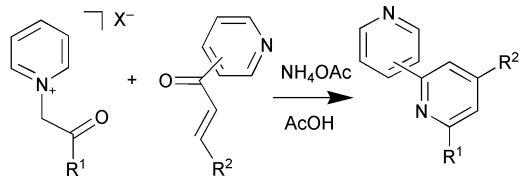
The rapid synthesis of 4-aryl-2,2′-bipyridines is described leading to some previously reported compounds in good yields in addition to some new functionalized bipyridines.

The 2,2′-bipyridine (bpy) ligand continues to play an important role in organic and inorganic chemistry,[1] photochemistry[2] and, more recently, materials science, polymer[3] science and dendrimer[4] chemistry. The functionalization of bipyridines is a crucial step for introducing these ubiquitous ligands in new applications. Unsymmetrical derivatization of bipyridyl ligands is of particular interest for applications in photo-induced energy and electron transfer processes. However, only a few recent examples of general methods for preparing such compounds are known.[5]

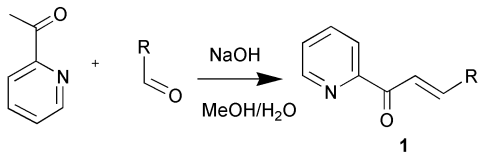
Early reports of the synthesis of mono-substituted bipyridines relied on the procedure developed by Kröhnke [eqn (1)].[6]



(1)

Although occasionally used today as a means of preparing 4-(aryl)-2,2′-bipyridines, the yields are low (usually around 30%) and can be inconsistent. In addition, isolation of the desired product can be difficult when isomers are formed. Alternatively, 4-bromo-2,2′-bipyridine can be functionalized *via* lithium–halogen exchange or palladium-catalyzed coupling reactions, giving mono-substituted products. The usefulness of this methodology is limited by the availability of the starting material (4 steps, < 40% yield for 4-bromo-2,2′-bipyridine) and the sensitivity of the reactions to oxygen and moisture. Mono-deprotonation of 4,4′-dimethyl-2,2′-bipyridine with a strong base followed by the addition of an electrophile has also been used, but with limited scope. Alternative methods[7] typically require multiple steps and often arduous reaction conditions. In view of these limitations, we sought to develop a convenient high-yielding synthesis of mono-substituted 2,2′-bipyridines.

Åkermark *et al.* and then Raston *et al.*[8] were able to synthesize terpyridines *via* an aldol condensation and Michael addition reaction utilizing acetylpyridine and substituted benzaldehydes. The resulting diketone is transformed into the pyridine product following treatment with ammonium acetate in acetic acid. Based on this methodology, we felt that bipyridines could similarly be synthesized using the product of the aldol condensation reaction. Employing 2-acetylpyridine and substituted benzaldehydes hetero-diene products **1a–i** were isolated in yields of 40–85% [eqn. (2)].[9] The reaction proceeds best

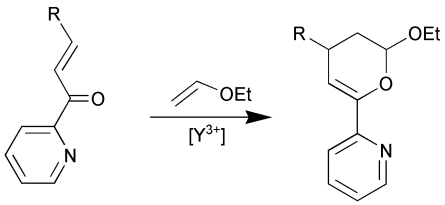


(2)

1

when freshly distilled 2-acetylpyridine is used. The product usually precipitates from the reaction mixture and can be recrystallized from methanol to obtain analytically pure material. Solids **1a–i** can be stored for months without noticeable decomposition but decompose readily in $CDCl_3$.

Ciufolini and others have shown that pyridines can be obtained from dihydropyrans.[10] The conversion of **1** to the dihydropyran **2** is catalyzed by commercially available yttrium(III) hexafluoroacetylacetonate, (abbreviated [Y^{3+}]) with a ten-fold excess of ethyl vinyl ether in THF or CH_2Cl_2 at room temperature [eqn. (3)].[11] The reaction can be run successfully without inert atmosphere protection.



