

ORGANIC

UNDERGRADUATE EXPERIMENT

Synthesis of Xanthene: Exploring Dynamic Structure via Benchtop NMR Spectroscopy

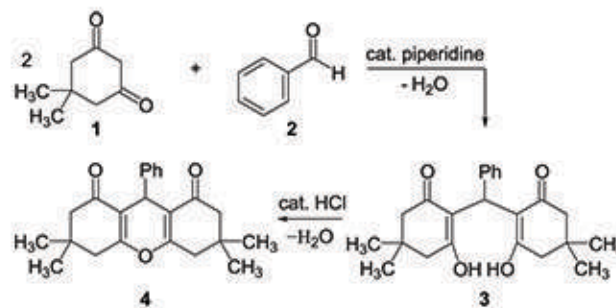
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INTRODUCTION

Organic synthesis is one of the most important skills to master in the undergraduate curricula. Organic synthesis is vital to the production of polymers,^[1] plastic electronics,^[2] pharmaceuticals,^[3] and fine chemicals^[4]. The practice of organic chemistry involves careful consideration towards the reaction sequence, conditions, and purification and characterization of intermediates and products. NMR spectroscopy is the most powerful analytical technique that organic chemists can use to identify and characterize their compounds. Therefore, laboratory experiences incorporating the synthesis and characterization of compounds by NMR spectroscopy should be addressed to undergraduate students in the most pedagogically worthwhile manner possible. In this Application Note adapted from a J. Chem. Educ. article published by A. M. Reeve^[5] an exciting, but simple, synthetic experiment is accompanied with some in-depth analytical exercises using NMR spectroscopy.

SYNTHESIS

Starting from dimedone (**1**) and benzaldehyde (**2**), 9-phenylxanthene-1,8-dione (**4**) can be synthesized in two steps^[5, 6] (Scheme 1).



Scheme 1. Two-step synthesis of xanthene **4**.

The first step involves an aldol reaction of the β -diketone ($pK_a \approx 9$)^[7] **1**, which forms stable enolates under basic conditions and attacks the electrophilic benzaldehyde (**2**).

After formation of a Michael acceptor intermediate (not depicted) via an initial Knoevenagel reaction, another nucleophilic attack of the diketone (two equivalents are employed) follows, leading to diol **3**. Under acidic conditions xanthene **4** is formed by a second condensation reaction.

PROCEDURE

Benzaldehyde (0.4 mL, 4 mmol), dimedone (1.24 g, 8.85 mmol), and piperidine (6 drops) were dissolved in a 1:1 (v/v) mixture of EtOH:H₂O (16 mL). The mixture was heated to reflux for 5 min and the product precipitated as a white solid. Diol **3** was collected by vacuum filtration after cooling the reaction mixture for 10 min in an ice bath. The solid was washed with 20 mL of an ice cold mixture of EtOH:H₂O (1:1 v/v) and the product was isolated as a white solid in 89% yield (1.32 g, 3.55 mmol).

Diol **3** (0.737 g, 2.00 mmol) was dissolved in hot absolute EtOH (20 mL). Subsequently, H₂O (5 mL) and HCl (6M, 12 drops) were added and the reaction mixture was heated to reflux for 5 min. After cooling to room temperature, water was added dropwise to the solution until the mixture turned cloudy. The mixture was then cooled to 0 °C, filtered, and the solid washed with an ice cold mixture of EtOH:H₂O (1:1 v/v, 10 mL). Compound **4** as isolated as a white powder in 90% yield (0.630 g, 1.80 mmol).

The ¹H NMR spectra of dimedone **1**, benzaldehyde **2**, diol **3**, and xanthene derivative **4** were acquired (1D experiment, 16 scans) on an NMRReady-60 spectrometer.

RESULTS & DISCUSSION

With the ^1H NMR spectrum of dimedone (**1**) in hand, the ratio of keto-enol tautomerism in CDCl_3 was determined to be 2.9:1 (keto:enol) by integration of the CH_2 groups of each tautomer (Figure 1). This corresponds to a value 74% in favor of the keto form, which is slightly higher but in good agreement with what students would expect.^[8]

The signals of the enol species in the ^1H NMR spectrum corresponds to a symmetric molecule. The reason for this is that a rapid intramolecular proton exchange from one oxygen atom to the other oxygen center is taking place. As this dynamic process is faster than the NMR time scale, both species are in equilibrium and the two CH_2 groups of the enol **1a** are observed as a broad singlet.^[8]

^1H NMR (60 MHz, CDCl_3):

