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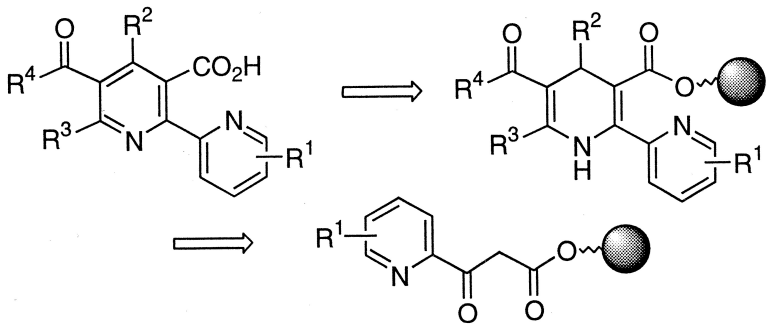

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Solid-Phase Synthesis of Highly Functionalized 2,2′-Bipyridines†

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Functionalized 2,2′-bipyridines have long been the focus of considerable attention as ubiquitous chelating ligands that form coordination complexes with transition metals across virtually the entire periodic table.[1] In particular, ruthenium complexes of biyridine and related diimine ligand systems have been extensively investigated for their fascinating photophysical and electrochemical properties[2] and have found numerous applications in studies of photoinduced electron transfer,[3] artificial photosynthesis,[4] and photocatalysis.[5] Moreover, because of the predictable coordination properties of these ligands, the bipyridines, along with higher oligopyridines, have become key building blocks in the formation of discrete metallosupramolecular species having well-defined geometries and stoichiometries.[6] In this report we disclose the first solid-phase synthesis of 2,2′-bipyridines via sequential Knoevenagel and Hantzsch condensation reactions. This work provides a foundation for future studies on the synthesis of libraries of metal−bipyridine coordination compounds and the evaluation of these complexes in screens for molecular recognition, electron and/or energy transfer, and catalysis.

Among the many classical approaches for preparation of 2,2′-bipyridines, the condensation of α,β-unsaturated ketones with pyridinium salts in the presence of ammonium acetate/acetic acid, due to Kröhnke, probably provides the most reliable and versatile synthesis of highly functionalized oligopyridines.[7] In recent years this method has been supplemented by the improved protocols introduced by Potts[8] and Jameson.[9] Newer transition-metal-mediated strategies based upon Pd-catalyzed heteroaryl cross coupling[10] and Co(I)-catalyzed [2+2+2] cyclotrimerization of alkynes and nitriles[11] also offer useful options for elaborating the 2,2′-bipyridine nucleus.

In a previous publication from these laboratories, a solid-phase adaptation of the Hantzsch condensation reaction was shown to provide an efficient synthesis of diversely substituted 2-methyl nicotinic acids.[12] We envisaged that highly functionalized 2,2′-bipyridine carboxylates **1** and **2** should be accessible via two complementary strategies as summarized in Scheme 1. In the first route, condensation of a polymer-supported picolinoyl acetate **3** with an aldehyde and an α-oxo enamine **10** would provide the 3-carboxylate **1** via a 1,4-dihydro-2,2′-bipyridine intermediate.[13] Alternatively, one 2-pyridyl fragment could be contributed by the α-oxo enamine building block **11**, with an aldehyde and a resin-bound β-ketoester **6** serving as heterocyclization partners en route to the 2,2′-bipyridine-5-carboxylate **2**. Resin-tethered β-ketoesters are key inputs to both routes, and we have found that a variety of hydroxyl-functionalized supports can be cleanly acylacetylated upon thermolysis with either *tert*-butyl esters **9** or the acyl Meldrum's acids **12**. These activated β-ketoester equivalents, **12**, are readily generated by carbodiimide-mediated reaction of carboxylic acids with Meldrum's acid and have been previously reported by Tietze and co-workers as valuable precursors of polymer-supported β-ketoesters for solid-phase synthesis.[14] While substituted picolinoyl acetates **3** generally can be prepared from either **9** or **12**, superior results are obtained through transesterification reactions of the *tert*-butyl esters **9**.[15]

