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Laboratory Experiment

Crossed Aldol Reactions in Water Using Inexpensive and Easily Available Materials as a Tool for Reaction Optimization Teaching in an Undergraduate Organic Chemistry Laboratory

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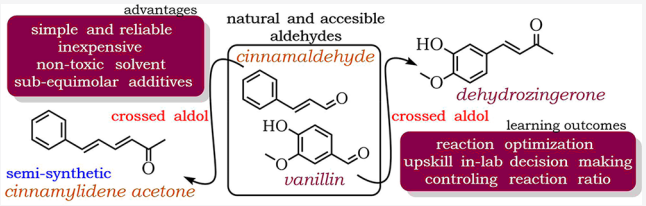
ABSTRACT: We present an experiment designed to hone the decision-making skills of (undergraduate) chemistry students by using aqueous crossed aldol reactions. Here, we present two simple crossed aldol reactions based on inexpensive and readily available materials: The condensation of vanillin and cinnamaldehyde with acetone. The procedure uses the variation of reaction conditions (including the use of inexpensive chlorides, namely LiCl or $NiCl_2$, as catalysts and variation between different mild reaction temperatures), as well as different simple preparative and analytical techniques such as filtration, recrystallization, melting point measurements, thin-layer chromatography and IR spectroscopy aiming for the students to find the optimal reaction conditions, thus honing their decision-making and time management skills. Furthermore, those experiments are designed for a laboratory session of 3 to 4 h.



KEYWORDS: *Organic Chemistry, Hands-On Learning/Manipulatives, Problem Solving/Decision Making, Aqueous Solution Chemistry, Synthesis, Thin Layer Chromatography*

Aldol condensation is undoubtedly one of the most important reactions for C−C bond formation and has been a very useful tool in the synthesis of complex natural and synthetic products for pharmaceutical purposes.[1] In the classroom, the adventure with aldol reactions starts with autocondensation, and then, topics usually move to the synthetically very useful crossed aldol reaction. The study of crossed aldol reactions for the undergraduate organic chemistry student may be difficult. Students need to assimilate many rules and be able to predict product outcomes, whereas many things need to be considered as to which molecule can enolize, which side of the molecule is enolizable, which molecule is more electrophilic, and, in the case of α,β-unsaturated aldehydes or ketones, where the addition occurs: at a carbonyl or a β carbon? These concepts can be strengthened and applied in the laboratory. Many protocols for aldol reactions adapted to organic laboratory teaching have already been published in this *Journal*; however, most of them require either relatively expensive or not readily accessible reagents and catalysts.[2−8]

The ideal crossed aldol reaction requires two carbonyl compound partners, one of which is enolizable and the other needs to fulfill two requirements: to be unable to enolize and to be much more electrophilic than the other compound. The simplest ketone, a very easy to acquire, inexpensive, and enolizable partner, can be acetone, which was our compound of choice. The electrophilic partner, preferably some aldehyde, normally requires acquisition from specialized chemical suppliers. In some developing countries in Africa, Asia, or Latin America, the supply of chemicals for teaching laboratories can be problematic. Cost is a major issue but can be partly minimized by scaling down the reaction and pairing students into larger workgroups per session. Another problem experienced by us, even greater from our perspective, is the delivery time of chemicals, reaching 5−6 months due to the extensive bureaucratic procedures in public procurements. Also, the importance of reducing or even avoiding the use of substances hazardous to humans and the environment, and hereby the importance of teaching a sustainable or "green" approach to chemical research and development, is often underrated in these regions of the world.

