

Introduction

Beta-keto compounds have vast utility as intermediates in organic synthesis. A unique methodology for the preparation of beta-keto carbonyl compounds involves the formation of an acyl Meldrum's acid adduct followed by fragmentation of the Meldrum's acid moiety. Beta-keto esters¹ and amides² have been successfully prepared by this method. The method has also shown utility on a multi-gram scale³ for the reaction shown in Figure 1.

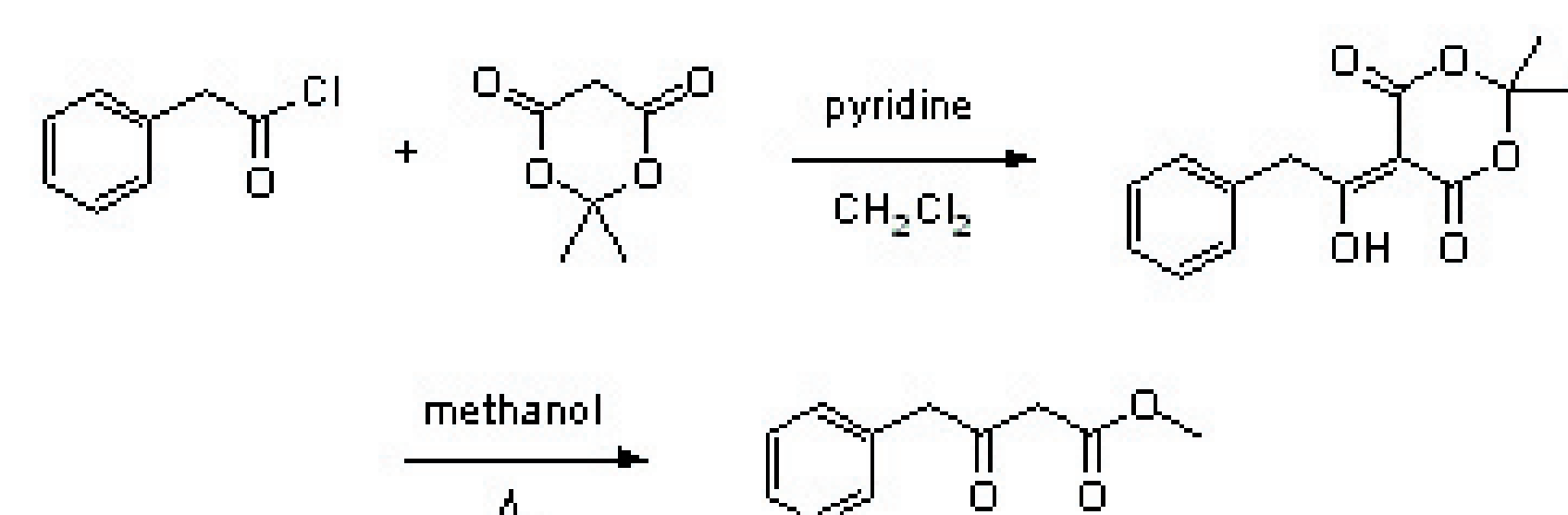


Figure 1. Preparation of a beta-keto ester via fragmentation of an acyl Meldrum's acid adduct.³

Originally, the mechanism was envisioned as nucleophilic attack on one of the carbonyls of the Meldrum's acid residue at elevated temperature. Subsequent fragmentation expelled acetone and carbon dioxide, unveiling the beta-keto carbonyl compound (Figure 2).¹

