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Synthesis of 1,3-DI(4-Pyridinyl)Acetone

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SYNTHESIS OF 1,3-DI(4-PYRIDINYL)ACETONE

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Approved by
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Dr. Robert Morgan
Dr. John Markiewicz

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APPROVAL OF THESIS

We, the faculty supervising the work of Zachary Tyler Boggs, affirm that the thesis, *Synthesis of 1,3-Di(4-Pyridinyl)acetone*, meets the high academic standards for original scholarship and creative work established by the Masters of Science Chemistry Program and the College of Science. This work also conforms to the editorial standards of our discipline and the Graduate College of Marshall University. With our signatures, we approve the manuscript for publication.

Dr. Michael Castellani, Department of Chemistry — Committee Chairperson — Date

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Although isoelectronic to benzene, the reactivity of pyridine-derived compounds can be quite different. Notably, routes to prepare pyridyl analogs to known phenyl compounds can be very different from how the phenyl compounds are made, even when the nitrogen atom would appear to play an insignificant role in the reaction. This is the case for 1,3-di-4-pyridylacetone. Its phenyl analog has been known for over 90 years and is easily prepared, while the only reported synthesis of 1,3-di-4-pyridylacetone occurs in very low yield. We report a preliminary synthesis from common starting materials, albeit in low yield, and offer an explanation for why previous preparations were unsuccessful and how yields could be improved.

CHAPTER 1

INTRODUCTION

The large majority of organometallic complexes of the first transition series have 18 electrons (18e) in their valence shells, giving them highly stable, noble gas configurations. 17-Electron radical organometallic complexes have also been extensively researched, including complexes of metals such as chromium, molybdenum, and tungsten and many others.[1-12] For many years, these 17-electron complexes were studied by either thermally or photolytically induced, homolytic cleavages of the metal-metal bonds. However, due to their reactivity, they quickly recombine to reform dimers or undergo further reactions if other substrates are present. The challenge in making stable 17e complexes is this very tendency to dimerize. Dimerization may be slowed or eliminated by the addition of large groups such as phenyl rings. It has been found that 17e chromium radicals ($(C_5R_5)Cr(CO)_3$) can be isolated when using a very large cyclopentadienyl ligand, which prevents radical dimerization.[6-8] These compounds are highly reactive and processes such as oxidation/reductions, substitutions, and electron transfers have been observed.[9]

Some organometallic complexes can coordinate to another metal center, creating bimetallic compounds.[13,14] Pyrazine is such a ligand and can act as a bridge between the two metal centers. In some cases, the metals have different oxidation states which leads to mixed valence compounds. Mixed valance compounds such as the Cruetz-Taube ion (Figure 1) which incorporated two ruthenium centers with oxidation states II and III, respectively, have been studied extensively.[10,15]

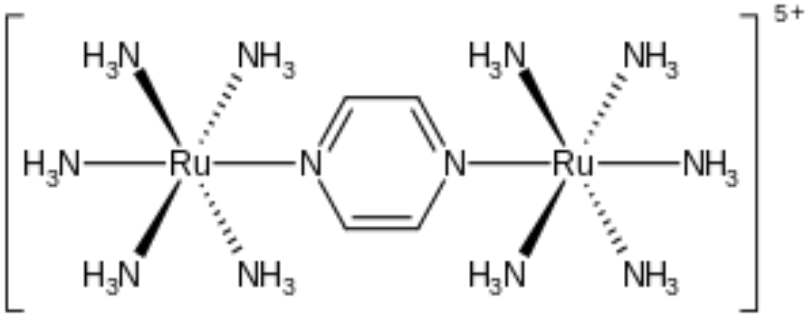


Figure 1: The Cruetz-Taube Ion

When these metal centers are bridged by π-conjugated systems, excess electron density can flow freely between the metals.[16-17]

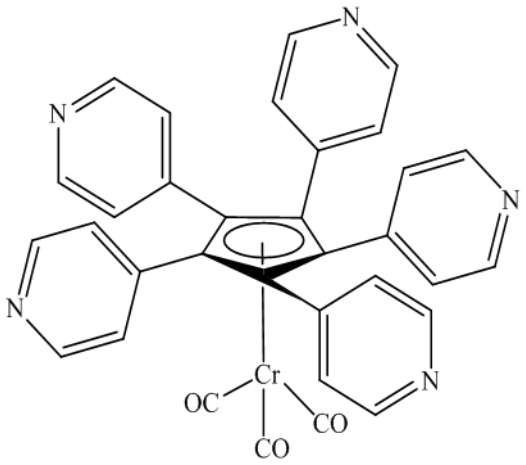


Figure 2: Tricarbonyl-η^5-penta(4-pyridinyl)cyclopentadienylchromium(I)

Tricarbonyl-η^5-penta(4-pyridinyl)cyclopentadienylchromium(I) (Figure 2) has been proposed as a new radical complex based on the previously isolated, and well-characterized, (η^5-C_5Ph_5)$Cr(CO)_3$.[18] This complex has the potential to act as a molecular switch, with the on/off

switching arising from the natural rotation of the pyridine rings, (Figure 3).

