

Updating Dimedone—The Humble Hero of the Organic Laboratory

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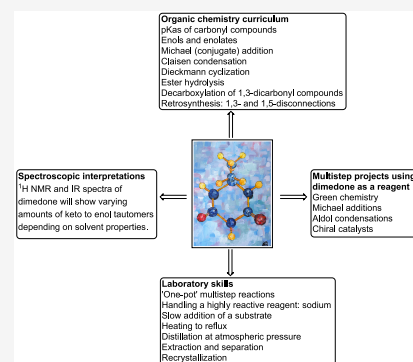
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ABSTRACT: In this paper, we present a concise and technique-heavy route to the synthesis of dimedone for a second-year organic chemistry curriculum. Our preparation of dimedone guides students through a Michael addition followed by a Dieckmann cyclization, basic ester hydrolysis, and thermal decarboxylation, while allowing time for mechanistic discussion and analysis of the product. The wide variety of techniques covered led this to be a pedagogically diverse experiment. This task is thoroughly tested and suitable for a 6 hour laboratory class (with a 1 hour lunch break) or two 3 hour stand-alone sessions.



KEYWORDS: Synthesis, Equilibrium, Reactions, NMR Spectroscopy, Hands-On Learning/Manipulatives, Organic Chemistry, Laboratory Instruction, Second-Year Undergraduate, Upper-Division Undergraduate

The synthesis of dimedone (5,5-dimethyl-1,3-cyclohexanedione) has a venerable history and remains present in several universities' second-year undergraduate laboratory courses^{1–4} (Figure 1). It is best performed as an “all-day” (6

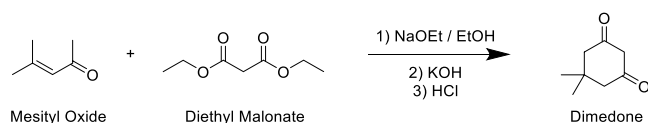


Figure 1. Student preparation of dimedone.

hour) laboratory experiment and is sufficiently robust that it works reliably and yields gram quantities of product, which makes it user-friendly from a student perspective.

The first step of the synthesis of dimedone is a Michael addition, which is then followed by a Dieckmann cyclization, basic ester hydrolysis, and decarboxylation⁵ steps, for all of which there are relatively few stage-2 undergraduate laboratory practicals available.^{5–9} The experiment offers both curricular flexibility and laboratory skill training, and therefore, it would be useful for educators to have an updated procedure with notes for instructors, including spectral interpretations and descriptions that can be readily adapted for use.

PEDAGOGY

Dimedone

Dimedone is a cyclic diketone and an example of 1,3-dicarbonyl compounds, which are often found as stable enols. For example, leptospermone¹⁰ is a naturally occurring

herbicide produced by *Callistemon citrinus*, and piroxicam is an anti-inflammatory drug used for the treatment of arthritis.¹¹ By learning how to synthesize dimedone, students will gain the skills to synthesize more complex analogues, such as spiro-1,3-cyclohexadiones,¹² which are key intermediates in the synthesis of pharmaceutical products such as CETP inhibitors¹³ (Figure 2). Dimedone itself has been used as a precursor for the synthesis of more complex molecules.^{14,15}

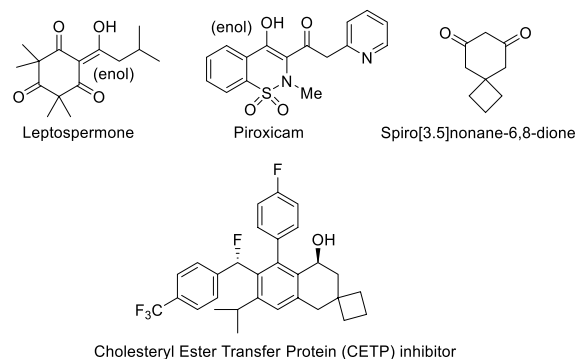


Figure 2. 1,3-Dicarbonyl-related compounds.

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Organic Chemistry Mechanisms and Synthesis

This experiment must run after students have been taught enolate chemistry in the classroom. The first of the two named reactions, the Michael addition, remains widely used,¹⁶ and it develops a good understanding of electrophilicity of reagents^{17,18} and principles of regioselectivity¹⁹ and furthermore has been adapted into a stereoselective process by the incorporation of chiral catalysts.²⁰ The subsequent Dieckmann ring closure, hydrolysis, and decarboxylation steps all offer good “curly arrow” mechanism practice.¹⁹

Ideally students will also have been introduced to the retrosynthetic concept in order to gain a fuller educational value from this reaction. Retrosynthetically,²¹ the preparation of dimedone illustrates principles of 1,3- and 1,5-disconnections, inter- and intramolecular reactions as well as the formation of six-membered rings, and functional group interconversions.