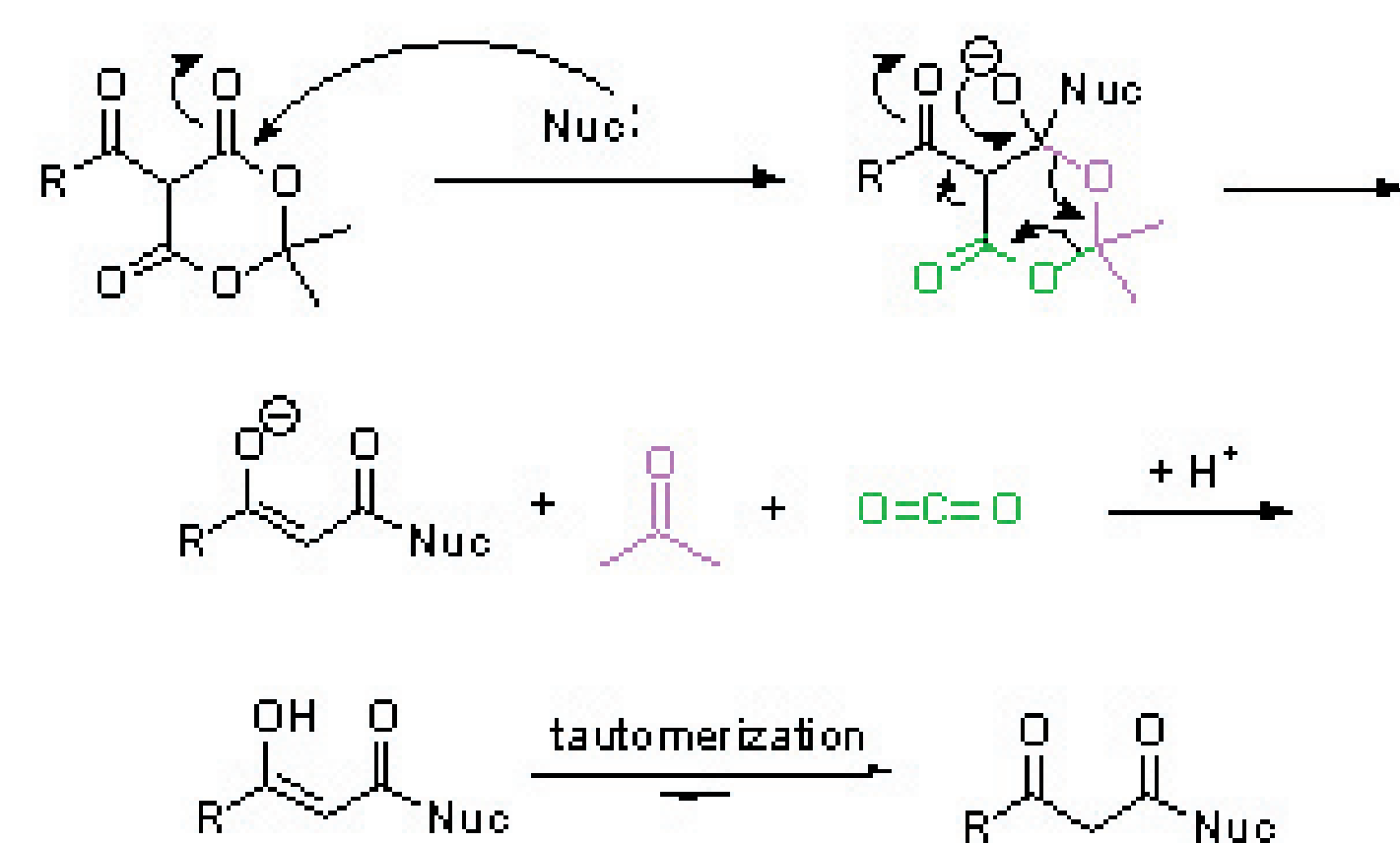


Figure 2. Mechanism initially proposed for the fragmentation of a Meldrum's acid adduct to provide a beta-keto carbonyl compound.

Xu et al. studied the reaction in detail and proposed a new mechanism that does not involve the direct attack of a nucleophile resulting in subsequent fragmentation.⁴ They have shown that heat incites decomposition of the Meldrum's acid residue into an alpha-oxoketene species, which then accepts a nucleophile (Figure 3). Their proposal was based on a study of rate laws and IR monitoring of the reaction.