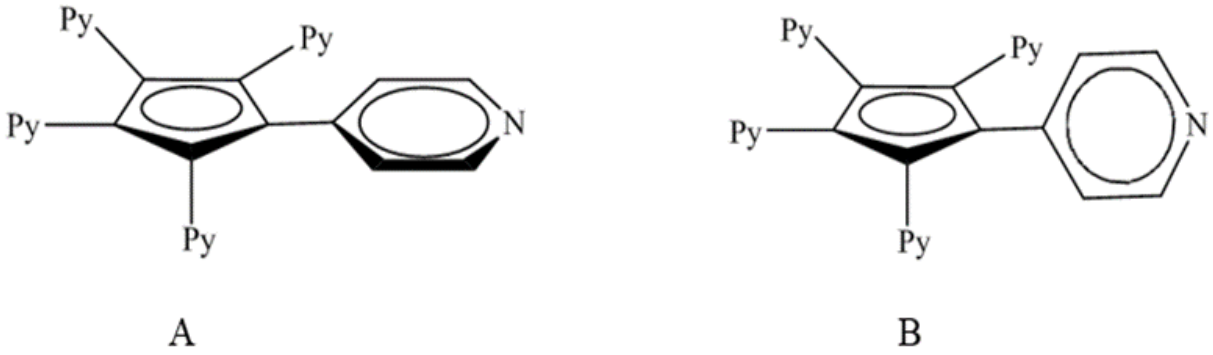


Figure 3: Two rotational isomers of $(C_5Py_5)Cr(CO)_3$ with $Cr(CO)_3$ omitted for visual clarity.

When the pyridyl group is in the plane of the Cp anion (Figure 3a) the system has full π-orbital conjugation. This overlap allows for electron flow from the chromium to the rest of the system. However, when the pyridine ring is out of the plane of the Cp anion (Figure 3b), there is no longer any π-orbital overlap which breaks the conjugation, preventing electron flow. The switch would arise from the forming of mixed valence compounds through the coordination of a nitrogen in one of the five pyridine rings to another metal.[19-21]

Preparation of the organic compound 1,2,3,4,5-penta(4-pyridinyl)-1,3-cyclopentadiene is first needed to synthesize the tricarbonyl-η^5-penta(4-pyridinyl) cyclopentadienylchromium(I) radical. The entire proposed preparative route may be seen in Scheme I.

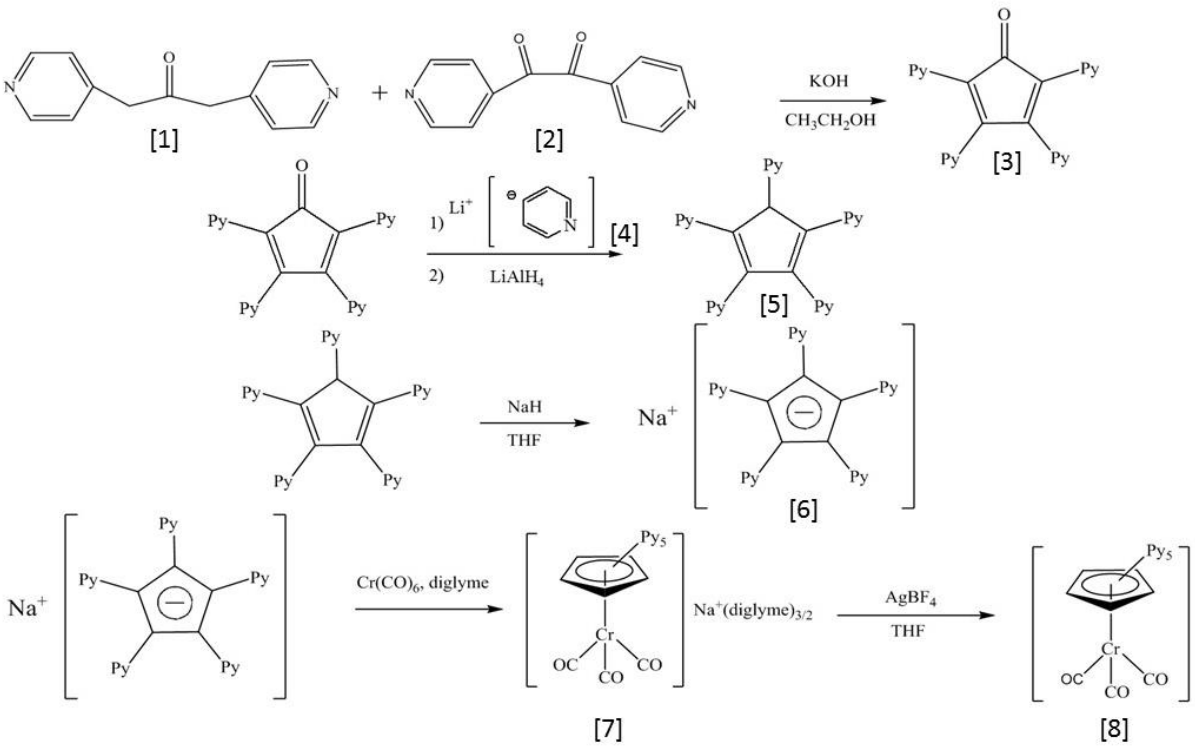
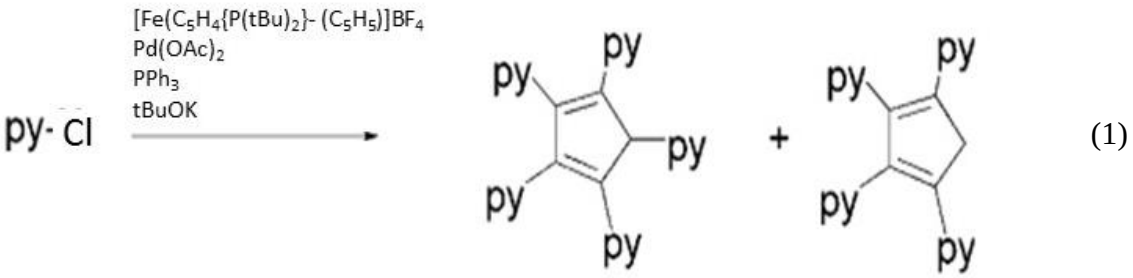