The use of diethyl malonate and sodium ethoxide ties in with acidities of carbonyl compounds and selection of bases.¹⁹

Green Chemistry Integration

Diethyl malonate is used as a starting reagent in the procedure, and as one of its carbons will eventually be lost as carbon dioxide, it opens discussions on balancing atom economy with yield and waste disposal considerations.²²

Solvents used in the reaction process are conventional, and students can be steered toward a discussion on the relative merits of each solvent used and the criteria by which this can be assessed, to include chemical compatibility, hazards such as toxicity, and safety of use (flammable, explosive). Alongside this, the lifecycle of a solvent, from production and its intrinsic nonrenewable dimension to recovery and reuse (if applicable) and waste disposal, can be discussed. Using these parameters, in this experiment, ethanol is considered to have a relatively low environmental impact, whereas this is less so for the use of acetone, petroleum spirits 60–80, and diethyl ether. These solvents, however, are still considered environmentally preferable compared to other organic solvents such as tetrahydrofuran and acetonitrile.²³ The dimedone preparation is also a good example of a “one-pot” process. Dimedone has recently been used as a reagent (Figure 2) in a procedure developed for the undergraduate laboratory: this showcases a green carbonyl condensation reaction involving solvent and organocatalysis recyclability (Figure 3).⁷ In tandem with the dimedone synthesis, this can form part of a multiweek laboratory process.

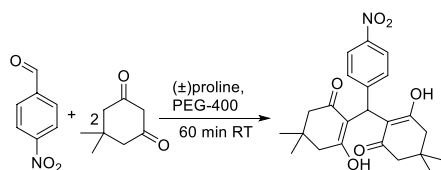


Figure 3. Green condensation reaction as outlined in ref 7.

Spectroscopic Interpretations

Dimedone is known to tautomerize between its keto and enol forms²⁴ (Figure 4), and solvent effects on the position of the equilibrium have been systematically investigated and typically rationalized by applying the Onsager–Kirkwood^{25–27} theory of solvent interactions.^{28–30} Such an explanation, however, is beyond the expectations of an undergraduate course.

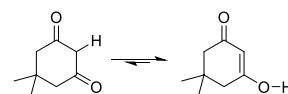


Figure 4. Keto (left)–enol (right) tautomerization of dimedone.

A more accessible interpretation is that the keto tautomer has a greater dipole moment than the enol tautomer,³¹ and when using aprotic solvents, each tautomer is more readily stabilized by solvents that more closely match its dipole moment.³² This explains why in the DMSO-*d*₆ ¹H NMR spectrum, only the keto tautomer is observed. The enol tautomer will be favored, however, if hydrogen-bond-acceptor solvents are used,³¹ as these will create thermodynamically favorable interactions with the hydroxyl of the enol structure. The enol tautomer is also observed in equilibrium with the keto tautomer in the CDCl₃ ¹H NMR spectrum. It may appear counterintuitive that a polar solvent, such as DMSO, shifts the equilibrium away from the enol form compared to less polar solvents, such as chloroform and dichloromethane, because the hydroxyl functionality is usually considered more polar than a carbonyl functionality. In discussion with students, therefore, it may also be useful to compare dimedone with acyclic systems such as 2,4-pentanedione, which unlike dimedone can form an intramolecular hydrogen bond in its enol form (Figure 5); in

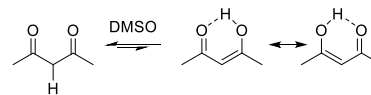


Figure 5. DMSO as a solvent better stabilizes the keto tautomer form of 2,4-pentanedione.

this case a solvent such as DMSO is again observed to favor the keto tautomer, and it has been rationalized on thermodynamic grounds that to disrupt the intramolecular hydrogen bond is less favorable in entropy terms.²⁹

Students will therefore gain a better appreciation that when considering solvation properties, a number of factors need to be considered, including dipole–dipole interactions, hydrogen-bonding interactions (if present), and thermodynamic parameters such as overall entropy and enthalpy. For dimedone, the ratio of tautomers in equilibrium in solution can be determined by ¹H NMR spectroscopy comparing respective integration values, provided that both tautomers are visible in appreciable quantities, as they are in CDCl₃, and this analysis¹⁹ offers a good example of laboratory classes reinforcing NMR interpretations.^{33–37} IR spectra will similarly show the absence or presence of a hydroxyl stretch depending on the method of acquiring the spectrum.

