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JAN 21 1986

An Efficient Preparation of Substituted
Cinnamaldehydes and Heterocyclic Acroleins

Robert J. Hrouda
13 December 1985
CHEM 499H
Professor C.W. Spangler

JAN 21 1986

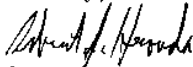

15 Jan 86

Eleanor P. Godfrey, Director
University Honors Program
Northern Illinois University
DeKalb, Illinois 60115

Dear Ms. Godfrey:

In response to your request of 6 Jan, please find enclosed a copy of the paper I authored in fulfillment of my Capstone Project requirements. Dr. Charles Spangler, in whose lab the work described occurred, also has a copy.

Sincerely,


Robert J. Hrouda

Introduction

Conjugated rings such as benzene, thiophene and pyridine with conjugated aldehydes such as 3-alkoxypropenals attached in various positions have proven to be ubiquitous synthetic intermediates, being useful in a variety of applications including natural products synthesis, as components in some industrial fragrances (1) and in Wittig condensations to yield conjugated polyenes (2), which may be synthesized with specific heterocyclic chain terminators (3). A great many procedures currently exist for obtaining these molecules, ranging from distilling them from naturally occurring oils, as in the case of p-methoxycinnamaldehyde from estragon oil (4) for an anticipated miserly yield of 0.6%, to oxidizing propylene derivatives with SeO_2 (5) or transition metal oxides (6), as well as condensation reactions (7), for better yields. Yields as high as 70% have been achieved (8), although higher yields generally seem to correspond to tedious procedures, limiting their practicality, especially for producing appreciable amounts of these compounds.

Of the molecules whose synthesis is described, the substituted cinnamaldehydes have been most extensively studied, and a vast body of literature exists describing various synthetic methods for achieving these aldehydes (9,10,11). The substituted heterocyclic molecules, though, have come into vogue relatively recently, and the literature lists only a few synthetic methods (3,12), which are again either tedious

or inefficient.

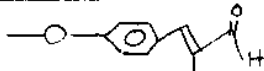
For these reasons, then, it was undertaken to devise an efficient preparation of substituted cinnamaldehydes and heterocyclic compounds by adapting work done earlier in the Spangler laboratory on conjugated and nonconjugated substituted dienals (13) to the particular needs of these molecules. The procedure involved formation of a Grignard reagent with brominated heterocyclics and substituted benzenes followed by addition of either 2-methyl-3-ethoxypropenal (14) or 3-ethoxypropenal, prepared by treating malonaldehyde bis(diethyl acetal) (14) with p-toluenesulfonic acid through a series of four vacume distillations (15). The acrolein or cinnamaldehyde was then formed by hydrolyzation, using saturated NH_4Cl for the nitrogen-containing compounds and 3N HCl as well, for the others. The product was then isolated in a variety of ways. Although this method appears to have general utility, time constraints permitted the successful synthesis of only five types of molecules: 2-methyl-3-(p-methoxyphenyl)propanal, 2-methyl-3-(p-N,N-dimethylphenyl)propanal, p-dimethylaminocinnamaldehyde, 2-thiopheneacrolein and 2-pyridineacrolein, but these are indicative of the method's usefulness and efficiency, and it is expected to be equally applicable to many more ring systems.

Methods/Results

A typical procedure involved forming a Grignard reagent with 0.10 mole of the brominated substituted benzene or

heterocyclic in 100 ml tetrahydrofuran (THF) being added dropwise to 0.11 mole Mg in 25 ml THF at room temperature. A few mg crystalline I_2 were added to all the reactions involving substituted benzenes, but not to those involving heterocyclics. If the reaction failed to initiate, as evidenced by heat evolution, 1 ml 1,2-dibromoethane was added. Following addition, the mixture was gently refluxed for an average of twenty minutes and then cooled to 0°C, upon which 0.08 mole of either 3-ethoxypropanal in 50 ml anhydrous ether or 2-methyl-3-ethoxypropanal in 50 ml THF was added dropwise. The mixture was again gently refluxed for twenty minutes, then hydrolyzed with, for nitrogen-containing compounds, NH_4Cl /ice/ H_2O , and also with 100 ml 3N HCl for the others. The product was extracted with ether which was dried over anhydrous $MgSO_4$. If an emulsion or polymer formed during extraction, both the mixture and ether solutions were washed with brine. If the dispersion or polymer persisted, they were filtered from the ether layer and saved for analysis. Following rotary evaporation of the ether, the product was isolated and recrystallized in a variety of ways, determined by trial and error:

2-methyl-3-(p-methoxyphenyl)propanal.