Figure 4: Scheme 1 the synthesis of tricarbonyl-η^5-penta(4-pyridinyl) cyclopentadienylchromium(I)

1,2,3,4,5-Penta(4-pyridinyl)-1,3-cyclopentadiene is a known compound. Williams and co-workers previously found that a palladium catalyzed reaction forms

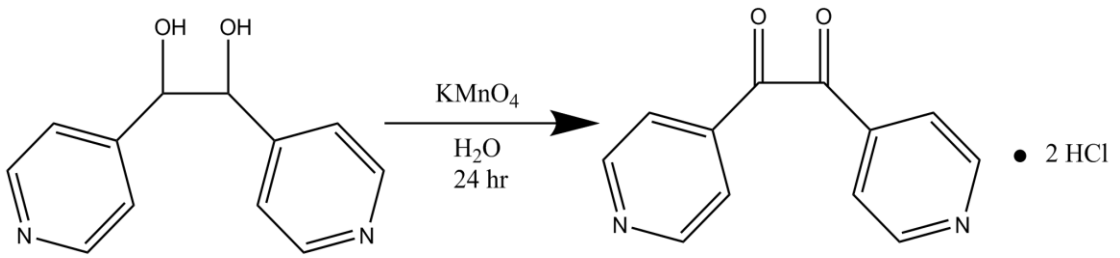


(1)

penta(4-pyridinyl)cyclopentadiene (eq 1), but this is an expensive reaction[22] because $P(^tBu)_3$ is employed as a reagent. In this case, isolation of the C_5Py_5 ligand would require decomposition of the metal complex, a process that might not have high yields and could be complicated to develop. The iron complex $CpFe(PBu_3)(CO)^-$ was also employed as a vehicle to convert C_5H_5 to $C_5(4\text{-}Py)_5$. It would be possible to try the same synthesis on $(C_5H_5)Cr(CO)_3^-$ but it seems likely $CpFe(CO)_2^-$ was tested before trying $CpFe(PBu_3)(CO)^-$. The likelihood that the reaction was unsuccessfully attempted on an iron analog to the desired chromium system led us to seek an alternative, which is presented in Scheme I.

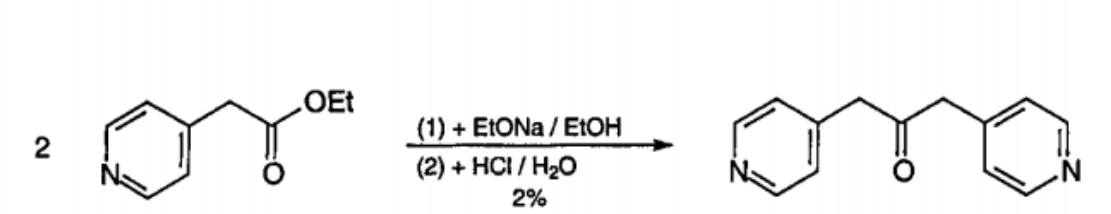
The two reactants in the first step of Scheme I, 4,4′-dipyridil diketone [2] and 4,4′-dipyridilacteone [1], have no reliable syntheses reported. The synthesis of 4,4′-dipyridil diol reported by Mathes[23] begins with the reaction of hydrochloric acid with pyridine carboxyalaldehyde and potassium cyanide to make an aldol-type cyanohydrin. The product is then heated in a sodium carbonate solution, filtered, and washed with water for a yield of 25% for 4,4’-dipyridil diol.

The precursor to 4,4′-dipyridil diketone, 4,4′-dipyridildiol, is oxidized by potassium permanganate over a period of 12 hours, followed by acidification, to yield 4-PyC(O)C(O)-4-Py•2HCl as seen in eq 2.[23] The acidification step is important because bonding the lone pairs to a proton stabilizes the molecule by preventing its rapid decomposition. Currently there is an elemental analysis showing the correct carbon-hydrogen-nitrogen ratio, but it shows there are impurities in the compound that still need to be removed.



