The Step-by-Step Robinson Annulation of Chalcone and Ethyl Acetoacetate

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An Advanced Undergraduate Project in Organic Synthesis and Structural Analysis

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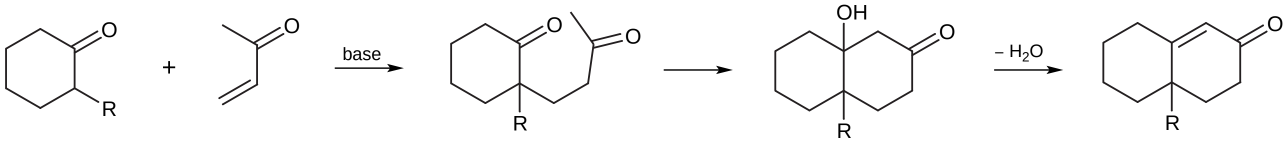
Carbonyl condensation reactions are among the most valuable methods available for the synthesis of complex organic molecules. They constitute a cornerstone in most introductory organic chemistry textbooks and undergraduate students quickly learn to associate the numerous possible variations based on the exact nature of the two carbonyl components with the names of the illustrious chemists who discovered them (Claisen, Knoevenagel, Michael, or Stork, to name just a few) *(1)*. Experiments involving an aldol condensation or a Michael reaction are frequently carried out in the undergraduate organic laboratory to illustrate the concept of carbonyl condensation reaction. A significant number of reports from this *Journal* also focus on these two reactions *(2)*. Comparatively, the Robinson annulation has received far less attention and experimental procedures based on this type of ring-forming condensation are seldom encountered in standard laboratory manuals. Yet, the reaction has found numerous applications, especially in the synthesis of natural products such as terpenes and steroids, because it easily gives access to fused ring systems with angular substituents, a recurrent motif in this important family of molecules (Scheme I) *(3)*.

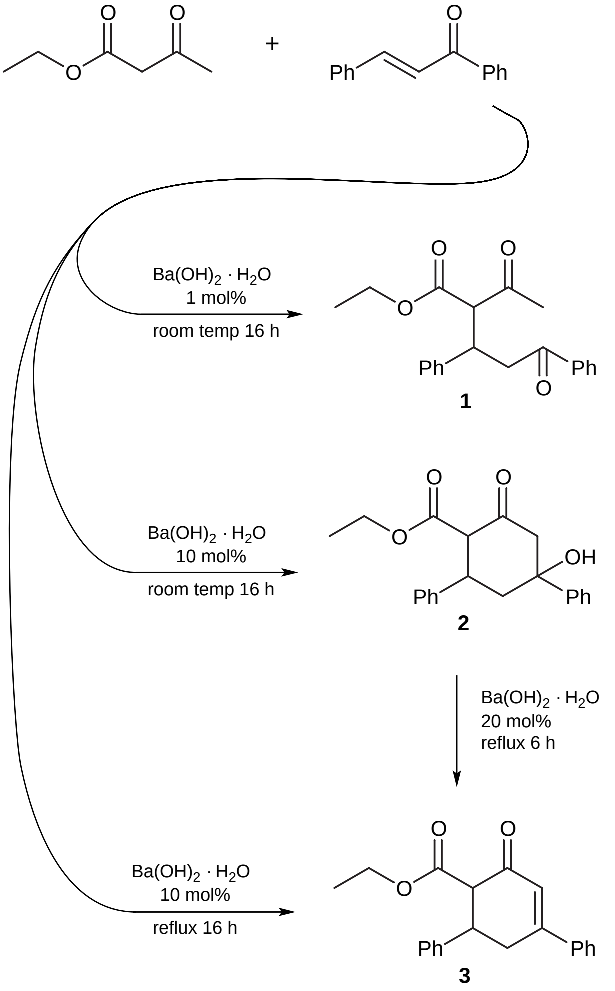
The Robinson annulation is a three-step process in which a stabilized enolate anion first effects a conjugate addition on an α,β-unsaturated ketone to afford the corresponding 1,5-diketone Michael adduct. In a second step this intermediate undergoes an internal aldol reaction and leads to the formation of a keto alcohol with ring closure. A dehydration concludes the sequence and generates the final annulation product that contains a new six-membered ring enone (Scheme I). Under appropriate experimental conditions, it is possible to stop the reaction after every step and to isolate the three products separately. This feature is particularly attractive in the frame of an organic chemistry course. It allows students to confirm experimentally the validity of the stepwise mechanism and to get a more thorough understanding of the process. It also permits the synthesis of a rich set of related molecules that can be compared and characterized through various analytical techniques.

In 1986, Sinisterra et al. succinctly described in this *Journal* the Robinson annulation of chalcone and ethyl acetoacetate using an activated barium hydroxide catalyst *(4)*. No spectral data were given and the products were characterized by their melting points only. Students have performed this synthesis repeatedly over the past few years as part of their advanced organic chemistry curriculum. Reaction conditions were carefully adjusted to obtain selectively each individual product in high yield and purity. Commercially available barium hydroxide monohydrate was also successfully introduced to replace the partially dehydrated, ill-defined catalyst prepared by Sinisterra et al. from barium hydroxide octahydrate *(5)*. Thus, a preliminary activation step that required the use of an oven at 200 °C was no longer necessary. The revised reaction sequence is summarized in Scheme II.

