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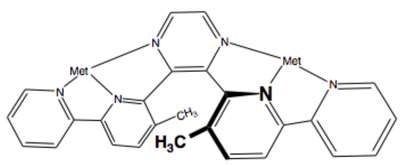
Preparation and Characterization of a Sterically Hindered Dipyridil Pyrazine Derivative

ABSTRACT:

With the intention of ultimately making a transition metal-containing helicene to be studied for use as a chiral drug recognition agent, 2,3-bis(3-methylpyridin-2-yl)pyrazine was produced from 2,3-lutidiene over a series of seven reactions.

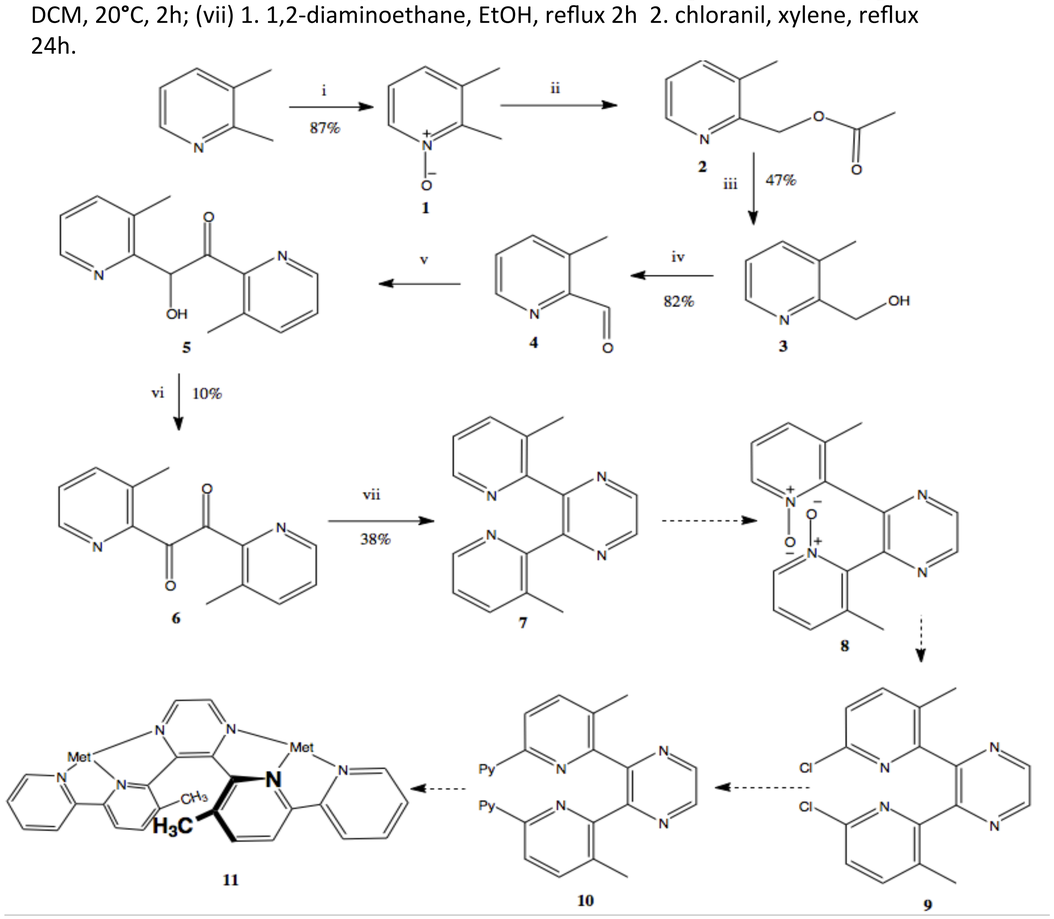
Figure 1. Target helicene molecule. "Met" represents a ruthenium atom coordinated to terpyridine.



INTRODUCTION:

- Helicenes are ortho-fused aromatic rings that adopt a helical conformation to avoid the overlapping of the terminal rings.
- Their inherent axial chirality and the possibility of enantiomeric resolution makes helicenes promising candidates as chiral catalysts, and as ligands for asymmetric synthesis.
- Here, we look to explore the potential bidentate ligand properties properties of sterically hindered dipyridil pyrazine derivatives.
- Specifically we are interested in the helical cavity, and a helicene's ability to accommodate guest molecules.
- Our hypothesis is that certain chiral molecules will fit, enantio-specifically, within the clefts of the resolved helicene enantiomes.
- With this, we hope to develop a method for using helicenes as chiral drug recognition agents.