(2)

With a viable synthesis of the diketone available, discovery of a pathway to 4,4′-dipyridilacteone became the next focus of this research. Reichardt and co-workers reported the synthesis of of 1,3-di-4-pyridylacetone,[21] by reacting (pyridin-4-yl)acetate and sodium ethoxide, but this method only yielded 2% of 1,3-di-4-pyridylacetone as seen in eq 3.



(3)

Reichardt reported that the compound is unstable and decomposes even when stored under argon at -18 °C. The instability initially seemed unlikely, but in light of our work on 4,4′-dipyridil diketone their results appear reasonable. As a result of the decomposition, Reichardt's characterization of of 1,3-di-4-pyridylacetone was poor,[21] which led us to develop an alternative synthetic pathway, and also a way of stabilizing the of 1,3-di-4-pyridylacetone for prolonged storage. This thesis describes a variety of preparative attempts and routes of 1,3-di-4-pyridylacetone.

CHAPTER 2

EXPERIMENTAL SECTION

GENERAL DATA

All chemicals were obtained from Sigma-Aldrich® or Acros and used as received unless otherwise noted. NMR spectra were obtained on a Bruker Ascend 400 MHz NMR. IR spectra were collected on Nicolet iS50 FT-IR. Reactions performed under an inert atmosphere employed nitrogen gas with a mineral oil bubbler unless otherwise stated. Yields of impure products are calculated based upon internal NMR standards.

SYNTHESIS OF 1,3-BIS(4-PYRIDINYL)PROPAN-2-OL

n-Butyllithium (5.6 mL, 2.5 M, 14 mmol) was added to a stirring solution of 2,2,6,6-tetramethylpiperidine (2.5 mL) in dry THF (15 mL) at -70 ºC. Over 30 min, the mixture turned pale yellow. The flask was then placed in an ice water bath. A $ZnCl_2$ (20 mL 0.7 M, 14 mmol) solution was added and allowed to react for 30 min. During this time, the solution went from pale yellow to orange. After an additional 30 min, 4-picoline (1.46 mL, 15.6 mmol) was added and reacted for 30 min. Ethyl formate (1 mL) was added and the solution was stirred overnight. The reaction was then exposed to air. Removing the volatiles under reduced pressure produced a yellow oil. Adding the oil to dichloromethane resulted in the precipitation of a yellow powder. The impure solid was collected by filtration (1 g of impure product, *ca*. 5% yield).

SYNTHESIS OF OF 1,3-DI-4-PYRIDYLACETONE:

METHOD 1

A potassium permanganate solution (0.074 g in 50 mL of water) was added to 1,3-bis (4-pyridinyl)-2-propanol (0.10 g, 0.48 mmol) and allowed to react for 12 hr, followed by acidification using excess HCl (12 M) in the air. The flask was then placed in a fume hood and allowed to evaporate to dryness overnight to produce a white solid with residual MnO_4 and KCl (3% yield).

METHOD 2

To a stirring solution of 4-(bromomethyl)pyridine hydrobromide (0.5 g, 1.98 mmol) in dry benzene (3 mL) at -70 ^{o}C, *n*-butyllithium was added (1.58 mL, 2.5 *M*, 5.03 mmol). After 30 min, the solution was placed in an ice water bath (10 min). 4-Pyridylacetic acid hydrochloride (0.124 g, 0.843 mmol) was added, reacted for 30 min, after which it was allowed to warm to ambient temperature over an additional 30 min. In the air, excess hydrochloric acid (3 mL, 12 *M*) was added followed by an excess of saturated sodium bicarbonate solution (5 mL) to neutralize the remaining acid. Extractions were performed with chloroform (4 x 10 mL), with the organic layers collected and evaporated under reduced pressure to obtain a red oil (0.68 g of impure product *ca.* 5% yield).

METHOD 3

To a solution of 4-(bromomethyl)pyridine hydrobromide (0.5 g, 1.98 mmol) in dry benzene (3 mL) at -70 ^{o}C, 2 equivalents of *n*-butyllithium were added (1.58 mL, 2.5 *M*). The mixture was allowed to react for 30 min, after which it was placed in an ice water bath. 4-Pyridylacetonitrile hydrochloride (0.124 g, 0.802 mmol) was added and allowed to stir for 1 hr, followed by warming to room temperature. Excess water (8 mL) was added to the solution,

followed by extraction with chloroform (4 x 10 mL). The organic layer was then evaporated to dryness under reduced pressure to produce a red oil (0.76 g of impure product *ca*. 15% yield).

METHOD 4

To a flask of stirring ethanol in air (100 mL), sodium metal was added (1.24 g, 54 mmol) and allowed to react completely. 4-Pyridylacetonitrile (503 mg, 0.325 mmol) and ethyl 4-pyridylacetate (506 mg, 0.306 mmol) were added and refluxed for 3 h. In the air, ice cold water was then added to quench the reaction, followed by extraction with chloroform (4 x 10 mL). The organic layer was collected and evaporated under reduced pressure to yield a dark violet liquid (5 mL mixture of products, *ca.* 15% yield).