Acylation of the acid-labile resin, Sasrin, was typically complete after overnight treatment with **9** or **12** at 70 °C. Knoevenagel reaction of β-ketoester resins **3** and **6** with aromatic aldehydes yielded stable arylidene intermediates **4** and **7**,[16] which underwent Hantzsch heterocyclization with enamino-esters (and enamino-ketones) to provide resin-bound 1,4-dihydro-2,2′-bipyridines **5** and **8**. Oxidation with ceric ammonium nitrate (CAN) afforded the fully elaborated bipyridines **1** and **2** which were liberated from the support upon brief treatment with trifluoroacetic acid (TFA). A wide range of picolinoyl acetate and aldehyde building blocks were evaluated in this synthetic sequence to assess the influence of electronic and steric factors on the reaction outcome. While both electron-withdrawing and -donating functionality were well tolerated in **3**, highly electron-rich aryl aldehydes (e.g., *p*-dimethylaminobenzaldehyde) failed to yield the desired bipyridines. Most 3-amino acrylate esters, **10**, examined underwent smooth conversion to bipyridines **1**, although enamines bearing strongly polarizing 3-substituents (e.g., ethyl 3,3-diaminoacrylate or methyl 3-amino-3-trifluoromethylacrylate) did not afford the expected products. Four 2,2′-bipyridine-5-carboxylates, **2a**−**d**, were generated from polymer-supported β-ketoesters **6** and 3-amino-3-pyrid-2′-yl acrylate esters **11**. These latter building blocks could be readily obtained from their corresponding β-ketoesters by treatment with ammonium acetate in benzene at 80 °C. A representative selection of bipyridines, **1** and **2**, obtained via these solid-phase protocols is shown in Table 1. While crude yields for these products typically exceeded 50% (based on initial resin loading), the purified bipyridines were generally isolated in ∼30% overall yield.

The feasibility of further adapting this chemistry to generate substituted 2,2′:6′,2″-terpyridines was demonstrated in a hybrid synthetic approach: condensation of resin-bound 6-Cl-picolinoyl acetate, 4-biphenylcarboxaldehyde, and methyl 3-amino-3-pyrid-2′-yl acrylate afforded terpyridine **13** in 48% yield. Combinatorial synthesis of bis-heteroleptic terpyridine ruthenium complexes has recently been explored by Hamilton and colleagues as part of a metal-templated strategy

† Dedicated to Professor Warren R. Roper on the occasion of his 60th birthday.

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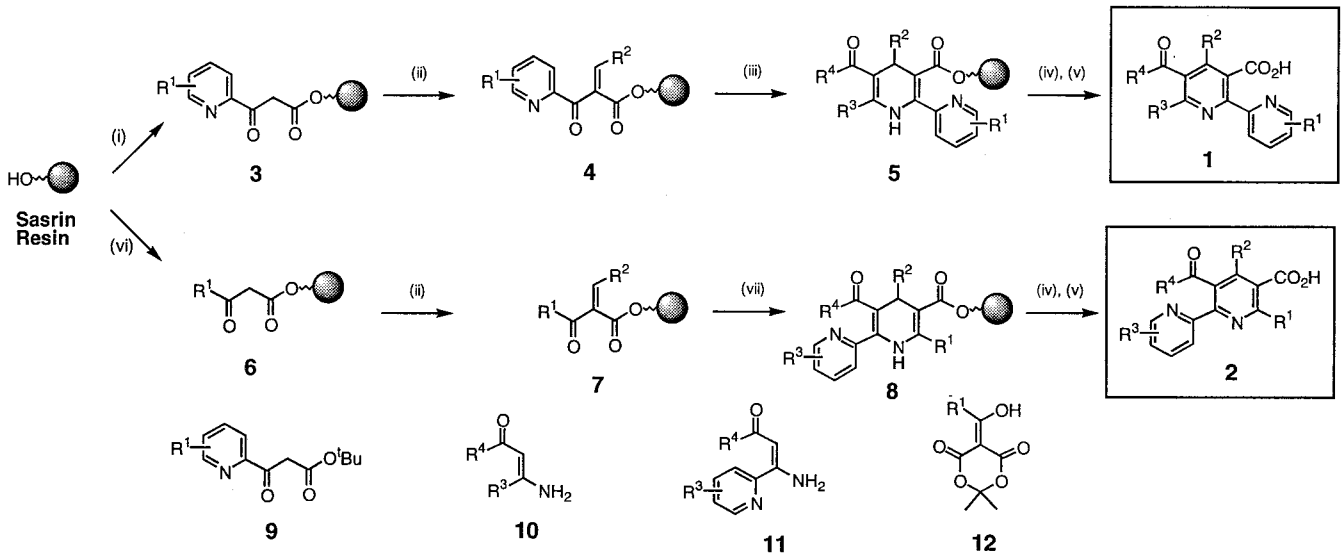
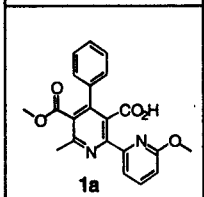
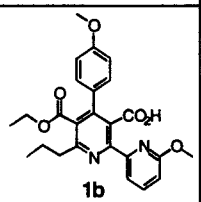
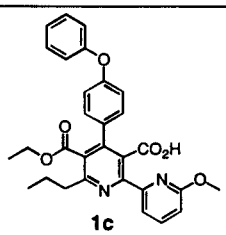
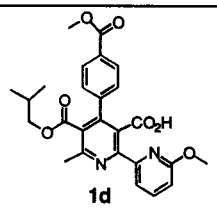
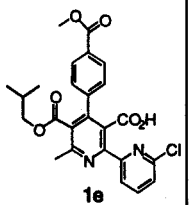
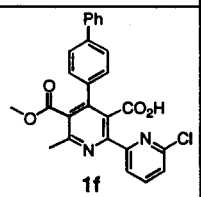
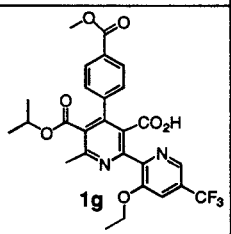
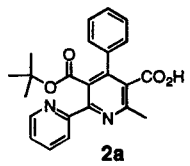
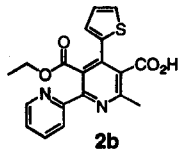
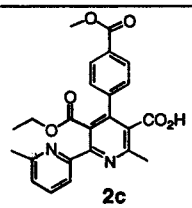
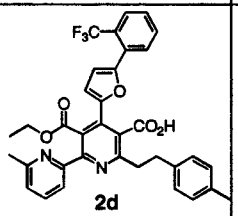
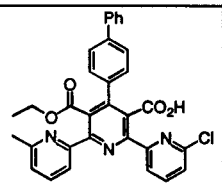
Scheme 1[a]



