5-1992

Senior Project

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The goal of my past research was to synthesize the odorant 2-Acetyl-1-pyrroline, a compound that had been isolated from popcorn and rice. It was ultimately hoped that five grams of the substance could be prepared for analysis by the FDA.

The compound 2-acetyl-1-pyrroline is a heterogenous ring compound derived from pyrrole. The pyrrole molecule consists of four carbons, a nitrogen, and five hydrogens. The overall shape is that of a pentagon formed by the carbons and nitrogen with one hydrogen attached to each carbon or nitrogen. The compound is unsaturated with two carbon to carbon double bonds. The molecular system is conjugated with the pi electrons from the carbon bonds overlapping with the free pi orbital of the nitrogen.

The method selected to synthesize 2-acetyl-1-pyrroline involved the complete reduction/hydrogenation of 2-acetylpyrrole.

\[
\text{pyrrole} \quad \xrightarrow{\text{POCL, DMA}} \quad 2\text{-acetylpyrrole}
\]

\[
\text{2-acetylpyrrole} \quad \xrightarrow{\text{Rhodium, } H_2} \quad 2\text{-}(1\text{-hydroxyethyl})\text{pyrrolidine}
\]

**1 Proposed Method**
This starting material is available commercially from a variety of chemistry supply houses, but the cost is prohibitive. It was decided that the syntheses should start at this compound. From readily available pyrrole and dimethylacetimide, 2-acetylpyrrole was synthesized using a POCl reaction found in *Organic Syntheses* (pp. 831-833); however, it was noted that the reaction was rather inefficient with approximately a 45% yield of crude product. Impurities in the crude compound seem to have consisted of various nitrogenous compounds as well as polymers of the desired product. Solubility in warm hexanes provided an useful method of removing some impurities, but the most effective method proved to be blotting with filter paper followed by a rinse of cold hexanes. The clean-up and purification alone seem to bear out the justification of the high commercial price. 2-acetylpyrrole was proven to be a crystalline, translucent solid, which impurities made yellowish. Its melting point is 89 - 90° Celsius. The NMR spectra 2-acetylpyrrole can be seen in $d_6$-DMSO (deuterated dimethylsulfoxide) on NMR #4 and in CDCl$_3$ on NMR #5.

Efforts at hydrogenating the 2-acetylpyrrole have generally met with limited success, which most references warned would be the case - citing nitrogen's tendency to poison catalysts. Two approaches were used to attempt hydrogenation. The first involved utilizing ethanol as the solvent. Ratios by mass of catalyst to 2-acetylpyrrole ranged from 1:1 to 1:3 with little apparent difference in effectiveness. Filtration of the catalyst through Celite followed by rotoevaporation of the ethanol left a brown, oily solid that was characterized by
a roasty odor. The development of the roasty odor seemed to be dependent on exposure to air which suggests the product requires oxidation after hydrogenation. NMR #1 is the spectrum of such a sample.

\[
\text{oxidant} \quad \begin{array}{c}
\text{2-}(-1\text{-hydroxyethyl})\text{pyrrolidine} \\
\end{array} \rightarrow \begin{array}{c}
\text{2-acetyl-1-pyrroline} \\
\end{array}
\]

2 Oxidation

Spectra that identified the source of the odor was exceptionally hard to obtain, suggesting that there is little of the 2-acetyl-1-pyrroline formed through the method. This is born out by Peter Schieberle in his paper in the J. Agric. Food Chemistry (1991,39,1141-1144). He reports the odor threshold for 2-acetylpyrroline is 0.2 nanograms/liter. The best NMR obtained of the possible pyrroline compound is #1. The compound for the NMR was obtained from past hydrogenation attempts in ethanol that had been stored in a drawer for several weeks, which I use to site as proof for the need of oxidation. The spectrum clearly shows a large percentage of starting material, a pyrrolline ring peak at 1 ppm, a singlet at 3.2 ppm, and a quartet at 3.5 ppm. The integrations do not clearly support the correct proportion of protons in the structure, but the existence of impurities render them imprecise. Further support for the hypothesis that the
compound is formed only after some oxidation comes from NMR #11 which is from a hydrogenation using ethanol as a solvent which was worked up immediately. The spectrum is that of 2-(1-hydroxyethyl)pyrrole. It is interesting to note that the ring proton's shifts have changed subtly from two multiplets near 7 ppm and one near 6 ppm to two multiplets near 6 ppm and one near 7 ppm.