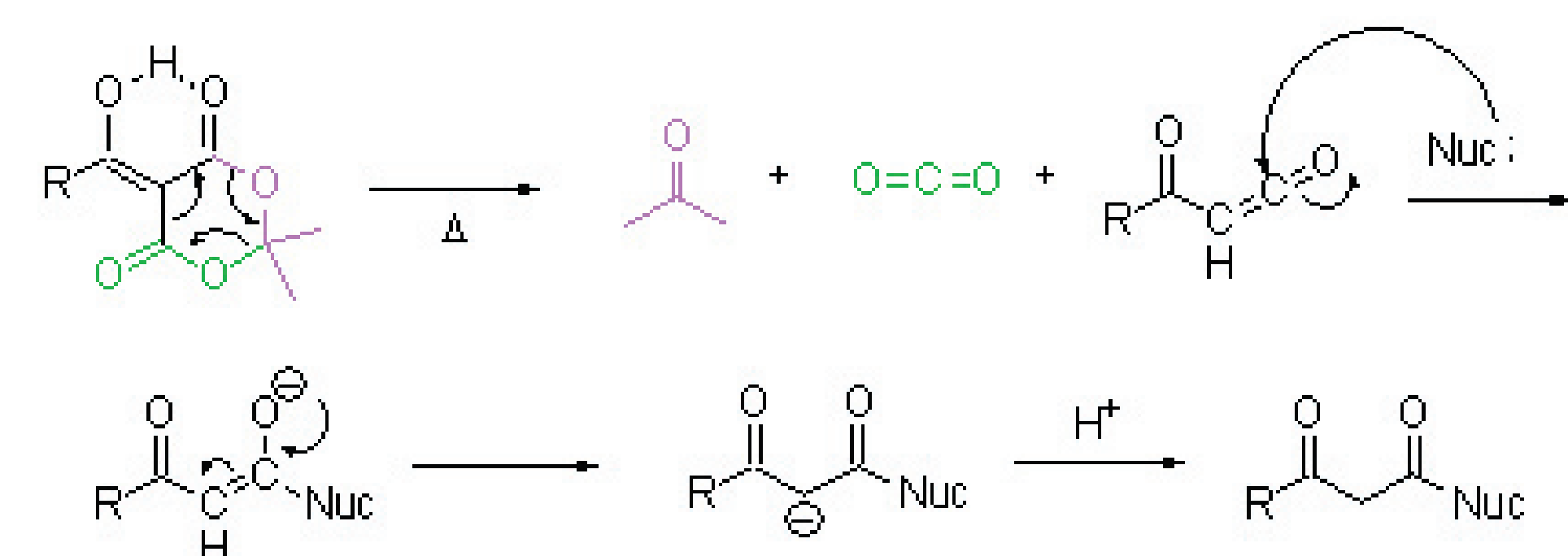


Figure 3. Currently accepted mechanism for the fragmentation of a Meldrum's acid adduct to provide a beta-keto carbonyl compound.⁴

Resorcinol, which is 1,3-dihydroxybenzene, and its derivatives are employed in a variety of products, ranging from rubber to glue (Figure 4).

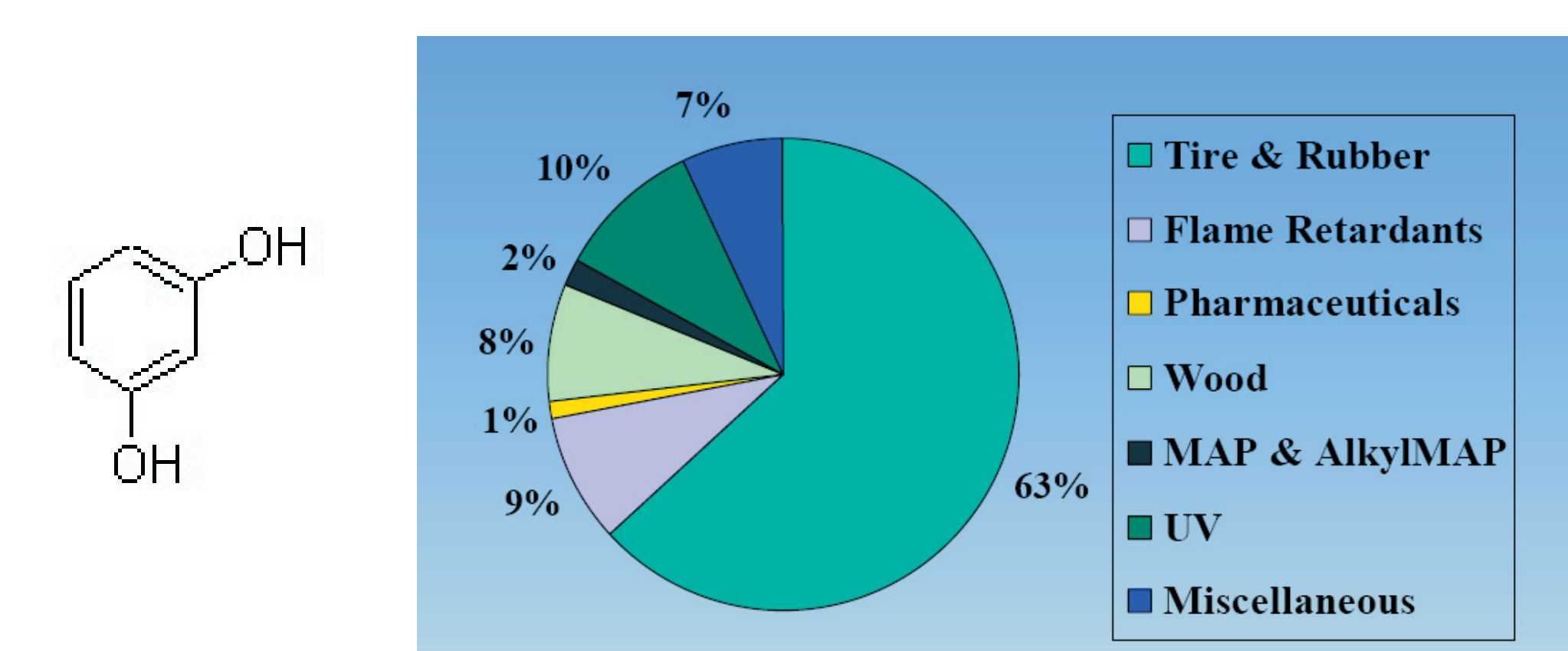


Figure 4. Structure of resorcinol and a representation of its utilization in a variety of applications.⁵

Given the widespread utility of this compound, the synthesis of novel derivatives is of interest. This study targets resorcinol derivatives bearing a substituent containing a beta-keto ester or amide. Such compounds could potentially be prepared via fragmentation of the corresponding acyl Meldrum's acid adduct (Figure 5).