[a] Reagents and conditions: (i) **9**, toluene, 70 °C; (ii) R^2CHO, piperidine, $CH(OMe)_3$, DMF, 65 °C; (iii) **10**, $CH(OMe)_3$, DMF, 80 °C; (iv) CAN, DMA; (v) 3% TFA in CH_2Cl_2; (vi) **12**, toluene, 70 °C; (vii) **11**, $CH(OMe)_3$, DMF, 80 °C.

Table 1

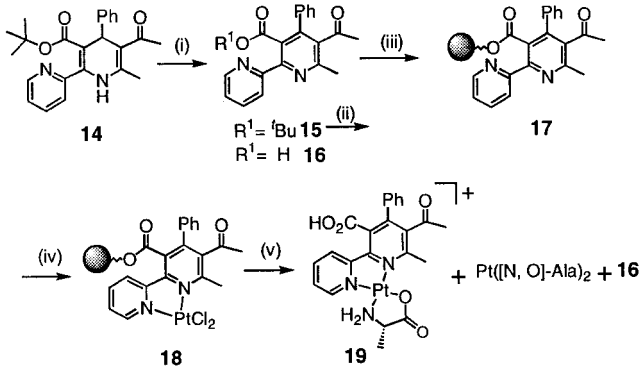
	Yield[a] (Purity)		Yield[a] (Purity)		Yield[a] (Purity)		Yield[a] (Purity)
 1a	31* (95)	 1b	33* (98)	 1c	28* (85)	 1d	31* (90)
 1e	63 (98)	 1f	84 (90)	 1g	47 (75)	 2a	79 (85)
 2b	47 (76)	 2c	65 (85)	 2d	54 (78) -	 13	48 (70)

[a] Yields designated with an asterisk represent isolated yields for purified bipyridines. In other instances, gravimetric analysis of crude material and purity assessment by HPLC (monitoring at $\lambda = 220$ nm) were used to estimate product yield.

for synthetic receptor design, and the results reported here could form one approach toward extending this work.[17]

In a preliminary study to understand the capacity for polymer-supported bipyridines assembled via the Knoevenagel/Hantzsch sequence to coordinate transition metals, the dihydro-bipyridine **14** was prepared in solution under standard conditions from acetylacetone, benzaldehyde, and *tert*-butyl 3-amino-3-pyrid-2′-yl acrylate, converted to the corresponding bipyridine-3-carboxylic acid **16**, and coupled to acid-labile Wang resin (see Scheme 2). The resulting bipyridine resin **17** could also be simply derived by transesterification of **15** with Wang resin in toluene at 70 °C. This resin was treated with an equivalent amount (based on initial resin loading) of *cis*-$Pt^{II}Cl_2(NCPh)_2$ in 1,2-dichloroethane (DCE) at 60 °C. The deep red−brown solution decolorized over 12 h, consistent with metalation of the

Scheme 2[a]

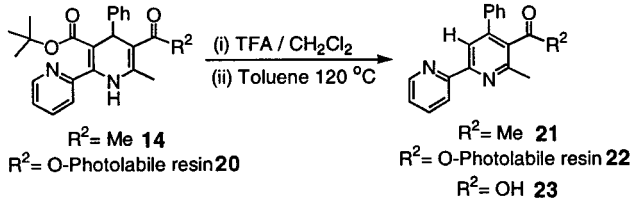


[a] Reagents and conditions: (i) CAN, DMA; (ii) TFA, CH_2Cl_2; (iii) Wang resin, DIC, DMAP, DMF; (iv) $PtCl_2(NCPh)_2$, DCE, 60 °C; (v) L-alanine, $NaHCO_3$, THF, H_2O, 80 °C.