METHOD 5

Under a nitrogen atmosphere, picoline (4-methylpyridine, 1.12 mL, 12.1 mmol) was combined with dry THF (5 mL) and cooled to -70 ^{o}C. Lithium di-isopropyl amide (1.5 *M* of LDA in ether, 2.51 mL, 17.6 mmol) was added to the flask and allowed to react for 30 min. After warming to ambient temperature, the mixture was transferred via cannula to a flask containing 4-pyridylacetonitrile hydrochloride (510 mg, 3.29 mmol). The mixture was allowed to react for 30 min at ambient temperature, followed by adding water in the air to quench the reaction giving a red liquid from which the volatiles were removed under reduced pressure (5 mL mixture, *ca.* 10% yield).

METHOD 6

To a stirring solution of 4-(bromomethyl)pyridine hydrobromide (1.24 g, 4902 mmol) in dry THF (5 mL) cooled to -70 ^{o}C, *n*-butyllithium was added (4.58 mL, 2.5 *M*, 14.5 mmol). The mixture was allowed to react for 3 hr, followed by warming to ambient temperature. 4-Pyridylacetonitrile hydrochloride (500 mg, 0.323 mmol) was added and allowed to react for 1 hr.

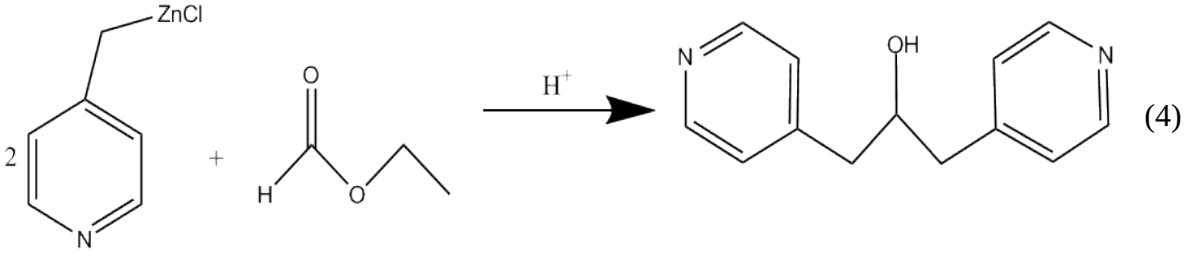
In the air, excess hydrochloric acid (3 mL, 12 *M*) was added. An excess of saturated sodium bicarbonate solution (5 mL) was then added to neutralize the remaining acid. Extractions were performed with chloroform (4 x 10 mL) and the organic layer was collected and evaporated under reduced pressure to remove volatiles to obtain a red oil (1.52 g of impure product, *ca.* 5% yield).

CHAPTER 3

RESULTS AND DISCUSSION

Several methods to prepare 1,3-di-4-pyridylacetone are presented (*vide infra*). The majority involve the addition of the picolinate, where the anion is on the methyl group, to a ketone. A variety of different deprotonation techniques of varying strengths were also examined with the goal of increasing the yields of 1,3-di(4-pyridyl) acetone.

Method 1: ***Addition of the Picolinate Anion to Ethyl Formate***



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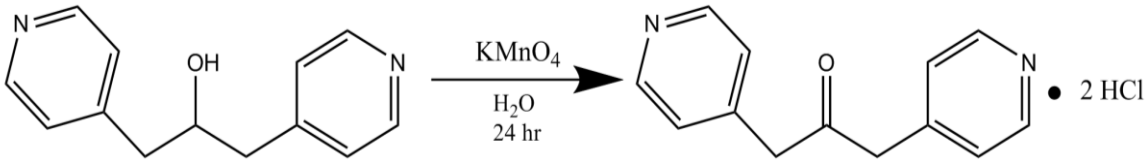


(5)

Equation 4 is the reaction of lithium picolinate with ethyl formate, followed by acidification, then oxidized to the target product (eq 5). This synthetic pathway gave very small amounts of product, so several variations were attempted to increase yields. The first factor that was modified was temperature, with the reaction attempted initially at -70 °C, then 0 °C, -50 °C and -100 °C. Final product yields did not change significantly across this range of temperatures. Ratios of reagents were also altered to increase yields with increasing the starting 2:1 ratio of picolinate to ethyl acetate to 3:1, followed by 4:1. None produced a change in yield.