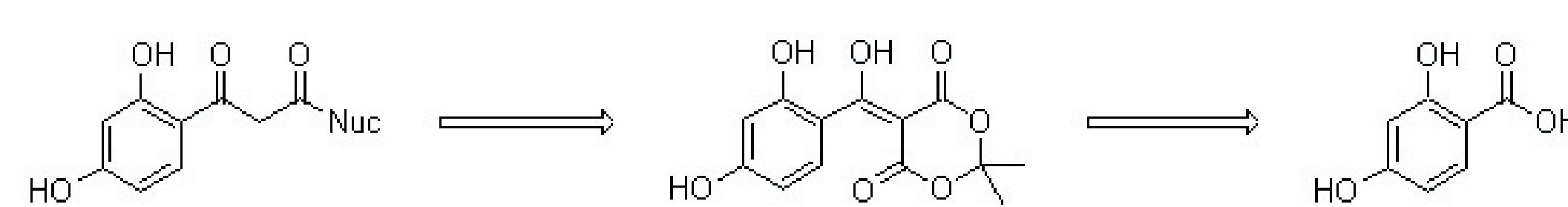


Figure 5. Retrosynthetic analysis of a resorcinol derivative bearing a beta-keto ester or amide.

Results and Discussion

A model study was used to assess the feasibility of this approach. Without the complication of the pendant phenols, an acyl Meldrum's acid adduct can be rapidly prepared from benzoic acid using modified Steglich conditions (DCC/DMAP), providing the desired product as confirmed by NMR analysis (Figure 6). Repeated acid washing during workup was necessary in order to obtain the adduct in its free form, as opposed to the DMAP salt.

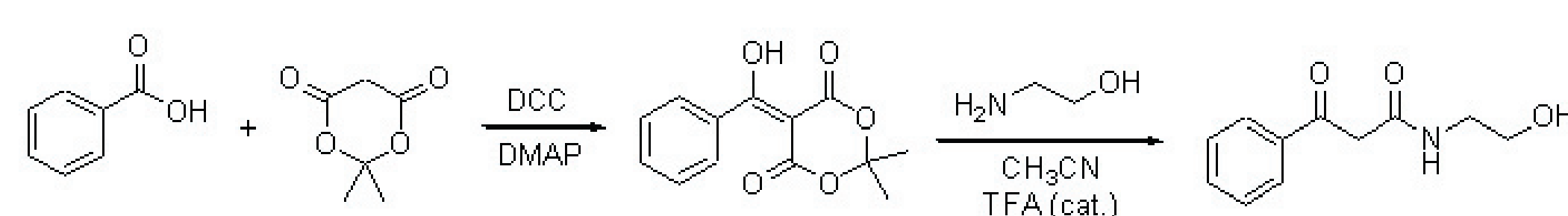


Figure 6. Coupling of benzoic acid with Meldrum's acid

Subsequent reaction of the adduct with ethanolamine in acetonitrile, using catalytic TFA, resulted in an encouraging crude NMR, displaying three peaks between 3.4 and 4.2 ppm. These peaks could correspond to the two methylenes from the ethanolamine residue and the methylene which is alpha to the two carbonyls.

Consequently, coupling of 2,4-dihydroxybenzoic acid to Meldrum's acid was attempted. However, unreacted Meldrum's acid was recovered, suggesting that the phenolic hydroxyls were sufficiently competitive nucleophiles. Therefore, protection of the phenols as the corresponding acetate esters was accomplished using acetic anhydride and catalytic phosphoric acid (Figure 7). Hydrolysis of the mixed anhydride and removal of residual acetic acid as an azeotrope with toluene provided pure diprotected product, exhibiting the expected singlets at approximately 2.1 ppm in the NMR spectrum.