We have found that cinnamaldehyde and vanillin are suitable aldehydes for our purpose. Cinnamaldehyde can be easily extracted from cinnamon bark by steam-distillation, and after liquid−liquid extraction, it can be used without further purification for aldol condensation with acetone to give cinnamylidene acetone (Figure 1a).[9] This crossed aldol condensation is very fast; after only a few minutes, precipitation of the product can be observed. Cinnamaldehyde has the

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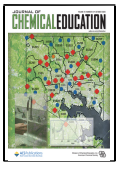

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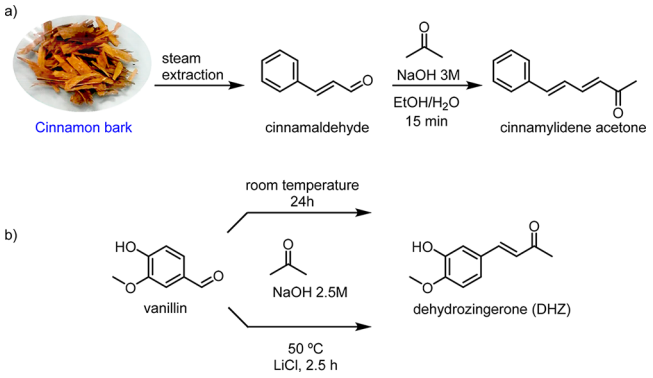

Figure 1. Vanillin and cinnamaldehyde as naturally occurring aldehydes used for crossed aldol condensation with acetone.

characteristic smell associated with cinnamon and possesses several pharmacological properties, such as antimicrobial, anticancer, antioxidative, antiobesity, and anti-inflammatory activity.[10]

Vanillin can be also obtained from a natural source by extraction from the vanilla plant; however, the compound is widely used as a flavoring agent in the food industry and is also available in drug, perfume, and hygiene stores as well as online. The vanillin condenses with acetone in basic aqueous media to generate the product named (*E*)-4-(4-hydroxy-3-methoxyphenyl)-3-buten-2-one; it is also known by its more common name dehydrozingerone (DHZ) or vanillidene acetone (Figure 1b). DHZ itself is present in a natural source as rhizomes of ginger; possesses biological activity as antifungal, anticancer, antioxidant, or anti-Alzheimer's activity; and became of interest as a molecular core for the preparation of other derivatives with improved activity.[11−18] The issue with the reported procedure of that aldol condensation is that vanillin is consumed within 24 h at room temperature. In a course where organic chemistry laboratory is given once per week, this becomes a problem. The optimization of the reaction by Smith[19] partially solves this problem as with specific conditions the reaction time could be extended to 1 week. Nonetheless, when time constraints need to be considered and the laboratory space, as well as material, needs to vacated after each session, this solution is suboptimal. Our goal was to reduce the time of the reaction to be suitable for a 3 h laboratory session. This was achieved after optimization at different temperatures with several additives (metal halides). Hosomi et al. reported successful aldol condensations with improved yields using catalytic amounts of metal chlorides, especially LiCl and $MgCl_2$ in acidic media with quite different systems as α-dimethylsilylesters.[20] In our work, the basic enolization of acetone and condensation with aromatic aldehyde as vanillin with the addition of catalytic amounts of lithium chloride improves the ratio of reaction. During the trials, we have seen that the kinetics of the reaction can be readily altered by the applied conditions and can be easily followed by thin-layer chromatography (TLC). The simple objective of giving a "ready to go" procedure to the student changed to teach the student to determine the best reaction conditions. This experimental approach not only teaches handling of laboratory material but also introduces the student to approaching research problem and laboratory related decision-making. Additionally, we have seen that this approach had a better reception by the students as they realize they are not just following a recipe but are applying analytic techniques to solve daily organic chemists' problems, and also incorporating the aspect of the developing a sustainable approach to a chemical synthetic route.