Examination of the IR and NMR spectra of compounds **1**–**3** helps uncover many challenging structural analysis problems that students do not usually suspect at first glance. For instance, the diastereoselective formation of chiral centers during the annulation process, the distinction between axial and equatorial substituents on a cyclohexane ring, or the possibility of a keto–enol tautomerism are topics that need to be addressed to fully discuss the spectroscopy data (see below). Thus, the Robinson annulation of chalcone and ethyl acetoacetate is proposed as part of an advanced undergraduate laboratory that combines organic synthesis and structural analysis. Students usually spend a week working on this project (6 half-day laboratory sessions). On day one, they first carefully read the experimental procedure and draw together the equipment and the chemicals they need from the laboratory store. Then they launch the three reactions concurrently leading to products **1**–**3** from the starting materials in an overnight run. Day two is devoted to workup, recrystallization, and thorough drying of the three products. Time allowing, melting points and IR spectra may already be recorded on that day to quickly assess the purity and the identity of the compounds. An additional experiment involving the dehydration of aldol **2** into final product **3** can be completed within a working day and is usually carried out on day three.



Scheme I. Example of the Robinson annulation reaction.



Scheme II. Revised reaction scheme for the Robinson annulation reaction of chalcone and ethyl acetoacetate.

The remaining time is devoted to the interpretation of the various NMR spectra supplied by the instructor.

Results and Discussion

Synthesis

A stoichiometric mixture of chalcone and ethyl acetoacetate was reacted in ethanol in the presence of barium hydroxide monohydrate as catalyst. When a minute quantity of base (1 mol%) was used, the Michael addition product **1** could be isolated in pure form after 16 h at room temperature. Increasing the proportion of catalyst to 10 mol% allowed the completion of both the Michael addition and the aldol condensation to afford product **2** within the same period. Heating the mixture of reagents and catalyst to reflux in anhydrous ethanol was necessary to achieve dehydration and led to the final Robinson annulation product **3** within 16 h. The final step could also be carried out starting from the cyclized intermediate **2**. In this case, the proportion of $Ba(OH)_2{\cdot}H_2O$ was further increased to 20 mol% and the reflux time was shortened to 6 h. In all cases, the products precipitated from the reaction mixtures. They were washed with cold water to remove the inorganic base and recrystallized from ethanol.

This procedure requires minimal organic skills and can be carried out using standard undergraduate laboratory equipment. Students usually isolate compounds **1**–**3** in pure form and in satisfactory to good yield without any difficulty. Losses occur mainly during the recrystallization process. Second and even third crops of precipitates generally form in the mother liquors. Students are encouraged to recover them, but are advised not to mix them with the first crop until their purity has been assessed. In most cases these additional fractions contain significant quantities of side-products and must be discarded or further recrystallized. Only the samples that display satisfactory melting points and IR spectra are given to the instructor for NMR measurements.

IR Analysis

IR spectroscopy provides a convenient method to quickly assess the identity and the purity of products **1**–**3**. Indeed, the three structures contain various types of functional groups that display intense characteristic absorptions easily assigned using standard correlation charts *(6)*. Thus, the three peaks at 1734, 1711, and 1685 cm^{-1} in compound **1** correspond, respectively, to the C=O stretching vibrations of the ester, the methyl ketone, and the phenyl ketone of the molecule (Table 1). The ester function is associated with the highest frequency because the ethoxy group next to its carbonyl has an electron-attracting effect that strengthens the C=O double bond. The phenyl ketone, on the other hand, has the lowest frequency because the conjugation between its C=O group and the aromatic ring allows the delocalization of the π electrons and therefore reduces the double bond character of the carbonyl group. The methyl ketone band lies between the two other ones. Its location is typical of a saturated aliphatic ketone. Despite the presence of a β-keto ester group, there is no sign of keto–enol tautomerism, as further discussed later.

In compound **2** the ester C=O stretching vibration is slightly shifted to higher frequency, while the alkyl ketone absorption remains almost unchanged (Table 1). The occurrence of the aldol reaction is revealed by the disappearance of the phenyl ketone band at 1685 cm^{-1} and the concomitant emergence of a strong OH stretching band at 3392 cm^{-1}. The sharp shape of this peak is characteristic of a highly hindered alcohol. After the final dehydration step the region above 3100 cm^{-1} is again free from any signal but a new line is visible at 1607 cm^{-1}. This fine band can be assigned to the C=C stretching vibration in molecule **3**. Its frequency is significantly lower than the one observed in a regular unstrained

Table 1. Characteristic Infrared Absorptions of Compounds 1–3

Cpd	$\nu_{C=O}/cm^{-1}$			$\nu_{C=C}/cm^{-1}$	ν_{O-H}/cm^{-1}
	Ester	Alkyl Ketone	Phenyl Ketone		
1	1734	1711	1685	–	–
2	1748	1709	–	–	3392
3	1734	1658	–	1607	–

NOTE: IR spectra of compounds in KBr pellets.

cycloalkene (around 1650 cm^{-1}) because of the extended conjugation with the phenyl substituent on one end and the carbonyl group on the other. Accordingly, the C=O absorption for the ketone function of compound **3** is now found at 1658 cm^{-1}, down from 53 or 51 cm^{-1} compared to its position in the spectra of intermediates **1** or **2**, respectively. The exocyclic ester group remains unaffected by the delocalization of the cyclohexenone π-system and still gives a strong band at 1734 cm^{-1} (Table 1).