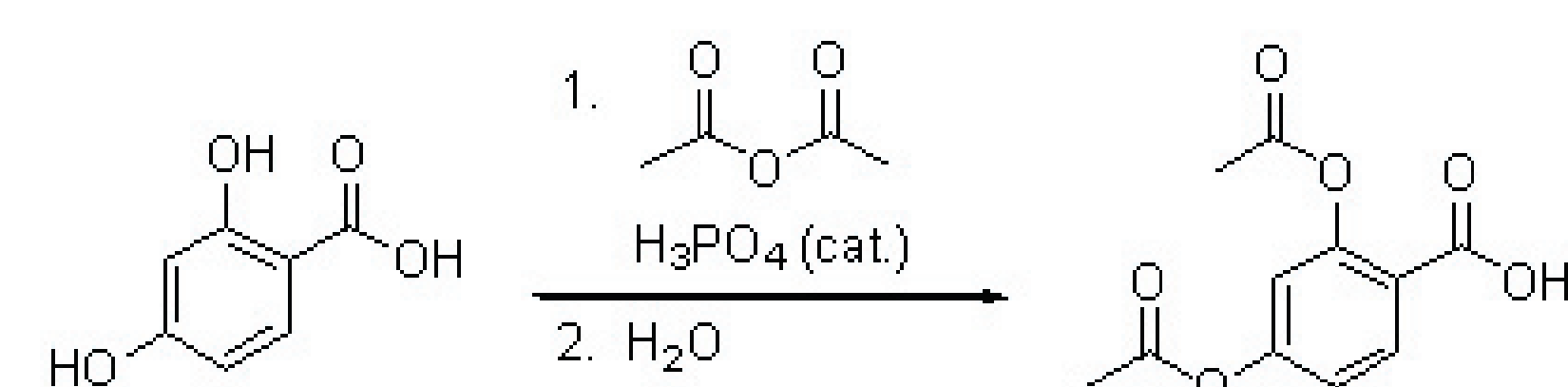


Figure 7. Protection of the phenolic hydroxyl groups of 2,4-dihydroxybenzoic acid.

The modified Steglich conditions used in the model study failed to provide an appreciable amount of product when applied to the diprotected substrate. The ortho acetoxy group may hinder the desired coupling. Consequently, a more reactive functionality, the acid chloride, was installed. This derivative successfully reacted with Meldrum's acid to yield the necessary adduct (Figure 8).

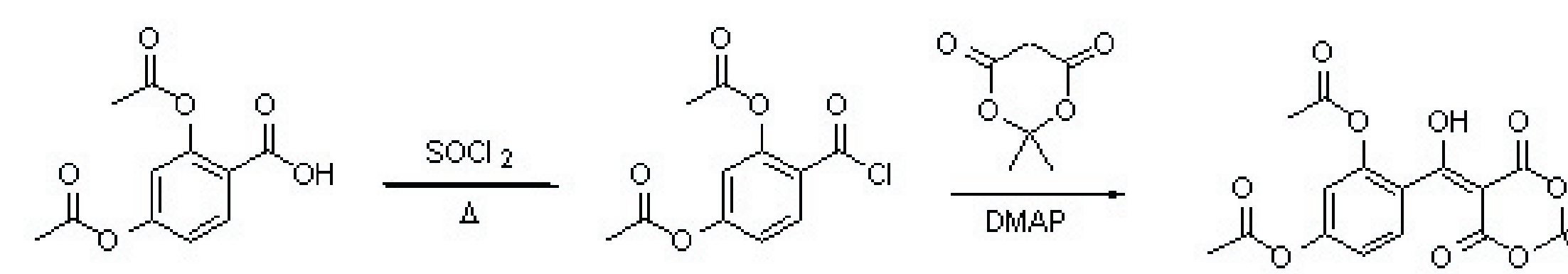


Figure 8. Coupling of the diprotected substrate with Meldrum's acid required the more reactive acid chloride derivative.

Heating this adduct in isopropanol at reflux yielded the beta-keto ester derivative as indicated by NMR (Figure 9). Column chromatography provided a pure sample bearing a methylene alpha to two carbonyls as revealed by the Dept spectrum. Deprotection was not investigated at this stage of the project.

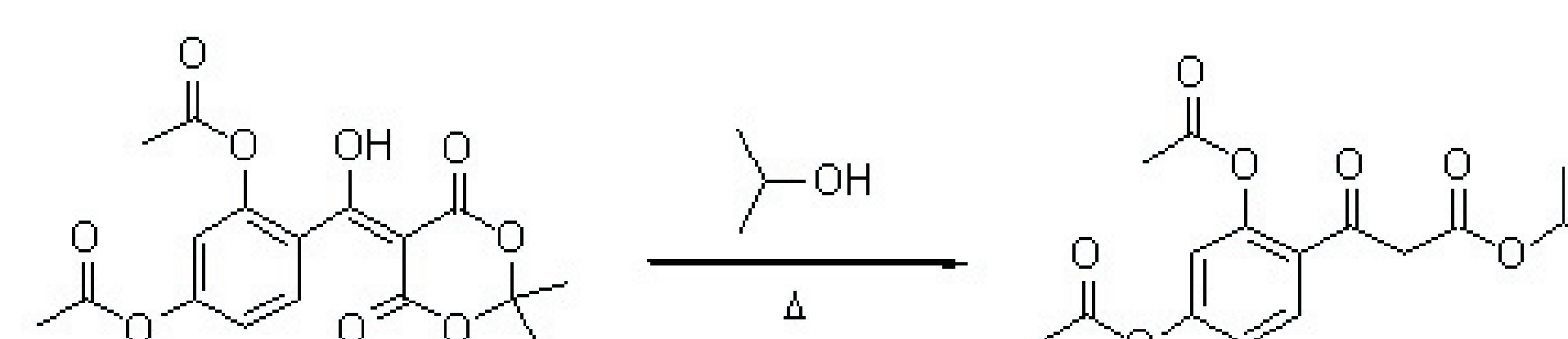


Figure 9. Synthesis of a beta-keto ester derivative via fragmentation of the acyl Meldrum's acid adduct.