The second method substituted acetic acid for ethanol as the solvent used during the hydrogenation. The rationale behind this was hoping the acid would help protonate the carbonyl and the nitrogen easing the addition of hydrogens to the double bonds. Upon neutralizing the acid with NaHCO$_3$, brown solids with the consistency of plastic apparently consumed most of the product. Only the NMR #7 which was performed on residues found in the water after neutralization of the acetic acid showed some sort of pyrroline structure at 1.2 ppm, but the different shifts prove hard to explain.

Finally, a test method using NaBH$_4$ in ethanol produced the 2-(1-hydroxyethyl)pyrrole at almost 100% yield. The NMR spectrum #3 provided the proof for this reaction. Ring protons show at 6.55 ppm, 6.05 ppm, and 6.00 ppm. The quartet at 4.65 ppm and doublet at 1.35 ppm result from the hydroxyethyl group.

\[
\text{3 2-}(1\text{-hydroxyethyl})\text{pyrrole}
\]
The best method for separation of the compounds was developed using TLC with a mobile phase of 1:1 ethyl acetate:hexanes. A silica gel column using this mixture resolved the 2-(hydroxyethyl)pyrrole in NMR #11 from starting material rather effectively.

While TLC effectively separated the different compounds in various reactions, much time spent on using gas chromatography to determine the success of reactions was wasted. The rings apparently disintegrate in the injection block into random fragments, rendering the data useless.

In summation, the most successful method for hydrogenation was in ethanol. The indications are that the oxidation of a completely reduced 2-(1-hydroxyethyl)pyrrolidine is required to produce the 2-acetylpyrrole. The oxidation is very gently achieved as evidenced by the simple air oxidation that occurred when the hydrogenation was not stored under argon. The use of acetic acid as a solvent for hydrogenation was probably as successful as ethanol, but problems encountered with polymerization during the work-up diminish its usefulness. The use of NaBH₄ to synthesize the 2-(1-hydroxyethyl)pyrrole might be an interesting way to produce another starting material for the hydrogenation. Further work is needed on the separation and purification of the small amount of 2-acetylpyrrole to get a better proton and perhaps carbon-13 NMR profile.
NMR #1

PAST HYDROGENATIONS 4/21/92 IN CDCL3
NMR #4
NMR Chart

PROTON=DO

MIN. INTENSITY = .900 P  MAXY = 10.000000  FP CONSTANT = 1.000000
INTENS. LEVEL = .900  NOISE = .01133  SENS. LEVEL = .84532
F1 = 2626.46 Hz = 10.5000 PPM  F2 = -49.80 Hz = -.1971 PPM

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PROTON=D2

MIN. INTENSITY = .900 P  MAXY = 10.000000  FP CONSTANT = 1.000000
INTENS. LEVEL = .900  NOISE = .01133  SENS. LEVEL = .84532
F1 = 2626.46 Hz = 10.5000 PPM  F2 = -49.80 Hz = -.1971 PPM
NMR # 11

HYDROGENATION 5/11/92 PURIFIED FROM SILICA GEL

[Diagram of NMR spectrum with peaks labeled A, B, C, D, E, F at various chemical shifts (in ppm)].

- Peak A: 0.877
- Peak B: 1.95
- Peak C: 1.99
- Peak D: 4.79
- Peak E: 7.3
- Peak F: 8.77

[Table of areas and integrals below the diagram].