NMR Analysis

Two chiral centers are created during the Michael addition of chalcone and ethyl acetoacetate. ^{1}H and ^{13}C NMR spectra of product **1** prepared in the presence of $Ba(OH)_2 \cdot H_2O$ revealed, however, that the reaction had proceeded diastereoselectively and that only one of the two possible pairs of enantiomers was obtained as a racemic mixture. Serendipitously, we also found that a rapid isomerization occurred when the diastereoisomer initially formed was dissolved in anhydrous DMSO-d_6 upon gentle heating. This was evidenced from the NMR spectra recorded in this solvent, that now displayed two sets of signals for most types of nonequivalent atoms. We were able to monitor the isomerization process by recording ^{1}H NMR spectra at various time intervals and to highlight the strong influence of the solvent nature on the chemical shifts in product **1**. Moreover, the relative stereochemistry of the two diastereoisomers was tentatively assigned on the basis of NMR considerations (Figure 1).

The intermediate keto alcohol **2** contains three asymmetric carbons atoms. Yet only two enantiomers were obtained as a racemic mixture in the presence of barium hydroxide monohydrate. Thus, the aldol condensation had also proceeded stereoselectively and a single diastereoisomer was again isolated after the second step of the Robinson annulation (Figure 1). Owing to the rigidity of the ring system, each cyclohexyl proton gave rise to a distinct signal in ^{1}H NMR spectroscopy, whose fine structure provided a clear picture of the local stereochemistry. Recourse to 2D spectroscopy proved very useful to establish with certainty the connectivity between the various axial and equatorial protons and to analyze the coupling constants between them.

During the final step of the Robinson annulation, the hydroxy compound **2** was dehydrated into cyclohexenone **3**. One asymmetric carbon atom was removed from the six-membered ring and a single diastereoisomer was isolated as a racemic mixture at the end of the synthesis. 1D and 2D NMR studies confirmed that this end product was indeed tautomerically and conformationally homogeneous, present only as the keto form with equatorial ethoxycarbonyl and phenyl groups in solution (Figure 1).

Hazards

There is no unusual safety risk associated with this experiment. Standard precautions apply when handling the reagents and solvents. Chalcone is a skin irritant, barium hydroxide is a poison, ethyl acetoacetate and ethanol are flammable liquids. All the reactions and recrystallizations should be carried out in a fume hood while wearing gloves, goggles, and a lab coat.

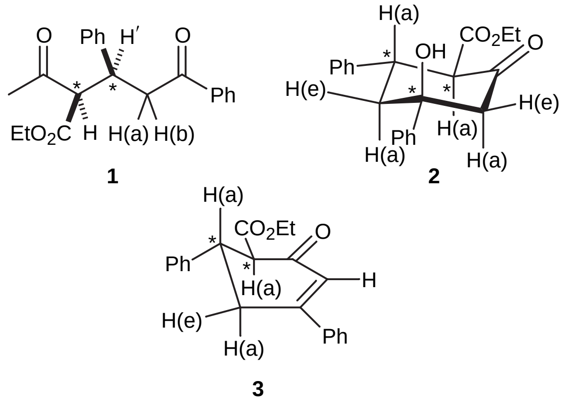


Figure 1. Perspective views of compounds **1**–**3** showing their conformational and stereochemical features.

Conclusion

The step-by-step Robinson annulation of chalcone and ethyl acetoacetate constitutes a fine example of a fundamental organic reaction that can be investigated at several different levels. Because all the synthetic steps are rather straightforward and easy to carry out, the experiment is suitable for an introductory laboratory course. Indeed, the identity and the purity of the products can already be established by recording their IR spectra and melting points. Discussion of the stereochemical features of the reaction (syn versus anti diastereoselectivity in the first step, conformation of the cyclohexane rings in products **2** and **3**, keto–enol tautomerism,…) should be reserved for more advanced courses. Emphasis can also be placed on IR and NMR data analysis for use within a spectroscopy course even if there is no activity component associated with it. Last but not least, the whole project provides ample materials for an advanced undergraduate laboratory that combines organic synthesis and structural analysis.

Acknowledgments

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WSupplemental Material

Experimental procedures, notes for the instructor, analytical data and detailed conformation analysis of compounds **1**–**3** together with their full IR, ^{1}H, ^{13}C, COSY, NOESY, and HETCOR NMR spectra, a list of the acquisition and processing parameters for 2D NMR spectroscopy, and CAS registry numbers for all chemicals are available in this issue of *JCE Online.* A commented slideshow presenting the main features of this project is also available as an Apple Keynote, Microsoft PowerPoint, or pdf file.

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