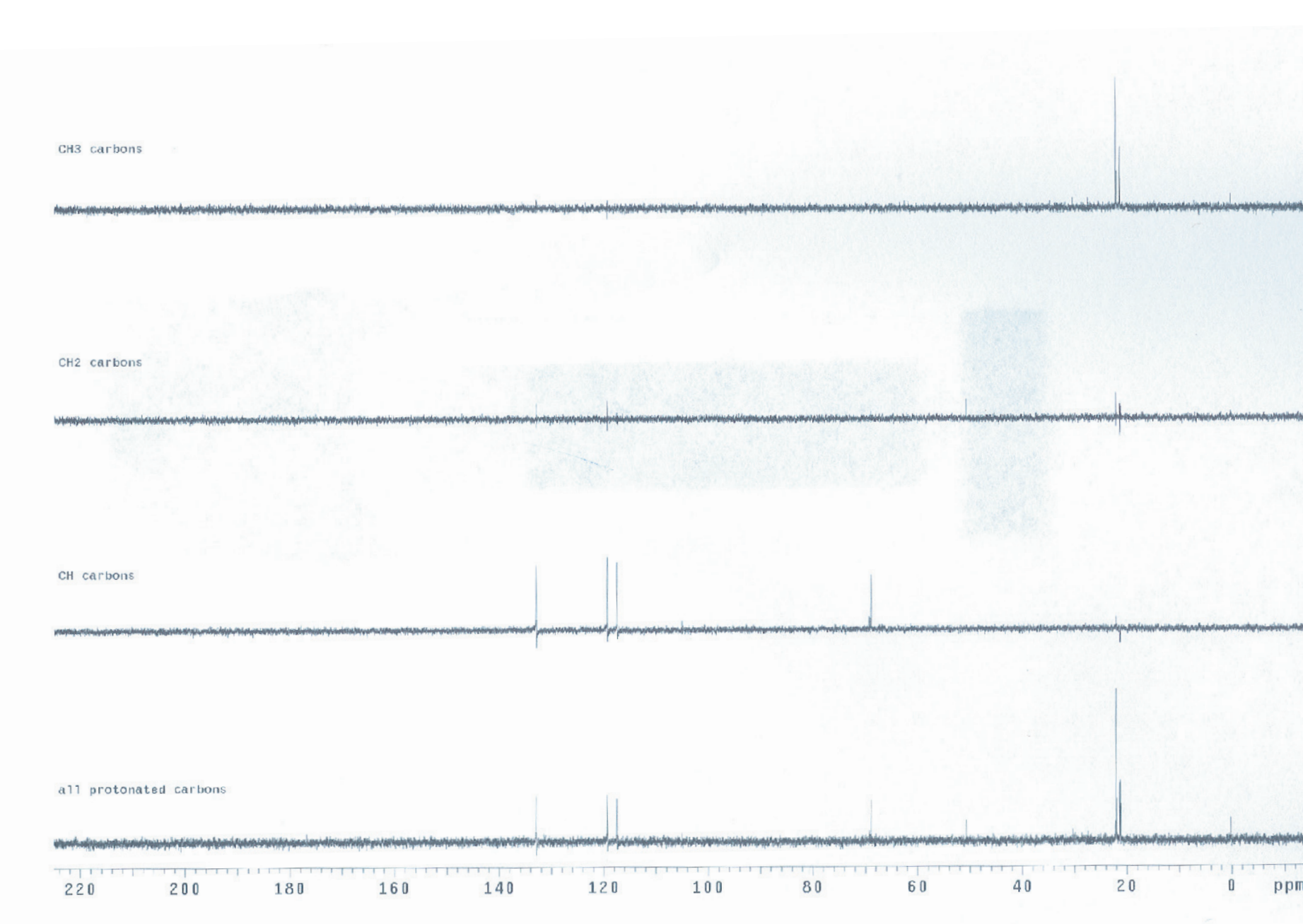


Figure 10. Dept spectrum of compound shown in Figure 9.