bipyridine to afford dichloro complex **18** (N.B. displaced benzonitrile was detected in the filtrate). However, attempts to cleave this complex from resin (10% TFA in CH_2Cl_2) provided a mixture containing the expected complex $Pt^{II}Cl_2$(**16**) along with the unmetalated ligand **16** and uncharacterized platinated species.[18] Because of the lability of $Pt^{II}Cl_2$(**16**) toward reverse-phase chromatographic analysis, we sought to convert **18** to a more inert complex by treatment of the resin-bound complex with alanine in aqueous THF under weakly basic conditions. The filtrate from this reaction was bright yellow, and electrospray MS analysis suggested that the bipyridine−amino acid Pt^{II} complex **19** had, unexpectedly, undergone spontaneous cleavage from the resin.[19] The solution also contained variable amounts of the bis-alanine platinum complex Pt([N,O]-Ala)$_2$ and the unmetalated ligand **16**. Formation of both this bis-amino acid complex and **16** could be minimized by treating the resin with a substoichiometric quantity of alanine, and under these conditions the major component of the filtrate was complex **19**.

These results underscore a certain lability of complexes of this highly functionalized bipyridine ligand that likely follows from unfavorable steric interactions between substituent groups at the 3 and 3′ positions when the *syn* geometry appropriate for bidentate metal binding is adopted. Such effects have been previously recognized and are manifested structurally in the form of significant out-of-plane torsions to minimize steric repulsion between the 3 and 3′ substituents.[20] A second factor that could substantially attenuate the coordinating strength of these functionalized bipyridines is the presence of strongly electron-withdrawing ester and carbonyl substituents at the 3 and 5 positions of the bipyridine ligand. We have explored the potential of removing the 3-alkoxycarbonyl group by oxidative decarboxylation in a model solution-phase reaction. TFA deprotection of the dihydro-bipyridine **14** followed by overnight thermolysis in toluene cleanly afforded the decarboxylated product **21** (see Scheme 3). This simplified bipyridine was converted to a single regioisomer of the mixed ligand complex [Pt([N,O]-Ala)(**21**)]Cl under the conditions described above. Mixed bipyridine−amino acid complexes have attracted interest as DNA-binding cytotoxic agents, and the synthetic methodology outlined here suggests one strategy

Scheme 3



for combinatorially exploiting this lead series.[21,22] There are also preliminary indications that the decarboxylation reaction can be performed on resin-bound dihydro-bipyridines (Scheme 3). Thus resin **20**, a product of Knoevenagel/Hantzsch condensation on the photolabile Hydroxyethyl-Photolinker NovaSyn resin (Novabiochem), was acid-deprotected and heated as previously described above to afford bipyridine **22** and characterized as its 5-carboxylic acid derivative **23** upon photolytic cleavage (λ = 365 nm) in ^{i}PrOH. Further studies will be required to optimize the efficiency of this on-resin decarboxylation reaction.

In summary we have developed a versatile solid-phase synthesis of highly functionalized bipyridines based on the classical Hantzsch three-component condensation reaction. This method has recently been applied to the generation of a library of 500 bipyridines by split/pool synthesis from 5 β-ketoesters, 10 aldehydes, and 10 electron-deficient enamines. These compounds can be exploited directly or modified to provide ligands useful for constructing combinatorial arrays of oligopyridyl coordination complexes having a potentially diverse range of functions, including DNA-recognition agents and photosensitizers. Our work in this area will be the subject of future publications.

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Supporting Information Available. Experimental protocols and characterization data for bipyridine products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Substituted picolinic acids were converted to the corresponding *tert*-butyl picolinoyl acetates by esterification (diazomethane) and then displacement with the sodium enolate of *tert*-butyl acetate.
(16) Previous on-resin analysis of ^{13}C-labeled benzylidene products by gel-phase ^{13}C NMR indicated that the Knoevenagel derivatives of aryl aldehydes were stable toward typical resin handling and washing; see ref 12.
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(18) These products were identified by electrospray MS and were not further characterized.
(19) The resin-bound precursor of **19**, [Pt([N,O]-Ala)(**17**)]$^+$ is a cationic complex, and this electropositive character may account, in part, for the hydrolytic susceptibility of the ester linkage. In a control experiment, the unmetalated bipyridine resin **17** was unaffected by treatment with alanine/$NaHCO_3$ in aqueous THF at 80 °C.
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