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Synthesis of a 2,3′;6′,3″-Terpyridine Scaffold as an α-Helix Mimetic

Jessica M. Davis, Anh Truong, and Andrew D. Hamilton*

Department of Chemistry, Yale University, P.O. Box 20810, New Haven, Connecticut 06511

andrew.hamilton@yale.edu

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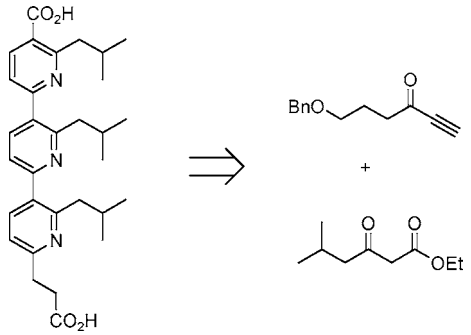
ABSTRACT



A terpyridine scaffold has been designed as an α-helix mimetic. A facile synthesis of the ortho-functionalized 2,3′-oligopyridine has been accomplished using sequential Bohlmann–Rahtz heteroannulation reactions.

α-Helices on protein surfaces function as recognition regions for protein−protein, protein−DNA, and protein−RNA interactions. Mimicking these domains with small molecules has proven to be an effective means to disrupt protein function.[1]

In many cases, residues in the *i*, *i* + 4, *i* + 7, and *i* + 11 positions on the helix play a key role in mediating protein contact. For example, the interaction of Bcl-x_L with Bak involves the residues Val74, Leu78, Ile81, and Ile85 on the α-helical BH3 domain of Bak, making contacts with a shallow hydrophobic cleft on the surface of Bcl-x_L.[2]

We have previously established that a trisfunctionalized 3,2′,2″-terphenyl (Figure 1) has the appropriate spacial arrangement of substituents to mimic the *i*, *i* + 3 or *i* + 4, and *i* + 7 residues of an α-helix.[3] In this study, we sought to expand the strategy to include scaffolds based on other aryl derivatives, such as pyridine.

Pyridines play important roles in pharmaceuticals, agrochemicals, and preparative organic chemistry. As a result, many methods of pyridine synthesis have been developed.[4] In the case of oligopyridines, several examples of 2,2′-bipyridine synthesis can be found in the literature, primarily because of their application in metal chelation.[5] Fewer examples of other substitution patterns can be found, although such systems are desirable for use as pharmacophores in drug design and in situations where metal chelation may interfere with the desired effect.

* Corresponding author. Tel: + 1-203-432-5570. Fax: + 1-203-432-3221.

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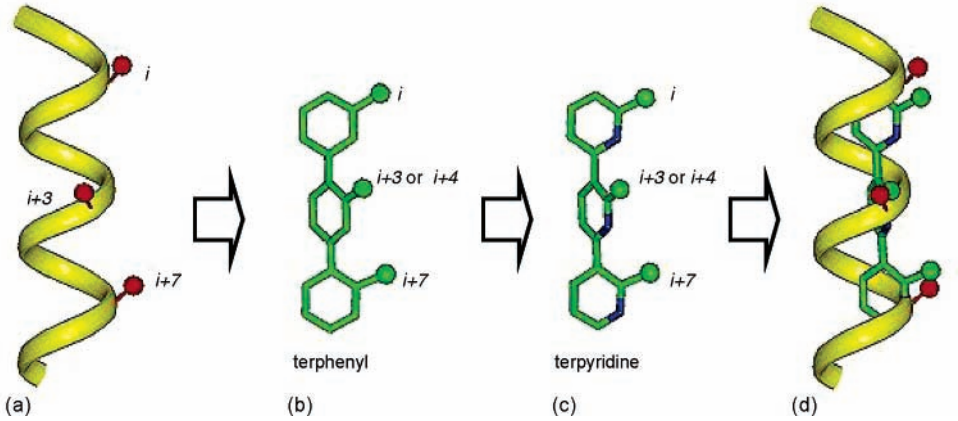
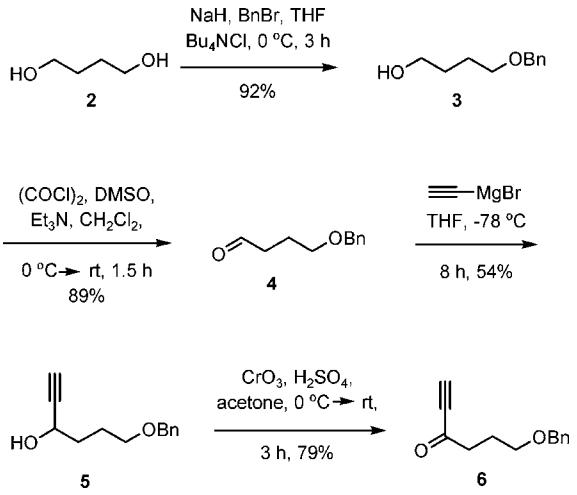


Figure 1. Evolution of α-helix mimetic design: (a) α-helix with *i*, *i* + 3, and *i* + 7 residues highlighted in red; (b) energy-minimized trimethyl-substituted terphenyl; (c) energy-minimized trimethyl-substitued terpyridine; (d) superimposed terpyridine on the α-helix (root-mean-square deviation of 1.14 Å). (Image produced using InsightII.)