Reaction of the same acyl Meldrum's acid adduct with the acetate salt of ethanolamine resulted in the formation of an unexpected product. Aminolysis of the acetate protecting groups liberated the free phenols (Figure 11), as evidenced by the absence of the acetyl signals in both proton and carbon NMR spectra of the product shown in Figure 12.

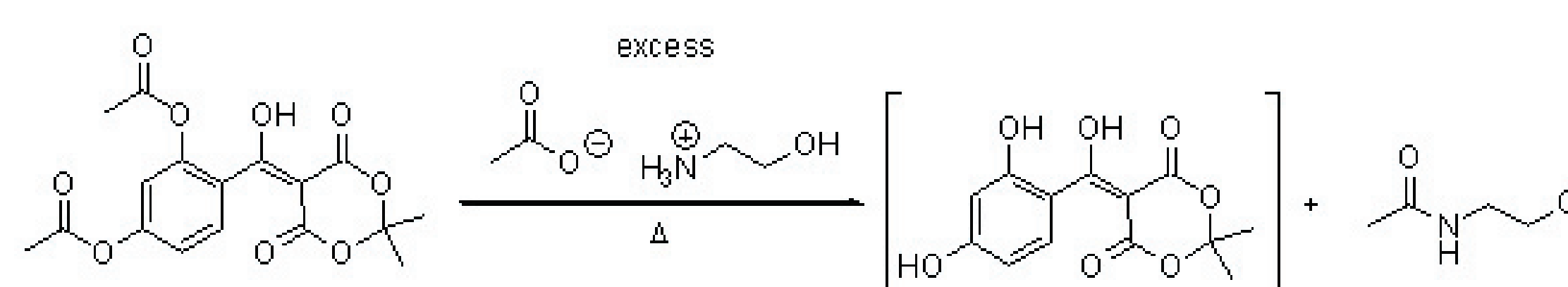


Figure 11. Treatment with ethanolamine results in cleavage of the protecting groups.

Donation of electrons by the hydroxyl groups could result in displacement of the conjugate base of Meldrum's acid (Figure 12). Nucleophilic attack on the resultant ketene forms a resorcinol derivative bearing an amide.

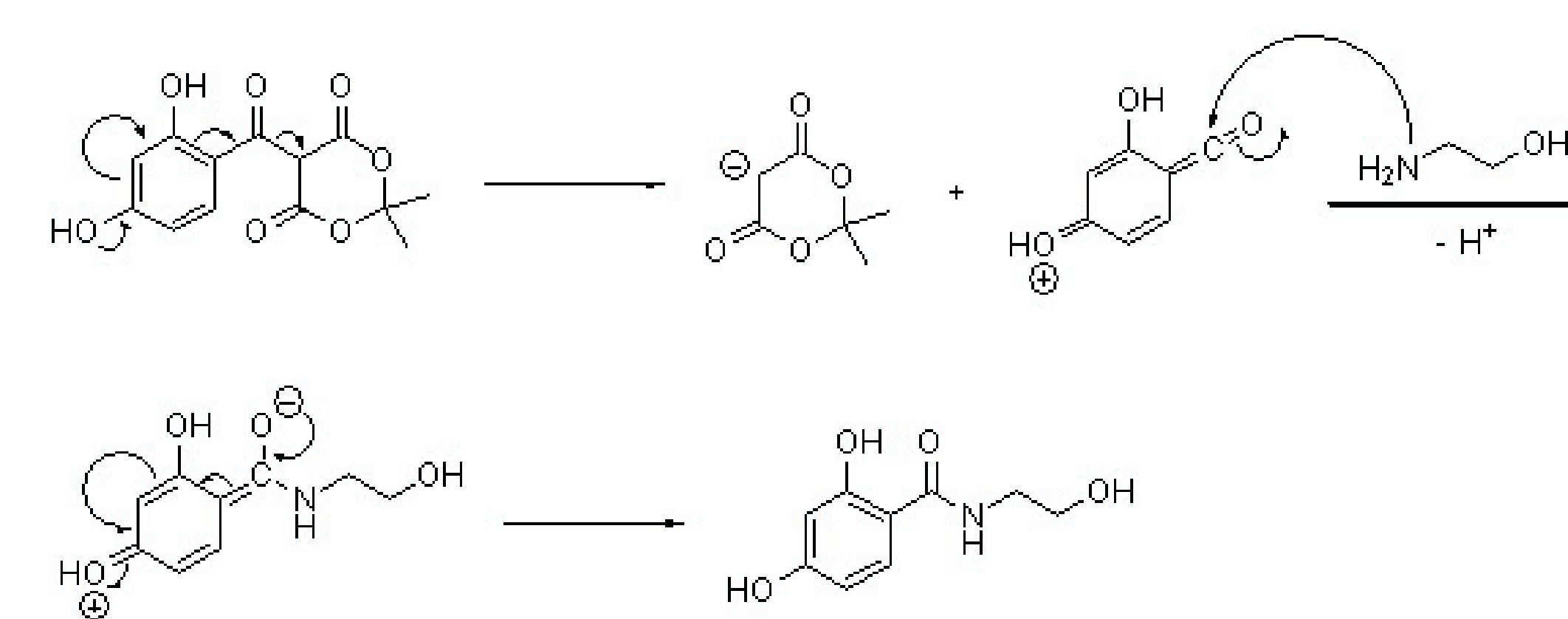


Figure 12. Upon cleavage of the protecting groups, an amide is generated (potentially via the mechanism proposed).

