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Synthesis of a Bipyridine Ligand for Metal-Triggered Supramolecular Polymers

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INTRODUCTION

In the natural world, there are many examples of polymerized monomeric biomolecules capable of spontaneously ordering their own structures into utile conformations. For example, the form and catalytic ability of enzymatic proteins are determined by transient forces known as non-covalent interactions, which occur between the residues of the amino acids of which that enzyme is composed (Busserson et al., 2013). Ionic interactions between oppositely-charged residues can generate an attractive force that pulls regions of the protein into closer proximity. The spontaneous clustering of hydrophobic residues promotes the inward “collapse” of the protein structure, generating a hydrophobic core with hydrophilic residues left exposed to the aqueous environment. Other residues might act as ligands for metal ions, both stabilizing the protein’s structure and sequestering the ion as a catalytic agent within the active site (Yang et al., 2015).

Taking inspiration from such biological analogs, material scientists are able to carefully design synthetic molecules that utilize non-covalent interactions to self-assemble into supramolecular polymers (Webber et al., 2016). Forming these superstructures does not require breaking or forming covalent bonds, and the final products can assume a variety of three-dimensional shapes...
(such as ribbons, sheets, capsules, or tubes), with unique characteristics and applications according to their monomeric subunits (Palmer and Stupp, 2008). For example, synthetic oligopeptides are of great interest to the field of biomimetics, where self-assembling polymers can be delivered to damaged organs to form an organic scaffold in which mesenchymal stem cells promote tissue regeneration (Gao et al., 2017). Applications outside of medicine include the catalysis of reactions that require metal ions. Much like enzymes, synthetic aggregates can promote the interaction of reagents with a chelated metal ion and catalytic residues. The monomeric subunits of such aggregates can be tailored to form a superstructure that presents an active site with a size and catalytic activity that accommodates the reagents of a particular reaction (Zhang et al., 2012; Zhao et al., 2018).

This report details the synthesis of one such molecule that will undergo further modification to yield an amphiphilic monomer that is expected to self-assemble through non-covalent interactions, forming a catalytic superstructure.

The molecule of interest, 2-(pyridin-2-yl) pyridine-5-carboxylic acid (referred to in this report as compound 5, see Scheme 1) is a known metal chelator, capable of forming transient, stabilizing interactions with divalent metal ions (such as Fe$^{2+}$, Ni$^{2+}$, Zn$^{2+}$ and Cu$^{2+}$) (Das et al., 2017). Once synthesized, compound 5 will be incorporated into an amphiphilic scaffold (see Figure 1), containing a lysine-derived “linker region” and an aromatic naphthoate group. This monomer, referred to as naph-X, is expected to demonstrate surfactant-like behavior, as it has clearly defined regions of hydrophobicity and hydrophilicity. In aqueous solutions, such molecules form micelle-like aggregates, wherein their hydrophilic groups face the external environment and shielding their hydrophobic regions are buried within a hydrophobic core. Similarly, the final Naph-X monomer is expected to arrange itself into an extended fibrous polymer, driven by a combination of the bipyridine chelating with metal ions and the clustering of the hydrophobic naphthoate groups, stabilized through π-π stacking.

The design of the naph-X monomer was specifically chosen such that the resulting polymer might mimic the function of naturally-occurring esterases. The bipyridine groups are capable of organizing metal ions around the polymer’s exterior, promoting the catalytic activation of water molecules to undergo nucleophilic attack of ester-derivatives also in solution (see Figure 2). If assembly is observed, then the final structure’s ability to catalyze ester and phosphoester hydrolysis will be assessed using UV/Vis spectroscopy, wherein the change in absorption of the hydrolyzed products will be
used to characterize the polymer’s kinetic activity (Bonomi et al., 2008). The final polymer could also demonstrate the ability to catalyze Suzuki-Miyaura coupling reactions, which could be identified by quantifying and characterizing the coupled-products through spectroscopy (Shaughnessy, 2013). Such catalytic abilities could be used in large-scale industrial applications, or perhaps by biochemists seeking to degrade phosphoester bonds found in DNA and RNA (Hegg and Burstyn, 1998).

![Amphiphilic Scaffold](image1)

**Figure 1.** Compound 5 Integrated Into Scaffold and Proposed Final Supramolecular Structure

**METHODS**

The synthesis of compound 5 was attempted through a five-step pathway previously published by Vasta et. al. summarized in reaction Scheme 1 (Vasta et al., 2016). The products of each reaction were characterized using proton nuclear magnetic resonance spectroscopy (1H-NMR) and gas chromatograph/mass spectroscopy (GC/MS).