Scheme 1. Synthesis of target helicene. Reagents and conditions: (i) m-CPBA, $CHCl_3$, 20°C 24h; (ii) acetic anhydride, reflux 24h; (iii) K_2CO_3, MeOH, H_2O, 20°C 24h; (iv) oxalyl chloride, DCM, DMSO, Et_3N, -60°C 3h. (v) NaCN, EtOH, H_2O, reflux 2h; (vi) I_2, DCM, 20°C, 2h; (vii) 1. 1,2-diaminoethane, EtOH, reflux 2h 2. chloranil, xylene, reflux 24h.



Scheme 2. Synthesis of terpyridine. Reagents and conditions: (i) N,N-dimethylformamide dimethyl acetal, reflux 24h.

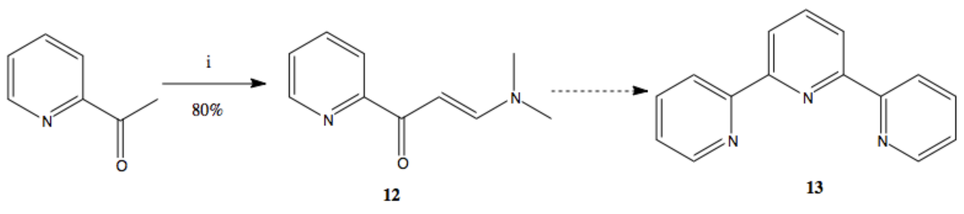
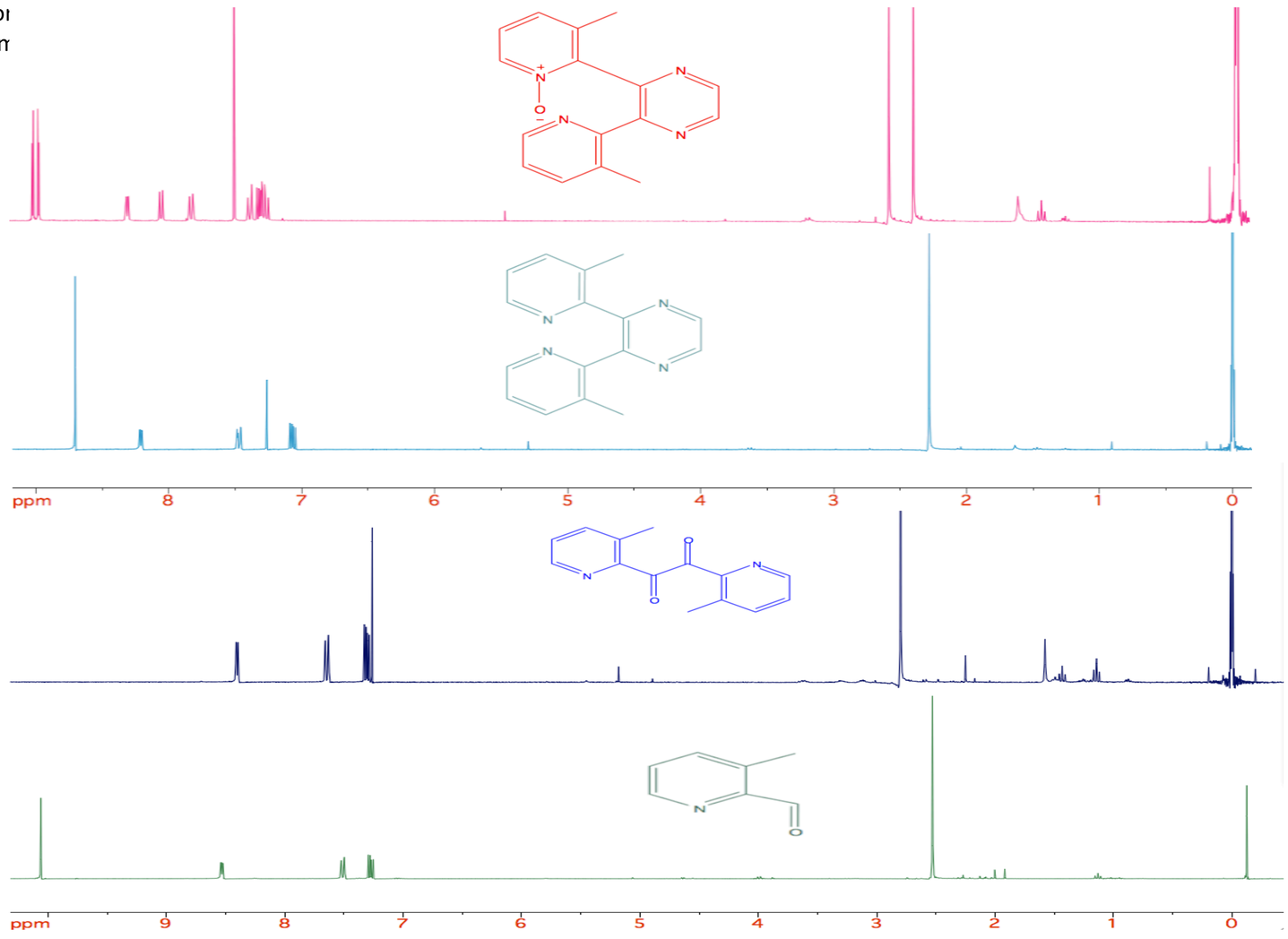