The 2,3′-substitution pattern desirable for an α-helix mimetic can be synthesized through heteroannulation conditions first reported by Bohlmann and Rahtz[6] and further developed by Bagley et al.[7] The reaction provides a handle for subsequent heteroannulations in the form of an ester. An efficient conversion of the ester to the ketoalkyne annulation precursor can be used for rapid oligopyridine synthesis.

Ketoalkyne **6** was synthesized from 1,4-butanediol (Scheme 1).[8] The diol was monoprotected using standard methods,

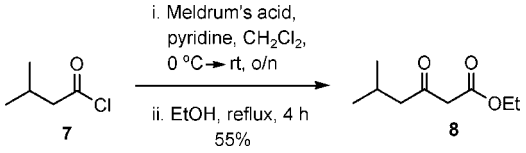
Scheme 1. Synthesis of **6**



with subsequent oxidation of the free alcohol, via Swern conditions, to afford the aldehyde **4**. The addition of ethynylmagnesium bromide, followed by Jones oxidation, yielded compound **6**.

Ethyl 5-methyl-3-oxohexanoate (**8**) was obtained by reaction of Meldrum's acid with pyridine and isovaleryl chloride in methylene chloride. The resulting intermediate was then refluxed in ethanol to obtain the β-keto ester **8**, as shown in Scheme 2.[9]

Scheme 2. Synthesis of β-Keto Ester **8**



The pyridine was synthesized through adaptation of the conditions reported by Bagley et al.,[7] who found that refluxing 1 equiv of β-keto ester with up to 2 equiv of the alkynone with ammonium acetate and a Lewis acid catalyst allows for a one-pot condensation to form a 2,3,4,6-tetrasubstituted pyridine. For our terpyridine scaffold, the easily obtained β-keto ester was used in excess and first refluxed in toluene with dry ammonium acetate for 1 h to generate the enamine. The alkynone was then added with the Lewis acid, and the reaction was refluxed for an additional 48 h. Similarly to Bagley et al., we found that ytterbium(III) triflate gave slightly better yields than zinc(II) bromide, as seen in Table 1.

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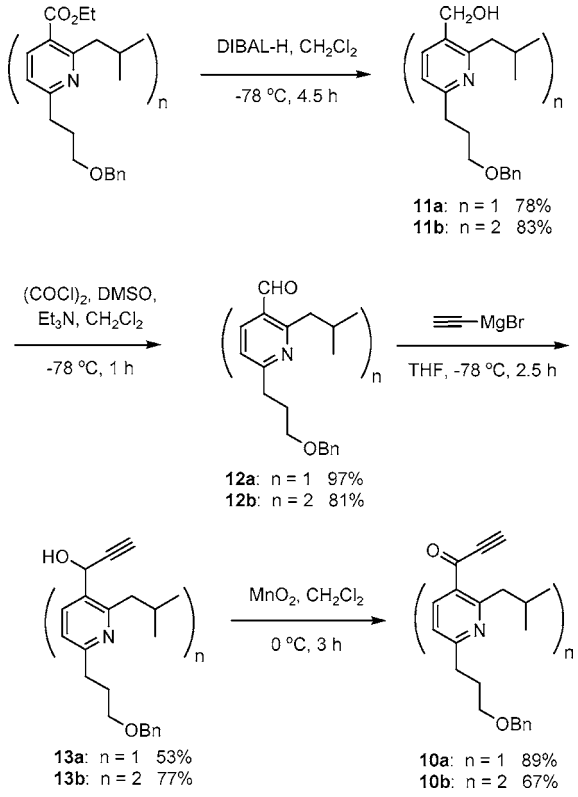
The desire for a facile route to oligopyridine scaffolds led to a thorough investigation of an efficient conversion of the pyridine ester to the pyridine alkynones (**10a**,**b**). Our route to compounds **10a**,**b** orginally involved a four-step sequence using well-established chemistry, as shown in Scheme 3. The

Scheme 3. Original Extended Synthesis of Pyridine Alkynones



ester was first reduced to the alcohol with DIBAL-H and then oxidized to the aldehyde under Swern conditions. Addition of ethynylmagnesium bromide followed by oxidation with manganese(II) oxide gave the alkynones **10a**,**b**.