Only the first two reactions have been attempted. Both reactions were monitored using silica-based TLC. All 1H-NMR samples were prepared by dissolving compounds of interest in 1.0 mL of deuterated chloroform (CDCl3). All 1H-NMR spectra were recorded using a Bruker Avance 300 MHz NMR spectrometer, at 298 K. 1H-NMR signals are reported in units of ppm and their splitting patterns are reported as follows; “s” for singlets, “d” for doublets, and “t” for triplets. GC/MS samples were prepared by dissolving the compound of interest into 1.0 mL of dichloromethane (CH2Cl2/DCM), and all spectra and chromatograms were collected using an Agilent Masshunter GC/MS 5977E, using a temperature gradient that transitioned from 50-300ºC, over the course of 15 minutes. The phrase “concentrated under reduced pressure” refers to the removal of solvents using a rotary evaporator.
Synthesis of 3-Methoxycarbonylpyridine N-oxide (compound 2)

Nicotinic methyl ester (3.0 g, 22 mmol) was oxidized through reaction with meta-chloroperbenzoic acid (mCPBA, 7.6 g, 11.2 mmol) in dichloromethane (DCM, 225 mL), for 16 hours at room temperature.

The reaction contents were concentrated under reduced pressure to yield a fluffy white solid. A portion of this crude product was then purified using flash column chromatography on silica gel, with a 1% MeOH/99% DCM mobile phase. Fractions containing product were identified using thin-layer chromatography (TLC) and combined into a single fraction, which was then concentrated under reduced pressure to yield a fine white solid. $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 8.8 (s 1H), 8.4, (d 2H), 7.9 (d 2H), 7.4 (t 2H), 4.0 (s 3H). GC/MS: calculated m/z of 153, measured 153.

Synthesis of 5-methoxycarbonyl-2-(pyridin-2-yl) pyridine N-oxide (compound 3)

The N-oxide pyridinemethylester (0.17 g, 1.1 mmol) was reacted with palladium acetate (Pd(OAc)$_2$, 0.25 g, 1.1 mmol), tri-tert-butylphosphonium tetrafluoroborate ([Bu$_3$PBF$_4$], 0.19 g, 0.65 mmol), and potassium carbonate (K$_2$CO$_3$, 0.16 g, 1.1 mmol) in toluene (2.0 mL). All reactants were combined in a flame-dried flask, under a nitrogen atmosphere. The reaction was then heated to 110°C and allowed to reflux for 16 hours. The reaction contents were cooled and filtered through a Büchner funnel packed with celite and washed with DCM. Organic solvents, were then removed under reduced pressure to yield a yellow-brown, crystalline solid, purified using flash column chromatography on silica gel with a 1% MeOH/99% DCM mobile phase. Fractions containing product were consolidated and concentrated under reduced pressure to yield a yellow-brown, crystalline solid, with a 59.2% yield (0.15 g, 0.75 mmol). $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 8.4 (d 1H), overlap of multiple signals at 7.8, 7.7 (s 1H), 7.6 (d 1H), 7.4 (t 2H), 4.0 (s 3H). GC/MS: calculated m/z of 230, measured of 227.

RESULTS

The $^1$H-NMR spectra of compounds 2 and 3A present various signals that indicate contamination by several residual solvents. Both spectra demonstrate signals at 8.0, 2.9, and 2.8 ppm, indicating trace amounts of N, N-
dimethylformamide (DMF). Similarly, both spectra show residual solvent peaks for CDCl₃ (at 7.3 ppm), water (1.5-1.6 ppm), and toluene (2.2-2.5 ppm).

Characterization of N-oxide pyridinemethylester (compound 2)

Figure 2 displays the experimentally-recorded ¹H-NMR spectrum for compound 2. This spectrum demonstrates four signals in the aromatic region (8.8, 8.4, 7.9, and 7.4 ppm) with splitting patterns (singlet, doublet, doublet, and triplet, respectively) that are representative of protons expected of the desired product. Similarly, this spectrum demonstrates a distinctive singlet at exactly 4.0 ppm (labeled as “E”), indicating the presence of the methyl ester group that differentiates this product from its
Figure 3 does, however, also present an unidentified doublet signal at 1.4 ppm, which was not readily identified with any possible solvent. Despite this contaminant, GC/MS analysis of compound 2 reveals a sample of significant purity, as demonstrated by the chromatograph in Figure 4. As shown in Figure 3, the m/z peak of this substance was 153 (retention time of 8.5 minutes), the exact calculated mass of the desired product. Furthermore, TLC analysis of this final sample (2% MeOH/98% MeOH) revealed a single spot close to the origin (Rf = 0.1). This data, in conjunction with the signals and splitting patterns observed in Figure 3, confirm that the product of this first reaction was the desired compound 2 and that its subsequent purification by columnar chromatography was successful.