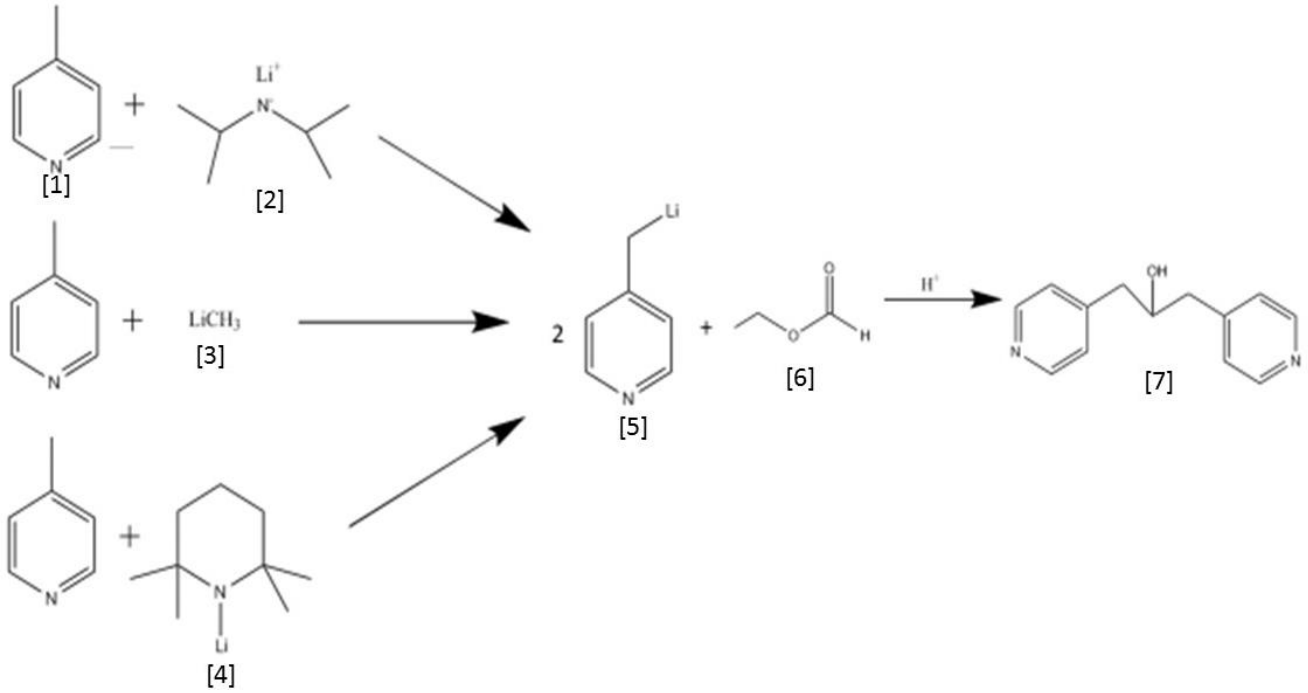


Figure 5: Scheme II the sythesis of 1,3-di(4-pyridinyl)-2-propanol

To accomplish the synthesis of the 1,3-di(4-pyridinyl)-2-propanol [7], preparation of lithium picolinate [5] was required first and this was attempted by the variety of procedures displayed in Scheme II. The first attempt employed *n*-butyllithium [2] as the deprotonating agent by the method of Mansour and co-workers,[24] but this method did not work in our hands. Preparation of a zinc reagent was attempted by the method of Love and co-workers.[25] While the reagent was successfully prepared, it did not react with ethyl formate [6] (at most 1% of 1,3-di(4-pyridinyl)-2-propanol was prepared). A ^{1}H NMR spectrum of this reaction mixture is displayed

as Figure 4. In it, some product may be seen in the inset,which has a pentet that correctly integrates with the pyridine doublets.

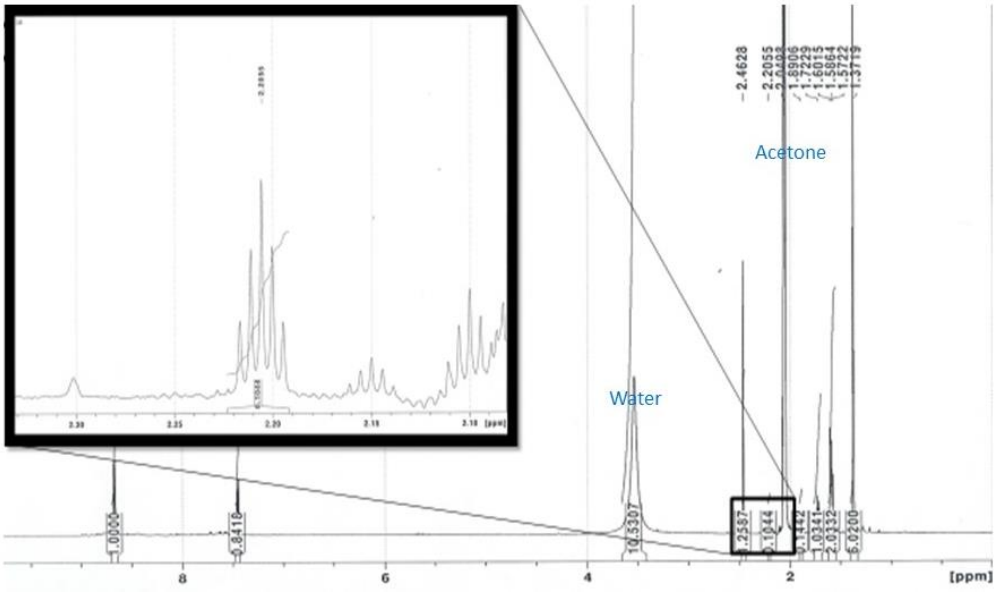


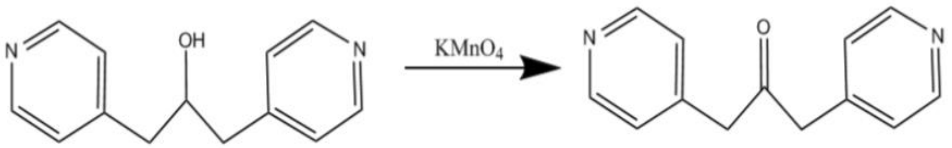
Figure 6: [1]H NMR spectrum of 1,3-di(4-pyridinyl)-2-propanol

Methyl lithium [3], lithium di-isopropylamide [2], and 2,2,6,6-tetramethylpiperidine [4] were also used to deprotonate picoline to make lithium picolinate, but all led to low conversions of the target alcohol (< 10%). The final product was not isolated. However, an internal standard was used for yields.