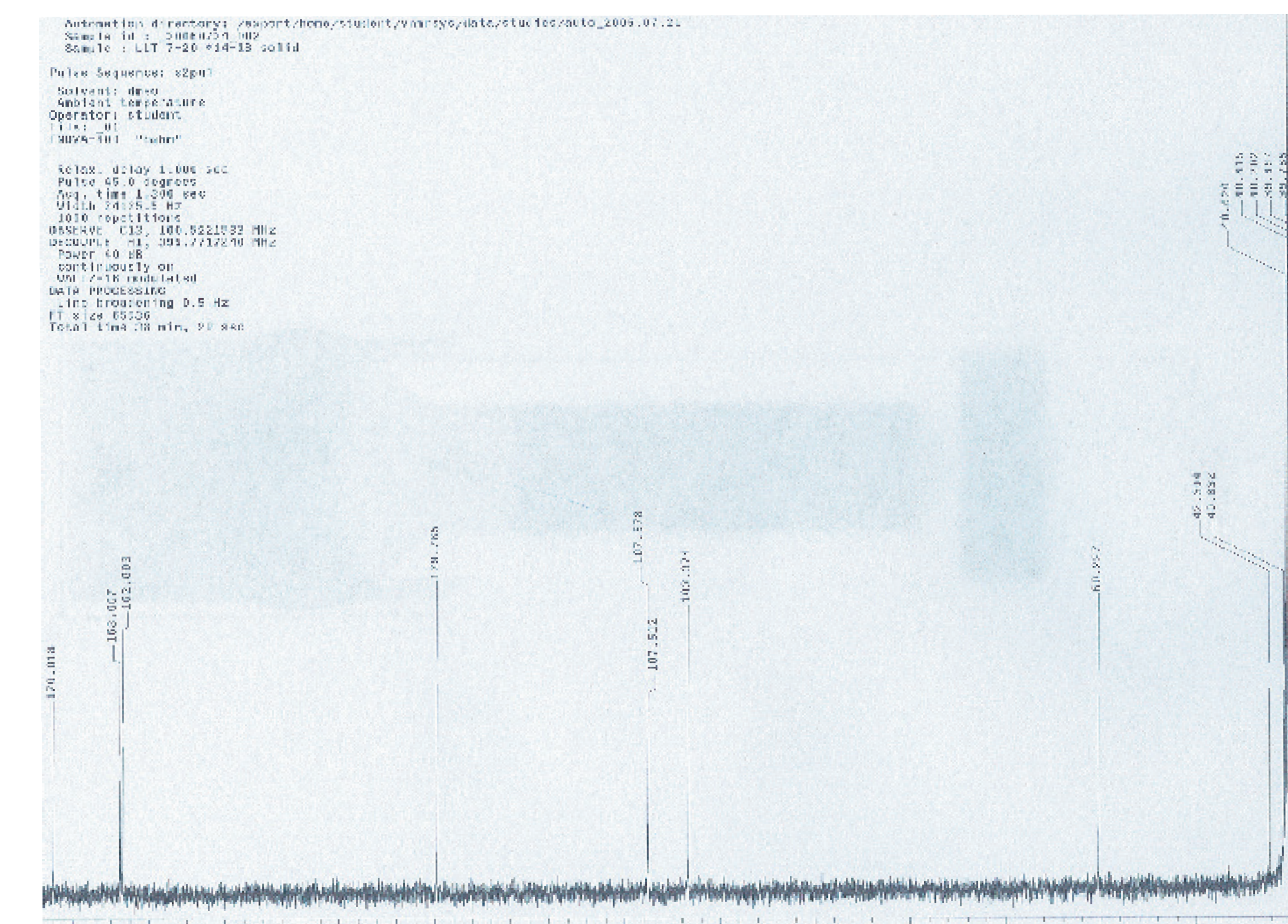


Figure 13. ¹³C NMR of amide prepared in Figure 12.

Conclusions

Key contributions to this project include:

- Successful synthesis of an acyl Meldrum's acid adduct bearing a protected resorcinol moiety.
- Fragmentation of this adduct to produce a beta-keto ester derivative of resorcinol.
- Formation of a novel resorcinol derivative containing an amide through an unexpected mechanism.

Literature Cited

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