Numerous articles in this journal have lamented the cookbook nature of undergraduate organic labs (1–4). Such experiments bear little resemblance to true organic research; students simply follow a “recipe” to make a product that can often be predicted by simply reading the textbook (3). By contrast, experiments that generate products not easily predicted by students require identification through analysis of data and a consideration of the possible reactions of the reagents and solvent (2, 4). Experiments of this nature enhance students’ analytical and problem-solving skills (2) while providing a more accurate portrayal of true organic chemistry. In this paper, we wish to add a lab exercise to the growing body of organic puzzles that promote these principles.

Background

Despite its name, Meldrum’s acid (1), or 2,2-dimethyl-1,3-dioxane-4,6-dione, is not a carboxylic acid (5). But the methylene hydrogens are unusually acidic (6–8) and the conjugate base can undergo reactions with electrophiles such as formaldehyde (9). The resulting Knoevenagel condensation product 3 is a potent Michael acceptor, and under these conditions, Michael addition of a second molecule of Meldrum’s acid occurs to yield the product, diisopropylidene methylene-dimalonate, 4. The mechanism of a tandem Knoevenagel–Michael reaction makes this an ideal experimental puzzle for the end of a unit on enol and enolate chemistry.

Experimental Procedure

To a 3-mL conical vial containing a stir vane was added 144 mg (1.0 mmol) of 2,2-dimethyl-1,3-dioxane-4,6-dione and 200 µL of DMF. The mixture was stirred until the solid had dissolved and 38 µL (0.50 mmol) of 37% aqueous formaldehyde was then added. The flask was capped and stirring was maintained for 90 min, during which time a solid formed. The flask was uncapped, 500 µL of water was added, and the mixture was cooled in an ice–water bath for 15 min. The solid was collected by filtration on a Hirsch funnel and rinsed with a minimum amount of cold water to yield 128 mg of diisopropylidene methylene-dimalonate 4 (85%) as a white solid (mp = 143–145 °C, lit. mp = 144.5–146 °C [9]; 1H NMR: [CDCl3] δ 4.53 [t, J = 1.76 Hz, 2H], 2.79 [t, J = 1.76 Hz, 2H], 1.84 [s, 6H], 1.79 [s, 6H]; 13C NMR: [CDCl3] δ 165.4, 105.7, 42.5, 24.5, 26.4, 23.2). Student yields ranged from 29 to 97% with an average of 57%.

The reaction time can be shortened by heating the same mixture to 65–70 °C for 45 minutes and following the same workup protocol. However, the formation of white solid in the reaction vessel, which provides visual evidence of a reaction, is not observed under these conditions and yields are considerably lower than in the room-temperature reaction.

Hazards

Formaldehyde is a lachrymator and suspected carcinogen. DMF is an irritant and teratogen. However, concerns about the safety of using formaldehyde and DMF are minimized by the small scale of the reaction.

Discussion

The exact mechanism of this reaction is not clear. One can envision a mechanism involving either an enol or an
enolate of Meldrum’s acid as the nucleophile. However, Arnett has shown that Meldrum’s acid is not appreciably enolized in solution (less than 5% is in the enol form) (8). On the other hand, the base needed for most enolate reactions is not used in this reaction. But Meldrum’s acid does condense with formaldehyde in polar solvents such as DMF (9) and clearly one of these two mechanisms is followed. We allow students to develop either mechanism and feel this exercise highlights the fact that not all questions in organic chemistry have been answered.

The symmetry of the final product leads to a strikingly simple NMR spectrum with hydrogens on different carbons appearing at the same chemical shift, a subtlety that catches many students off guard. Additional information, however, can be gathered by considering how Meldrum’s acid might interact with formaldehyde. Most students will recognize that Meldrum’s acid is similar to the more familiar malonate esters. What kinds of reactions might a malonate ester and formaldehyde undergo? Is an aldol reaction or a Knoevenagel condensation more likely? Does the NMR spectrum agree with the product of either of these reactions? Does either reaction lead to a molecule that is unlikely to react further? Most students recognize that neither reaction product 2 nor 3 is consistent with the NMR spectrum but that the methylene malonate 3 formed via a Knoevenagel condensation could go on to react with another molecule of Meldrum’s acid. This possibility and the reaction stoichiometry (2:1 Meldrum’s acid/formaldehyde) lead most students to identify the correct product 4, which is consistent with the NMR spectrum.

This lab exercise produces a product that students cannot immediately predict. But they can identify the product using its NMR spectrum and knowledge of reactions covered in most sophomore organic courses. The experiment can be performed using glassware that is typically available in an undergraduate organic laboratory.

Supplemental Material

Notes for the instructor, a handout for students, and some sample spectra are available in this issue of JCE Online.

Note

1. The term Knoevenagel condensation is used here to describe condensations of active methylene compounds with aldehydes and ketones (10). The classical Knoevenagel condensation, however, requires an amine base and the mechanism involves formation of an iminium ion that is attacked by the conjugate base of the active methylene compound (11). In the reaction described here, the so-called Hann–Lapworth mechanism is invoked (11).

Literature Cited