Figure 2. ^{1}HNMR (300MHz, $CDCl_3$) of intermediate products.



RESULTS & DISCUSSION:

Compound **3** was produced in a 47% yield based off of conditions adapted from *Kotar et al*[1]. Compound **4** was prepared from **3** in a Swern Oxidation giving a 82% yield. Compound **5** was produced from **4** and NaCN. I_2 and **5** afforded compound **6** in a 10% yield. Compound **7** was produced in a 38% yield from **6**, 1,2-diaminoethane, and chloranil in a procedure adapted from *Heirtzler et al*[2]. The synthesis of the di-N-oxide of **7** was attempted, but initially only the mono-N-oxide was produced. Attempting the synthesis again, this time refluxing with excess m-CPBA in dichloroethane, gave what seemed to be a mixture of di- and mono-N-oxide. We were unable to separate this mixture however, and the material was exhausted in the process.

The di-N-oxide is required in order to make the dichloride (**9**) but because of unexpected low yields (particularly in the synthesis of the alpha-diketone derivative) the material was exhausted before this synthesis could be completed. After the isolation of **9**, the next step in the synthesis of the target helicene would be a Stille coupling reaction with $Sn(Bu)_3$-pyridine which should give **10**. Compound **10** will then be reacted with ruthenium terpyridine to give the target helicene.

To make the terpyridine (**13**) to be cordinated to ruthenium and reacted with **10**, compound **12** was prepared from 2-acetylpyradine and N,N-dimethylformamide dimethyl acetal in an 80% yield based off of conditions adapted from *Jameson et al* [3].

After the target helicene has been made, we will attempt chiral resolution via precipitation of diastereomeric salts. Once the enantiomers have been resolved, they will be examined to see how well certain chiral guest molecules fit with in the helicene's cleft and if the resolved helicene can be used to detect chiral drugs.

Figure 2. shows ^{1}HNMR spectra of compounds **4**, **6**, **7**, and the mono-N-oxide derivative, which was unintentionally produced in the attempt to make the di-N-oxide. This is the first reported synthesis of these compounds.

REFERENCES

1. Kotar, Berta; Vrecer, Franc; Segula, Zakelj Mojca; Ritlop, Gregor. Novo Mestro. European Patenting Office. EP1681056A1. 19.07.2006
2. Heirtzler, Fenton; Neuburger, Markus; Zehnder, Margareta; Constable, Edwin C. Liebigs Ann. Recueil 1997, 297-301
3. Jameson, Donald L.; Guise, Lisa E. Tetrahedron Lett. 1991, Vol. 32 No. 18 1999-2002

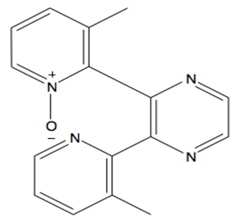


Figure 3. Structure of , 2,3-bis(3-methylpyridin-2-yl)pyrazine-mono-N-oxide.