Each of these different lithiation techniques went through the same range of temperatures used previously (0, -50, -70 and -100 °C) with very little difference in yields. Also, reagent ratios were altered as previously described (2:1, 3:1, and 4:1 picolinate to ethyl acetate), but, again, this showed no improvement of yield. A new method of producing the picolinate employing 4-(bromomethyl)pyridine and the various lithio reagents shown in Scheme 2 was also attempted. There was a slight increase in product yield (*ca*. 5-10%) with all attempts. Each reagent pairing used for producing the picolinate using 4-(bromomethyl)pyridine gave approximately equal yields.

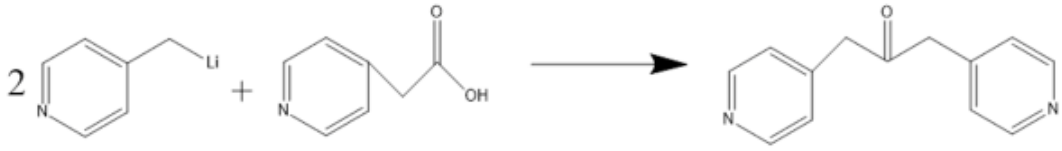
Another method using 4-(bromomethyl)pyridine with *n*-butyllithium became the standard lithiating technique used for all subsequent reactions because it was the most reliable and highest yielding of the methods employed for producing the picolinate.

Because of low yields of 1,3-di(4-pyridinyl)-2-propanol, the oxidation was only attempted once with potassium permanganate and also produced a poor yield from 1-5% (eq 6).



(6)

METHOD 2: ***ADDITION OF PICOLINATE TO ACETIC ACID***

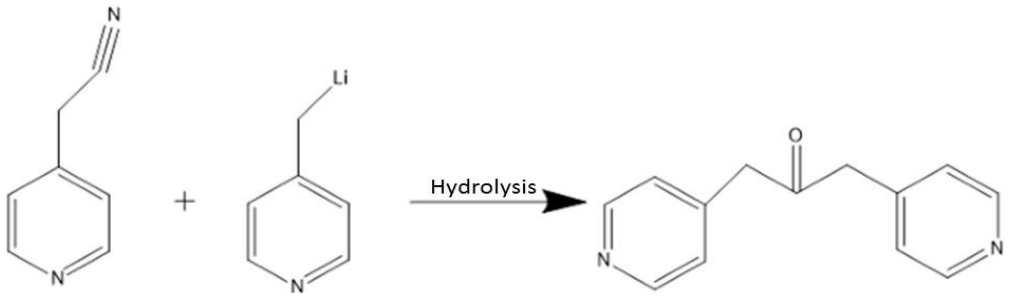


(7)

Attempts to produce the of 1,3-di-4-pyridylacetone directly began because of unacceptably low yields of 1,3-di(4-pyridinyl)-2-propanol. A reaction that bypasses the propanol is similar to that shown in step 2 of Scheme 1, but with the need only of one molar equivalent of picolinate ion because employing pyridyl acetic acid provides the second pyridinyl ring (eq 7). This reaction was attempted with a variety of lithiating agents in an attempt to increase yields. Reagents such as lithium diisopropylamide and methyl lithium with the 4-(bromomethyl)pyridine were employed to determine if the bromine would more readily be replaced by the lithium. Previous work with lithiating pyridines in the para position has proven to have low yields of 20%. In order to increase the yields of the picolinate, reaction conditions were altered to see if there would be any effect. The preparation of the picolinate ion was also attempted in solvents of

varying polarity including THF, benzene, toluene, diethyl ether and hexane. In general, yields increased with increasing solvent polarity, which was expected because pyridine additions were often conducted in solvents such as THF in the literature. It is likely that polar solvents stabilized an intermediate in the reaction.[26] However, regardless of solvent, the yields for this reaction were low (<10%), likely because both reagents were anions that would repel one another. There was no noticeable difference between the lithiating agents in our hands, but some picolinate ion was being produced, which was an improvement over previous attempts.

METHOD 3: ***ADDITION OF PICOLINATE ANION TO PYRIDYL ACETONITRILE***



(8)

Another attempted synthesis of 1,3-di-4-pyridylacetone can be seen in eq 8. This reaction employed pyridyl acetonitrile instead of a carbonyl containing group as was employed in all previous methods. The 15% yield is the highest of any synthesis to date. This method showed promise, so many variations were attempted. By changing temperatures (0, -50, -70 and -100 °C), it was found cooler temperatures increase yields which can be seen in Table 1. It is believed lower temperatures stabilize an intermediate and potentially the product.[26]

Temperature (°C)	Percent Yield
0	4
-50	5
-70	7
-100	10

Table 1: Reaction Temperature and Corresponding Yields

Also, a range of solvents was once again used (THF, benzene, toluene, diethyl ether and hexane) finding that benzene gave a slightly increased yield. As with the previous attempt, the yield increase is likely due to a polar solvent stabilizing an intermediate.[26] Three trials of each were conducted with the average results appearing in Table 2. The yields were calculated based off internal standards.