RESULTS AND DISCUSSION

Optimization of Synthesis of Dehydrozingerone

The optimization of the reaction was carried out using different temperature conditions with LiCl, $NiCl_2{\cdot}6H_2O$, $ZnBr_2$, and $MgCl_2$ as additives. We have found that the best condition is using LiCl (0.1 equiv) with $NiCl_2{\cdot}6H_2O$ (0.1 equiv) at 40 °C or just LiCl (0.1 equiv) at 50 °C where the time of full conversion is shortened from 24 h, as reported in the literature,[16,19] to 2 and 2.30 h, respectively. Lithium chloride alone as an additive requires 0.5 h longer heating, but the reaction is simpler and greener, as only very little salt is used and nickel is avoided. The typical reaction condition was carried out on a scale of 0.5 g (3.3 mmol) of vanillin, 5 mL (67.5 mmol) of acetone, and 2.6 mL of NaOH 2.5 M aqueous solution and additive. The progress of the reaction can be followed by TLC using toluene/AcOEt (9:1) and vanillin developer (check SI for details) every 30 min, since the product reveals a deep purple spot that can be easily distinguished from the starting material. After the reaction mixture is cooled and acidified, precipitated product can be isolated and recrystallized. Caring out the process on reflux shortens the reaction time; nevertheless, this way a sticky paste is obtained, which greatly complicates isolation of the product.

With the following findings, we propose different reaction conditions (Table 1) for several student groups, which require

Table 1. Proposal of the Different Conditions and Expected Results

Additive (Equivalents)	Temperature/°C	Time after Vanillin is Consumed	Yield (after 3 h)
LiCl (0.1 equiv)	Room temperature	8−10 h	40−45%
LiCl (0.1 equiv)	40	3 h	
LiCl (0.1 equiv)	50	2.5 h	
LiCl (0.5 equiv)	40	3.5 h	65−90%
LiCl (1.0 equiv)	40	3.5 h	
LiCl (0.1 equiv) + $NiCl_2{\cdot}6H_2O$ (0.1 equiv)	40	2.5 h	

different times for total consumption of the starting material. Those conditions were chosen as a consensus of appreciable changes in the progress of reaction and quantity of product that can be obtained within the time constraints of a typical laboratory session. Students need to follow the reaction by TLC every 30 min and assess if the reaction should continue or not, considering the presence of starting material and the remaining time of the laboratory session. Then, students need to share and collect the information of every group and finally decide which condition is the best, with the progress of the reaction and economical as well as environmental aspects in mind. Possible decision-making is shown in Figure 2. We do not recommend to base the final decision entirely on the reaction yield as our experience showed that occasionally yields can be misleading since the quantity of precipitate is sometimes erratic, as it depends on the students' abilities to handle the product as well as the post-recrystallization process.

Postsynthesis analysis of the product is a very important topic to be taught, which can be easily executed in a not fully equipped laboratory as DHZ is a solid and can be analyzed simply by

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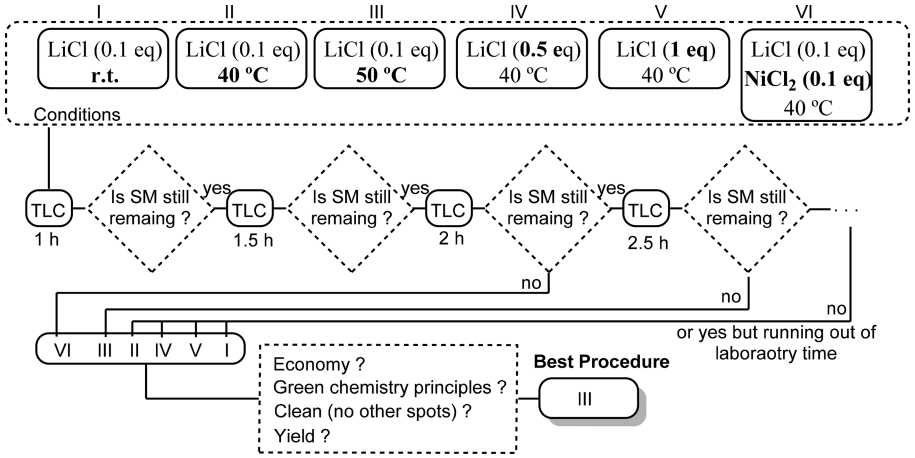

Figure 2. Possible decision-making algorithm to select the best reaction condition.

comparison of the melting point and retention factor reported in the literature (BP, 127−131 °C; R_f 0.18, toluene/AcOEt 9/1). Spectroscopic and chromatographic data for further characterization can be found in Supporting Information.