Characterization of 5-methoxycarbonyl-2-(pyridin-2-yl) pyridine N-oxide (Compound 3A)

Spectral analysis of the products of the second reaction did not confirm its identity as compound 3A. Figure 5 presents the $^1$H-NMR spectrum for this compound, which has 8 signals in the aromatic region, whereas the desired compound 3A is expected to have 7. This could indicate that an unexpected side product was formed during the second reaction and remained in the sample, despite the efforts of purification by chromatography. There is a complicated overlapping of signals ranging from 7.8 – 7.6 ppm, which makes proper identification and labelling of protons difficult. Also, missing from this spectrum is a distinctive aromatic singlet, expected around 8.8 ppm, which was previously observed in Figure 3. This signal is representative of the lone hydrogen between the ester and oxide.
groups of the N-oxide pyridine methyl ester. Had the coupling of 2-bromopyridine yielded the desired 1,2,5-isomer (compound 3A), this singlet would still be apparent in the $^1$H-NMR spectrum. The absence of this signal in Figure 5, combined with the excessive number of aromatic signals, could indicate the formation of an a 1,2,3-isomer side product (compound 3B), which would have resulted from the coupling of 2-bromopyridine at the wrong position, occupied by the aforementioned lone hydrogen. GC/MS analysis of this sample (Figure 6) did not reveal any unreacted starting material (which would have a retention time of 8.5 minutes and m/z of 153). Similarly, TLC analysis of the final sample (run in 2% MeOH/ 98% DCM) yielded a single spot with an Rf value of roughly 0.5, clearly different from that of compound 2. The absence of unreacted starting material in the final sample indicates that the abundance of aromatic hydrogens in Figure 5 is not the result of an incomplete reaction and contamination by compound 2. Even after purification by chromatography, there appear to be multiple

![Figure 6. Combined Gas Chromatogram and MS Spectrum for Compound 3A, with Potential Compound 3B Isomer](image-url)
species present on the chromatogram presented in Figure 6. While one of these compounds was merely residual DMF (retention time of 3.1 minutes and m/z of 73) two species have almost identical retention times of 11.6 and 11.8 minutes, and identical m/z peaks of 227. This is slightly less than the 230 expected of the final product. The similar size and retention times of these molecules further corroborates the theory of mixed isomerization, indicating that the two products are structurally similar, but different compounds of the same mass.

Therefore, given the evidence of contamination or possible side-product formation presented in Figures 5 and 6, one cannot reasonably conclude that compound 3A was synthesized or isolated successfully.

**DISCUSSION**

While spectral analysis of compound 2 indicates that its synthesis and purification were both successful, it cannot be reasonably concluded that its subsequent coupling with 2-bromopyridine yielded a pure sample of compound 3A. As seen in Figure 5, the $^1$H-NMR spectrum for the final product of this coupling reaction reveals a number of aromatic hydrogens that is inconsistent with that of the desired product. There is a distinct absence of a particular aromatic singlet, around 8.8 ppm (signal A in Figure 3), which would have indicated the presence of a lone proton at the 6-position of compound 3A. Similarly, Figure 6 reveals that there are at two species in the final sample of compound 3A, despite attempts at purification by chromatography. These two species have similar retention times and identical m/z peaks, possibly indicating the presence of the desired product and an unpredicted isomer. This isomer could have resulted from improper pairing of the 2-bromopyridine at carbon 6 (between the N-oxide and ester groups) of compound 2, resulting in an uncertain amount of compound 3B. Moving forward, the environmental conditions and procedure with which the coupling reaction is conducted will be put under close scrutiny. For example, the coupling reaction detailed in this report was an initial attempt at synthesis that utilized quantities of reagents that were much smaller than stipulated by the literature (roughly 1:2, nBu$_3$PBF$_4$: Pd(OAc)$_2$ and compound 2). The smaller scale reaction detailed in this report was merely a proof of concept. Future experimentation will therefore scale-up the quantities of reagents, paying attention to equivalencies that match those of the literature. Should the observed isomerization pattern
continue, separation of the two isomers could be possible using high-pressure liquid chromatography (HPLC). This would at least result in a pure quantity of compound 3A, with which the total synthesis could be concluded. Furthermore, one should also entertain the possibility of exploring alternative pathways to synthesize compound 5. One such pathway, described by Zhang et al. (Scheme 3), uses a stille reaction to pair pyridine methyl ester a stannyl-derivative of 2-bromopyridine. This pathway would require only three reactions and therefore could prove to be a simpler method of synthesis. Regardless of the pathway utilized, synthesis of compound 5 is hurdle that must be overcome for this project to continue. The bipyridine ligand can be easily incorporated into the amphiphilic scaffold through reaction with commercially-available naphthoic acid and doubly-protected lysine, yet compound 5 is not so easily accessible and therefore must be synthesized.

Although the final naph-X monomer has yet to synthesized or characterized for catalytic ability, the findings of this report could be of interest to researchers utilizing a similar pathway to synthesize a bipyridine derivative of a particular conformation.

REFERENCES