(3)

1 **2**

Additionally, by adding 4 Å molecular sieves to the reaction flask it was found that the need to use pre-dried solvents was eliminated.[12] The reaction does proceed without sieves but reaction times are generally longer. The hygroscopic catalyst [Y^{3+}] can be stored in a desiccator and used as needed. Typically, concentrations of 0.20 M **1** and 2.0 M ethyl vinyl ether were required to observe $t_{1/2}$ = 18 h; lower concentrations of **1** drastically increased the reaction time. The reaction was also attempted without a catalyst and with other catalysts. Heating **1b** with neat ethyl vinyl ether in a thick-walled glass vessel at 95 °C gave little or no reaction after 24 h. Employing $bpyCu(OTf)_2$ (OTf = trifluoromethanesulfonate) as the catalyst in CH_2Cl_2 required heating the solution to 50 °C and appeared to give a polymer as a side product. Most products were isolated *via* chromatography to give oils. Compounds **2c**, **e**, **h** and **i** can be crystallized directly from the crude reaction mixture.‡

Attempts to convert **2** to **3** using refluxing AcOH with NH_4OAc provided low yields of the bipyridine and unwanted side products. Replacing AcOH with MeOH or EtOH did not improve the yields and required heating the solution to 135 °C in a sealed flask. Using water as the solvent gave no detectable reaction even after prolonged heating, presumably due to the poor solubility of **2**. In our reaction, an oxidation is necessary to achieve the required oxidation state in the new pyridine ring, which may explain the unidentifiable reaction products. Turning again to the work of Ciufolini,[10] we utilized $H_2NOH{\cdot}HCl$ as the source of nitrogen for making pyridine derivates from

† Electronic supplementary information (ESI) available: experimental details and full characterization of new compounds. See http://www.rsc.org/suppdata/cc/b2/b203595b/

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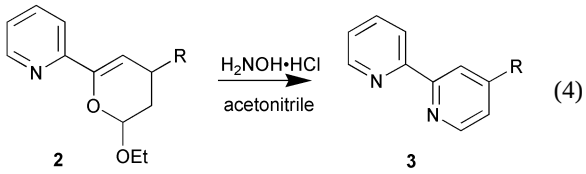
dihydropyrans [eqn (4)]. Substitution of NH_4OAc with



(4)

$H_2NOH{\cdot}HCl$ resulted in successful transformation of **2** to **3**. Refluxing acetonitrile gave good yields of bipyridine for all substrates in reaction times near 6 h. To our surprise, the reaction is very sensitive to solvent. Methanol, ethanol and acetic acid all give the desired bipyridine product but in low yields (< 30%). The product was usually purified *via* crystallization from methanol or crystallization of the hydrochloride salt from acetone–H_2O.†

The range of substituents covered in this three-step reaction sequence illustrates the functional group compatibility of this methodology (Table 1). Yields for the isolation of the final bipyridine products range between 10 and 40% from the starting aldehyde, which is considerably more efficient than previously published methods. This reaction sequence reduces the number of steps required to access many interesting ligands. For example, bipyridinyl ligands **3h** and **3i** have been synthesized in multi-step reactions[13] and have found use in the study of light induced energy and electron transfer processes.[14] Although no photophysical studies have been done, the anthracenyl ligand **3e** could potentially enhance luminescence from chelated metals. The bromo-substituted aryl-bipyridine **3b** is poised to undergo various coupling or lithiation reactions as previously demonstrated.[15] We hope this new method for the synthesis of unsymmetrically substituted bipyridinyl ligands will provide additional stimulus for the use of this robust and versatile ligand in inorganic and materials chemistry.

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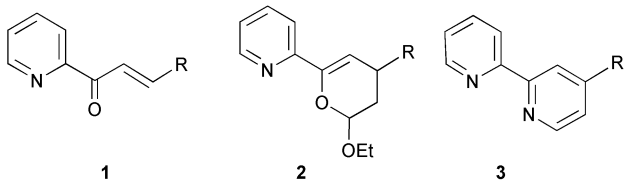
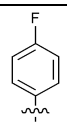
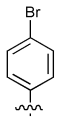
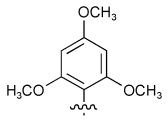
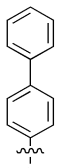
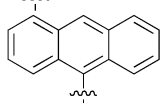
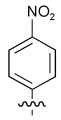
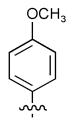
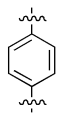
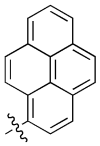
Table 1 Yields for reactions in eqn. (2)–(4)



Series	R	% yield (**1**)	% yield (**2**)	% yield (**3**)
a		51	98	35, 21[a]
b		66	92	41
c		78	56	41
d		86	87	51
e		79	90	57
f		57	95	18
g		73	77	36
h		65	66	25[b]
i		46	65, 78[c]	51

[a] Yield of product without isolation of intermediate **2a**. [b] Crude yield, see supporting data. [c] Isolated yield *via* chromatography

Notes and references

‡ The crude product **2** was successfully used in the last step of the reaction, although yields were diminished. See entry **2a** in Table 1.

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