Extraction Cinnamaldehyde and Synthesis of Cinnamylidene Acetone

This two-step procedure takes place in two (at least 3 h each) laboratory sessions. In the first session, the students extract cinnamaldehyde from cinnamon barks using a simple distillation apparatus by steam-distillation. For that, distilled water is used, and small pieces of cinnamon bark. The distillate is a cloudy suspension of cinnamaldehyde, which can be extracted with chloroform or ethyl acetate. About 30 g of cinnamon bark is suitable for the extraction, as with that amount 280−310 mg of cinnamaldehyde can be obtained, which is a comfortable quantity of aldehyde to work with, in the next step. Surprisingly, after HPLC analysis of the crude, we have found that no further purification was needed, as the spectral purity is about 92% at 254 nm and crude cinnamaldehyde works without any problems in an aldol reaction. The crossed aldol reaction using cinnamaldehyde is much simpler than using vanillin, as condensation with acetone is almost immediate at room temperature. For that, the procedure using acetone and cinnamaldehyde in a 1:1 mol ratio was used in ethanol and an aqueous solution of sodium hydroxide.[4]

We think that this simple two-step semisynthesis of cinnamylidene acetone can be a good alternative to the dehydrozingerone synthesis when vanillin is somehow difficult to acquire. This approach for the introduction of the crossed aldol reaction to the students uses the extraction of a natural product which is then modified. Once again, the product is solid so it can be analyzed using inexpensive equipment and simple analytical techniques. The melting point of cinnamylidene acetone is 70−74 °C and R_f = 0.53 (toluene/AcOEt 93/7). Chromatographic and spectroscopic data are available in the Supporting Information.

TROUBLESHOOTING AND TIPS

- After the reaction of dehydrozingerone is finished and cooled, hydrochloric acid is added for precipitation. A greater quantity of precipitate is obtained when the mixture is cooled in an ice bath and left for at least 10 min. If precipitation does not occur, the product can be extracted with chloroform or dichloromethane 3 times, washed with brine, and dried; the solvent can be removed and the crude material recrystallized from hot ethanol.
- For efficient cinnamaldehyde extraction, cinnamon bark should be flaked into small pieces; however, it should not be pulverized as this causes foam buildup when boiled with water and can pass to the collecting flask.

HAZARDS

As in every chemistry laboratory practice, the use of a lab coat, safety eyewear, and protecting gloves is mandatory. The entire procedure must be carried out in the fume hood. Reagents must be handled appropriately; in the case of sodium hydroxide, it is corrosive and may cause burns. Acetone is flammable and may cause drowsiness or dizziness if inhaled. Vanillin and cinnamaldehyde used in these laboratory experiments are used for food flavoring and although relatively safe, can produce skin and eye irritation.

CONCLUSIONS

Two nonexpensive laboratory experiments introducing crossed aldol reactions were designed and successfully adapted to a typical session of the undergraduate organic chemistry laboratory. The starting material cinnamaldehyde and vanillin are two natural occurring aldehydes that are safe to handle but also easy to acquire, even in countries with limited chemical supplies. Additionally, we took advantage of the flexible reaction kinetic of vanillin condensation with acetone to teach students about the typical optimization process in the organic laboratory. Students were able to use and reinforce the basics of IR spectroscopy and thin-layer chromatography to follow the reaction and analyze the results. Besides, the importance of Lewis acids, additives and catalysts in organic chemistry were discussed and demonstrated in the synthesis of dehydrozingerone. The reaction is carried out in an aqueous medium, and students are encouraged to evaluate their synthetic procedure under the aspect of sustainability. Ready-to-implement in-classroom laboratory guides for student and instructor can be found in Supporting Information.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available at https://pubs.acs.org/doi/10.1021/acs.jchemed.0c00519.

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Laboratory guide for extraction of cinnamaldehyde and cinnamylidene acetone synthesis (PDF, DOC)

Laboratory guide for synthesis optimization of dehydrozingerone (PDF, DOC)

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Notes

The authors declare no competing financial interest.

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