This product came out of the reaction mixture and into ether cleanly without dispersion or polymer formation, and was a reddish oil after stripping off the ether. This oil was distilled under vacume to give a light yellow product with a boiling point of 106 - 116°C under 0.10 mm Hg and an index of refraction of 1.6220. The yield was 65%, and the 2,4-

dinitrophenyl derivative of the liquid had a melting point of 236 - 239 C. A proton nmr scan further substantiated the product's identity (Fig. 1).

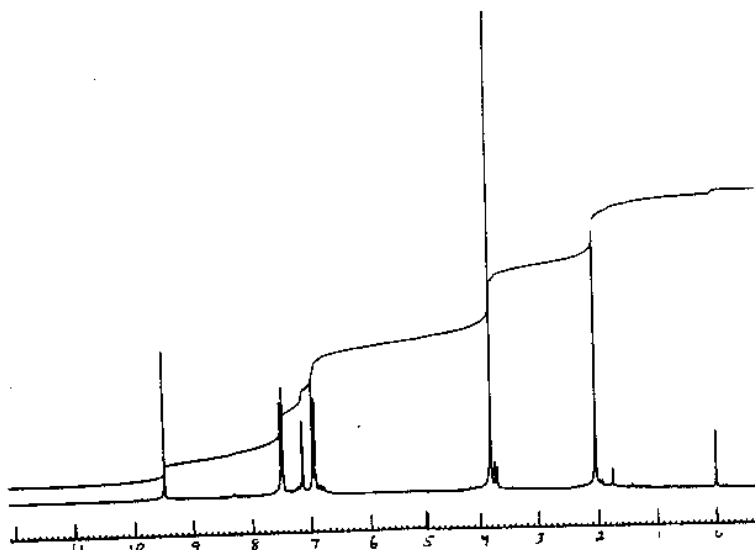
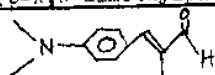


Fig. 1. Proton nmr scan of 2-methyl-3-(p-methoxyphenyl)propanal.

2-methyl-3-(p-N,N-dimethylphenyl)propanal.



Since the first ether wash of the reaction mixture containing this compound apparently did not collect much of the compound (no color was gained by the ether), the aqueous layer was basified with 2N NaOH, when successfully extracted with ether. The initial ether fraction was extracted with saturated aqueous bicarbonate, resulting in a pink aqueous layer and a yellow organic layer. The ether fractions were combined and dried with anhydrous MgSO_4 , then the solvent was evaporated to give a greenish solid which was recrystallized in hexane/toluene to give round yellow crystals with a melting point of 94 - 96 C. The yield of this compound was 62%, and a proton nmr

revealed that the product was indeed the one desired (Fig. 2).

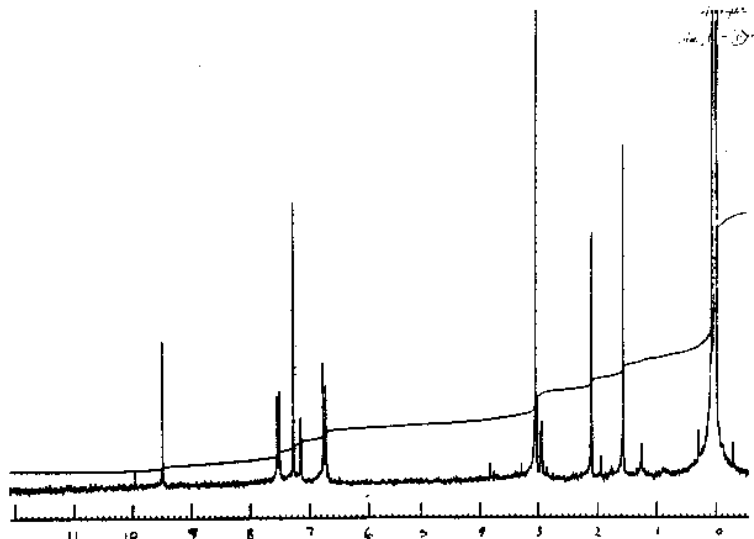
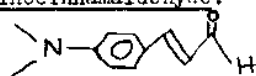
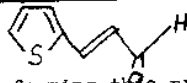


Fig. 2.
Proton nmr scan of 2-methyl-3-(p-N,N-dimethylphenyl)propanal.

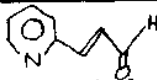
p- dimethylaminocinnamaldehyde.



The reaction mixture containing this product was simultaneously extracted with ether and brine, but an ugly dispersion which had formed could only be slightly attenuated. Consequently, the dispersion layer was combined with the ether fractions, then filtered, and the slimy solid matter was extracted with ether, then saved. The combined ether layers were then dried over anhydrous $MgSO_4$. A dark red oil, achieved by evaporating the solvent, was dissolved in 95% ethanol, filtered and stored overnight at $10^\circ C$ to give an orange-red, roundish crystal with a melting point of $136 - 138^\circ C$. The yield of this product was only 46.4%; an unknown amount was lost in the dispersion. A proton nmr scan confirmed the structure of the product.