Laboratory Skills

The reaction of sodium metal with water remains a favorite school demonstration,³⁸ and students remember the reactivity and potential danger of sodium. The preparation of dimedone can be effected using prepurchased sodium ethoxide rather than generating it *in situ*, which offers a safer alternative to exposing students to sodium metal. However, there are only a small number of undergraduate experiments that teach undergraduates the safe handling of sodium,³⁹ and at the University of Kent we have safely used the procedure for over 20 years without incident.

The experiment elicits much excitement from the students and is one that involves several reaction mixture and glassware manipulations: handling sodium; the delivery of two separate reagents via a dropping funnel on a three-neck flask; changing the apparatus to a distillation; performing an azeotropic removal of ethanol; performing a solvent wash; acidifying and collecting a foamy/oily crude product, and performing one or more recrystallizations.

■ EXPERIMENT

Students work individually for most of this experiment, although they may form small groups to prepare stock reagents and for mechanistic discussions. The experiment is best performed in a single day over a 6 hour period, split halfway for a lunch break. If required, it can be interrupted after the ethanol has been removed from the distillation and continued in another session, allowing for a split day (two 3 hour sessions). In our experience of running this experiment in the early stages of the second year, students need regular support and encouragement with respect to managing their time to ensure that all the tasks are completed before close of the lab. To ensure that the majority of students are busy but not rushing, we have shortened the reflux stages from the traditional 45 minutes to 25 minutes, and this has not compromised the final yields.

We have found it useful to explain the individual steps on a whiteboard. The safe handling of sodium is demonstrated on the day, and students must complete the risk assessment, which compels them to read the manual beforehand.

■ HAZARDS

A risk assessment is included in the [Supporting Information](#), along with the procedural notes. The students need to be shown how to safely cut and weigh sodium metal. Given the risks associated with using sodium metal, a **careful** evaluation of the risks to benefit considerations, if this part of the procedure is adopted, will need to be effected at the local level. The reaction mixture may bump after addition of the potassium hydroxide solution, but this may be reduced by vigorous stirring. Flammable solvents are used, in particular diethyl ether, which can be very dangerous near hot surfaces. Students also need to be shown how to safely add concentrated hydrochloric acid solution to the reaction mixture.

■ ASSESSMENT OF LEARNING OUTCOMES

The assessment of the learning outcomes was established through the analysis of the laboratory reports, interactions with the students, and the occasional exam question. The procedure presented has been completed by over 500 students.

The experiment is a great learning process for the students with respect to increasing familiarity with glassware setups and gaining confidence handling reagents safely. Nearly all students manage to obtain the dimedone product, although a few occasionally do not manage to perform the recrystallization step. An approximate ratio of 10 students per demonstrator in our experience allows students to be supported throughout the experiment, which allows for many opportunities for each student to ask questions and to receive one-on-one attention. Students are not allowed to commence until they have produced a risk assessment that has been checked and approved by a demonstrator, and this reinforces good laboratory practice safety training. Time management and

organization are also important, but only around 10% of students fail to run a melting point or acquire an infrared spectrum. As part of their induction, students have been given exemplars of different experiment writeups, and over 95% of the reports follow the expected layout and writing style.

As part of their laboratory report, the students are expected to provide mechanistic pathways for the reaction steps. They are also asked to prepare a brief introduction section for the reports to show they understand the wider context of the reaction and to encourage them to explore the literature of modern uses for the chemistry. Most of the students can provide a correct interpretation for the Michael addition and the Dieckmann cyclization steps, but the decarboxylation step is sometimes omitted. This may be a reflection of the associated organic teaching module, whereby the students are exposed to more examples of the first two reactions. Most of the students are also able to correctly interpret the NMR and IR spectra. The retrosynthetic approach to dimedone synthesis has been assessed occasionally as part of an exam question in a related organic chemistry module. In these cases, it has been answered correctly by the students who attempted it.

■ CONCLUSIONS

The preparation of dimedone is a didactic procedure that underpins both academic and practical skill progression in undergraduate chemical sciences courses.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available at <https://pubs.acs.org/doi/10.1021/acs.jchemed.3c00069>.

Laboratory manual and notes for students, including background information, experimental procedure, materials, hazards and safety; hazards; and additional experimental notes for instructors, including chemicals, CAS numbers, equipment needs, synthetic notes, NMR and IR interpretations, mechanistic tutorial, retrosynthetic analysis and references ([PDF](#), [DOCX](#))

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Notes

The authors declare no competing financial interest.

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