This route was deemed unsuitable for an efficient oligopyridine synthesis because of the length of the sequence and the overall low yields. Therefore, various conditions were explored to synthesize the alkynone in one or two steps. We found that conditions similar to those reported by Williams et al. gave the best results.[10] They reported that with excess Grignard, the ketone can be obtained in one step from the

Scheme 4. One-Step Pyridine Alkynone Synthesis

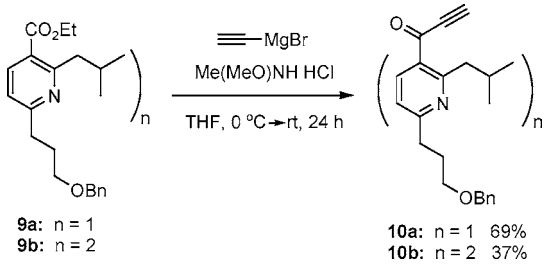
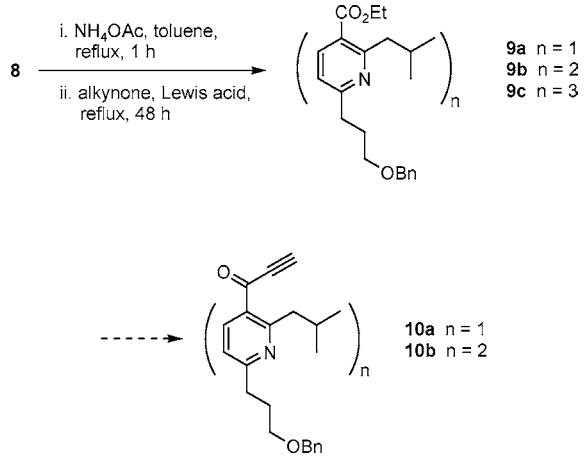


Table 1. Bohlmann−Rahtz Heteroannulation

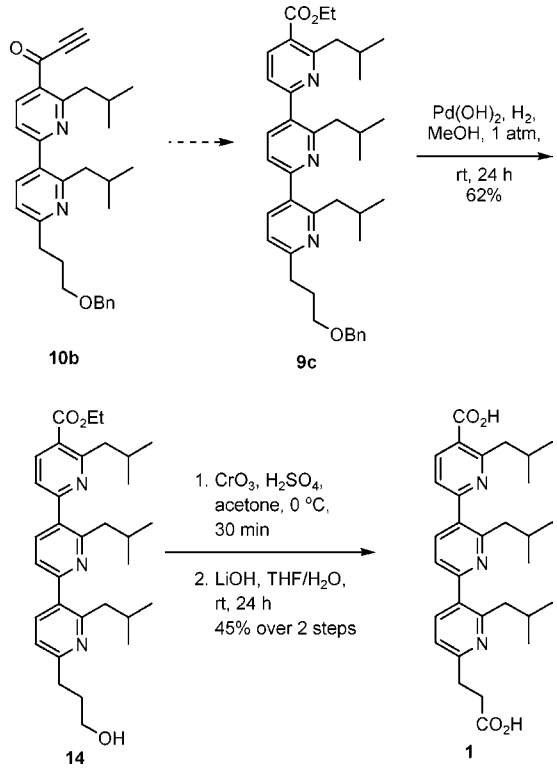


alkynone	Lewis acid	product	yield (%)
6	$ZnBr_2$	**9a**	61
6	$Yb(OTf)_3$	**9a**	65
10a	$ZnBr_2$	**9b**	47
10a	$Yb(OTf)_3$	**9b**	78
10b	$ZnBr_2$	**9c**	45
10b	$Yb(OTf)_3$	**9c**	57

ester. The pyridine alkynone was synthesized in reasonable yield with in situ generation of the Weinreb amide from the ester, as shown in Scheme 4.

As shown in Scheme 5, the final product, terpyridine **1**, was obtained in three steps from **10b**. The benzyl ether was

Scheme 5. Completion of Terpyridine **1**



deprotected with palladium hydroxide as a catalyst under a hydrogen atmosphere. Jones oxidation was used to obtain the monoacid, and the ester of the crude oxidation product was saponified with lithium hydroxide in water and THF.

Terpyridine **1** was synthesized in 15 steps from 1,4-butadiol. The key repetitive sequence of the synthesis, seqential condensation followed by ketoalkyne generation, provides a route to 2,3′-oligopyridines. The terpyridine **1** and other analogues will be tested against the Bcl-x_L/Bak peptide interation, the results of which will be reported in a subsequent report.

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Supporting Information Available: Experimental procedures and characterizations of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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