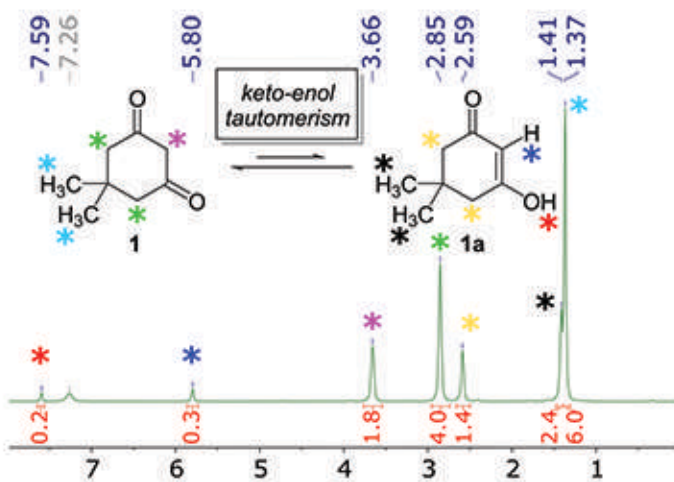


Figure 1. ^1H NMR spectrum of dimedone (**1**).

For the exact same reason, the chemical shifts of all the CH_2 groups in the aldol condensation product **3** are the same and they appear as a singlet that integrates for 8 protons (figure 2). For the CH_3 groups a broad singlet was observed. This is due to the small difference in the chemical shifts of the pseudoaxial and pseudoequatorial methyl groups of the different ring conformers. As the energy barrier between those conformers is small and a rapid

equilibrium is present at room temperature, both signals are observed as a broad singlet at 60 MHz.^[5]

^1H NMR (60 MHz, CDCl_3):

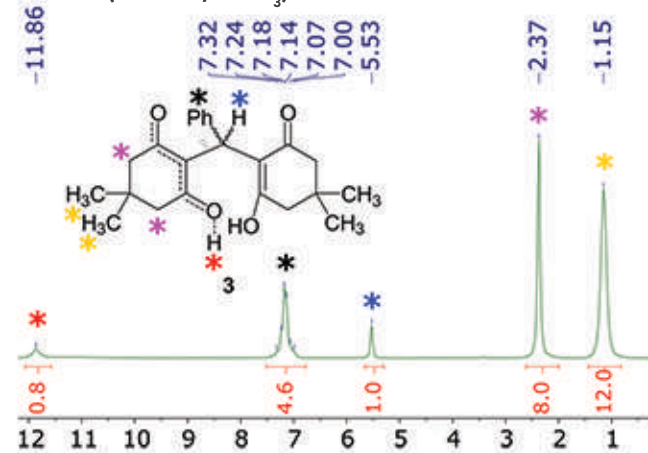


Figure 2. ^1H NMR spectrum of diol **3**.

While the diol **3** gives a symmetric ^1H NMR spectrum, the signals of the CH_2 and CH_3 groups of xanthene **4** are no longer equivalent as a result of the rigid, fused heterocycles in the xanthene scaffold (figure 3).

^1H NMR (60 MHz, CDCl_3):

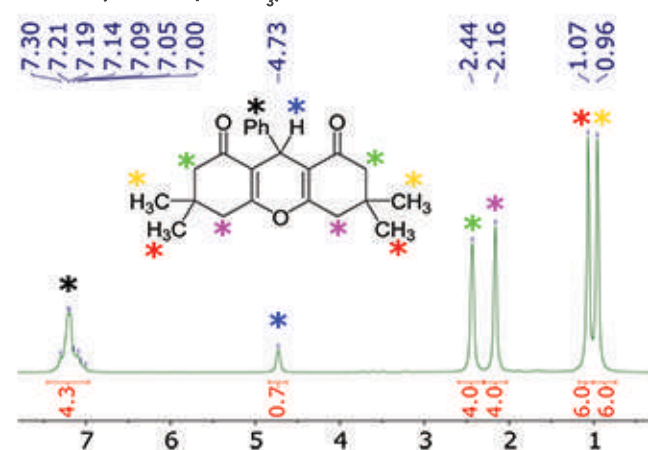


Figure 3. ^1H NMR spectrum of xanthene **4**.

Due to the fixed ring confirmation, the signals of the CH_3 groups split up to separate singlets due to its chemical inequivalence. This situation can be confirmed by considering the positions of the CH_3 groups relative to the phenyl substituent in a 3D model of xanthene **4**.

CONCLUSIONS

In this experiment 9-phenylxanthene-1,8-dione (**4**) was obtained in a straight forward two-step synthesis, employing basic aldol chemistry starting from dimedone (**1**). Aside from the assignment of the substrate, the intermediate- and the final product, the effect of dynamics such as keto-enol tautomerism and ring conformation to ^1H NMR spectroscopy was discussed.

REFERENCES

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DATA ACCESSIBILITY

The data can be processed directly on the NMRReady-60 and printed and/or exported directly to a USB or networked file where it can be worked up using third party NMR processing software.

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