2-thiopheneacrolein.

When forming this product, the reaction mixture was refluxed only 10 min to form the Grignard and only stirred in warm water after addition of 3-ethoxypropanal. The product appears to be sensitive to oxidation by the air, as it turned progressively darker, from yellow to dark red within 5 min of opening the reaction flask. The effect of air oxidation was also noticed on a portion of MgSO_4 which had been used for drying, then set aside; within 10 min it turned from white to pink to purple to blue to black. This occurred on the side of the chunk directly exposed to atmosphere, but not on that next to the pyrex flask. The effect of oxidation was apparently to polymerize the product, as a black polymer formed during extraction which partially adhered to the pyrex extraction vessel, and was minimally soluble in acetone. After drying the organic layer with anhydrous MgSO_4 and evaporating the solvent, the dark red oil left was washed out of the evaporation flask with a minimal amount of 95% ethanol, then stored overnight at -30°C to give a blackish liquid over a small amount of black polymer strongly adhering to the flask, which was slightly soluble in acetone and reasonably soluble in chloroform. It was dissolved and combined with the mother liquor, which was then vacuum distilled into a receiver cooled with dry ice to give a thermochromic liquid boiling at 58°C under 0.10 mm Hg; it changed color from bright orange at -30°C to brilliant green in dry ice to clear yellow at room temperature to bright blue under a heat gun. A proton nmr spectrum of the product confirmed that it has the structure of 2-thiopheneacrolein.

2-pyridineacrolein.

This compound also appeared to be air sensitive; a great deal of a brown-black polymer insoluble in all the usual organic solvents but soluble in 3N HCl, and strongly adherent to the pyrex extraction vessel, was formed during extraction. It was filtered out of the ether, which was dried over anhydrous MgSO_4 , and then evaporated, leaving a blackish oil. Crystallization was attempted in toluene, but repeatedly resulted in the black polymer being formed on the flask, which was insoluble in boiling toluene. Repeated crystallization attempts resulted in nothing but "polymer" formation, so the toluene was finally extracted with 3N HCl and the polymer dissolved with 3N HCl. The HCl fractions were combined and neutralized

with NaOH, resulting in a small amount of tan precipitate becoming suspended in the black solution, accompanied by re-formation of the polymer. At this point it was decided an entirely different approach to the problem was required. The organic contents of the neutralized aqueous solution were extracted with ether which was consequently evaporated to give the black oil. A proton nmr spectrum of this oil indicated that, besides a great deal of impurities, the 2-pyridineacrolein appeared to be present in small amounts; the majority of it apparently was lost to gradual polymer formation over the course of attempted recrystallizations. It is anticipated that distillation of this oil immediately upon forming will result in high yields, as was the case with 2-thiopheneacrolein, which also formed a black polymer in the mother liquor, but was liberated in pure form by vacuum distillation.

Discussion

In addition to these successful syntheses, a few attempts were met with ^{with}ill fate. Although twice attempted a Grignard reagent could not be formed with p-bromonitrobenzene. Perhaps harsher reaction conditions or pretreating the Mg in an acid bath will yield the Grignard. Attempted synthesis of p-methoxycinnamaldehyde and p-dimethylaminocinnamaldehyde also resulted in failure, once for both compounds. Although the reactions for these products appeared to be proceeding normally, a proton nmr scan of the results indicated that they were not the desired aldehydes. Investigation into just what they are and what what went wrong is continuing.

As mentioned previously, it was necessary to make the reactant 3-ethoxypropanal from malonaldehyde bis(diethylacetal). The method used reported a yield of 28% (15). This was increased to 45% simply by extracting the NaHCO_3 used to neutralize the last step addition with ether and combining the ether fractions prior to the last distillation.

In summary, the method described here for the efficient preparation of substituted cinnamaldehydes and heterocyclic acroleins is a significant improvement over previously published methods for obtaining these molecules, and is expected to have general utility for a variety of systems, as will be shown later.

The primary interest with these molecules in this particular laboratory is in producing linear polyenes of a specific length, terminated by specific substituted benzenes or heterocyclic molecules, raising exciting possibilities concerning organic conduction technology. It is noted that the molecules synthesized by this procedure, having a single carbon-carbon double bond ($n=1$), may be lengthened considerable with a chain extension method whereby two ethylenic bonds are serially added by Grignard addition without isolation of intermediates (6). Using this method, 15-p-methoxyphenyl-pentadeca-2,4,6,8,10,12,14-heptaenal has been isolated as red prisms (6). The methods described here, in conjunction with forthcoming methods to make polyenes with these molecules, are sure to provide a foundation for a great deal of exciting and enlightening research.

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