Solvents	Percent Yield
THF	10
Diethyl Ether	10
Toluene	12
Hexane	13
Benzene	15

Table 2: Reaction Solvents and Corresponding Yields

Ratios of lithio to 4-(bromomethyl)pyridine reagents were also changed (1:1, 2:1, 3:1 and 4:1) with 4-(bromomethyl)pyridine remaining constant; however, product yield was not significantly affected.

Ratio of 4-(Bromomethyl)pyridine to Lithio Reagents	Percent Yield
1:1	9
2:1	10
3:1	8
4:1	11

Table 3: Reactants Ratios and Corresponding Yields

The excess lithio reagent does not change the amount of picolinate anion produced. Reaction times were also changed allowing the reaction to take place for 30 min, 1 hr, 2 hr, and 3 hr as seen in Table 3. There was slight decrease in yields once it was allowed to react for 3 hr, so no further time tests were conducted.

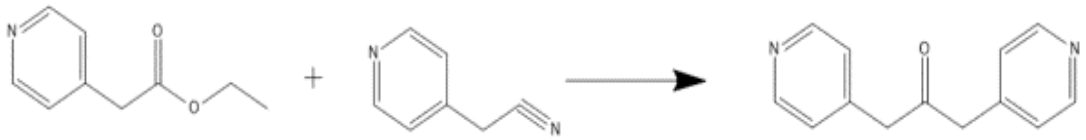
Reaction Time (hr)	**Percent Yield**
0.5	7
1	10
2	11
3	9

Table 4: Reaction Times and Corresponding Yields

Ratios of picolinate ion to the 4-pyridyl acetonitrile were also changed (1:1, 2:1, and 3:1) which can be seen in Table 4. A 2:1 ratio of picolinate to nitrile saw a very slight improvement in yield. The highest yielding reaction was just above 20%, but, on average, it was approximately 15%. It was considered that reaction conditions might not be the sole reason for the low yields. It was possible that product was lost on isolation and work-up. It was believed that the product was unstable which is why some acid work-ups were attempted, which included stabilizing the

pyridine compounds by the addition of HCl, extractions with various solvents such as chloroform and diethyl ether. None of these methods showed any yield improvement. These yields are an improvement compared to all previous attempts to synthesize 1,3-di-4-pyridylacetone.

METHOD 4: ***CONDENSATION OF 4-PYRIDYL ETHYLACETATE AND 4-PYRIDYLACETONITRILE***



(9)

Through all previous methods, one aspect remained constant: the addition of the picolinate anion to another compound. The method displayed in equation 9 employs the use of a non-lithiating condensation reaction. A condensation reaction removes the possibility of the picolinate ion being the limiting factor.

This reaction in early tests was found to match the best attempts with any previous methods. With some refinement of the conditions and techniques this reaction might have much higher yields. Another consideration warrants comment: these early results are consistent with product instability. This reaction was conducted at several time intervals ranging from 1 hr to 12 hrs, with one particular test being allowed to run for 12 hrs. Previous work in this lab showed that 4-pyC(O)C(O)-4-py is thermally unstable and acidification appears to stabilize the material indefinitely. The low yields observed in the system described in this thesis could arise from a similar instability. In that event, to significantly increase the yield of of 1,3-di-4-pyridylacetone might require isolating the product as it is formed.

CHAPTER 5

CONCLUSIONS

The synthesis of 1,3-di-4-pyridylacetone continues to have low yields. Further work should be done on the development of a reaction that will have much larger yields. Organometallic based reactions seem to be limited to roughly 20% yield. Further work needs to be done to determine if the low yields are a limitation of the picolinate or due to product decomposition. The changing of reaction conditions gave a negligible difference in yields. Nonetheless, this work lays a foundation for a potential synthetic pathway for 1,3-di-4-pyridylacetone.

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APPENDIX A: APPROVAL LETTER

MARSHALL UNIVERSITY.
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Office of Research Integrity

May 14, 2019

Zachary Boggs
736 South State Hwy 1
Grayson, KY 41143

Dear Mr. Boggs:

This letter is in response to the submitted thesis abstract entitled *"Synthesis of 1,3-DI(4-Pyridinyl) Acetone."* After assessing the abstract, it has been deemed not to be human subject research and therefore exempt from oversight of the Marshall University Institutional Review Board (IRB). The Code of Federal Regulations (45CFR46) has set forth the criteria utilized in making this determination. Since the information in this study does not involve human subjects as defined in the above referenced instruction, it is not considered human subject research. If there are any changes to the abstract you provided then you would need to resubmit that information to the Office of Research Integrity for review and a determination.

I appreciate your willingness to submit the abstract for determination. Please feel free to contact the Office of Research Integrity if you have any questions regarding future protocols that may require IRB review.

Sincerely,

Bruce F. Day, ThD, CIP
Director