

Solvent-Free Synthesis of Chalcones

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One of the principles of green chemistry is the use of safer solvents and auxiliaries, or their elimination altogether, whenever possible (1). Over the past few years we have developed and optimized organic syntheses in the absence of organic solvents for the sophomore organic chemistry laboratory (2). Students were excited to explore well-known reactions under unusual experimental conditions where heating under reflux was replaced by the grinding of solids with mortar and pestle. Among these reactions, the Baeyer–Villiger oxidation of ketones and the formation of chalcones by aldol condensation were the most popular with our students. Some of these reactions have been previously studied by Toda and co-workers in the late 1980s (3–5). It was discovered that the absence of solvent usually leads to faster and cleaner processes.

The synthesis of chalcones is a typical preparation included in introductory organic chemistry laboratories (6, 7). It illustrates an emblematic reaction that proceeds with high atom economy (1) and is relatively easy to perform in teaching labs. In addition, chalcones are important compounds in their own right with applications in medicine (8) and physics (9, 10). This article presents the synthesis of 20 different chalcones in the absence of solvent. Overall, it was found that the reactions proceed rapidly and afford very good yields of product. Of the 20 chalcones investigated, we found that 17 can be obtained in a matter of minutes by mixing the corresponding benzaldehyde and acetophenone in the presence of solid NaOH in a mortar with pestle; the yields of crude product were in the range 81–94%. The reaction is shown in Scheme I and the products are described in Table 1.

Each cell in Table 1 shows an assigned chalcone (and reaction) number, the percent yield of the crude material, the proportions of chalcone, ketol, and Michael addition product found in the crude material (written as %chalcone/%ketol/%Michael), and the melting point of the recrystallized product.

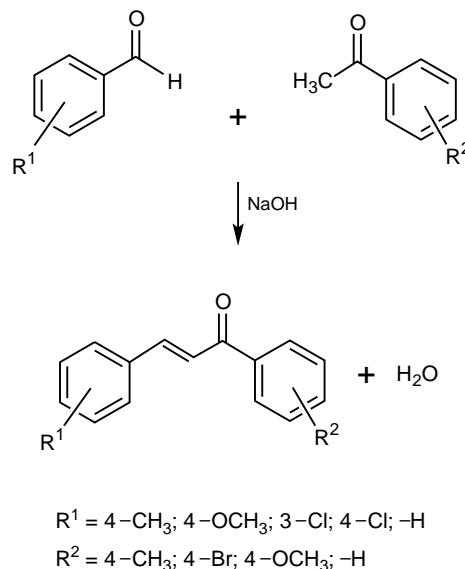
Results and Discussion

The results in Table 1 show that the reactions proceeded with high yields. The analysis of the ^1H - and ^{13}C -NMR spectra showed that in most cases the expected chalcone amounted to more than 90% of the crude material. Minor side-products found in the reaction mixtures were the corresponding ketol and the Michael addition product (Figure 1). The proportions of these products were calculated from the ^1H -NMR integration lines. It is worth mentioning that the Michael addition product has not been reported as a significant side product in the synthesis of chalcones in solution (5–7). The percent yields for reactions 8, 17, and 20 are not

reported in Table 1 because the crude products were contaminated with water and other materials as their low melting points and rubbery consistencies indicated. It is interesting to note in these three cases the melting points of the desired chalcones were relatively low (below 80 °C).

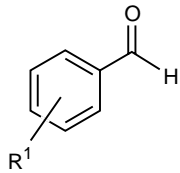
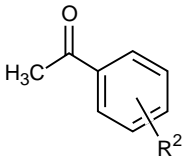
Our results indicate that, in general, the synthesis of chalcones in the absence of solvent proceeds quickly, with very good overall yields, and the crude products are rather pure or easy to purify. Chalcones 1, 4, and 16, which are more difficult to obtain by solution chemistry (5, 7), were produced here in very high yields. A tendency that can be observed is that the two reactions that yielded large quantities of ketol (15 and 19) involved 4'-methoxyacetophenone as a starting material. It can also be noted that the reactions of 4-chlorobenzaldehyde consistently gave a noticeable quantity of ketol (5–42%). It is likely that these results reflect a combination of several factors, as explained below, rather than pure electronic effects.

One of the most tantalizing aspects of many solvent-free reactions, including some "solid–solid" reactions where all the reagents are solids, is that they usually occur faster than when performed in solution (3–5). In a recent article, Rothenberg and co-workers showed that many reactions between solids actually take place because a liquid melt is first formed (11). Their results indicate that the existence of a liquid phase,



Scheme I. Reaction to produce the chalcones.

Table 1. Yield of Crude Material, Ratio of Products, and Melting Point of the Recrystallized Product of the Chalcones^a

					
	R _i (i = 1 or 2)	4-CH ₃	4-Br	4-OCH ₃	-H
4-CH ₃	1^b 81% ^c 98/0.5/1.5 ^d 126–127.5 °C ^e	2 83% 95/2/3 163–164 °C	3 94% 97/2.5/0.5 127–127.5 °C	4 93% 97/≈0.1/3 94–96 °C	
4-OCH ₃	5 94% 96.5/0.5/3 94–96 °C	6 91% 95.5/0.5/4 145–146 °C	7 87% 97/≈0.1/3 100–101.5 °C	8 – ^f 90/–/10 69–71 °C	
3-Cl	9 83% 94/2/4 109–110.5 °C	10 87% 91/1/8 113–113.5 °C	11 84% 94/4.5/1.5 118–119 °C	12 89% 94/–/6 70–72 °C	
4-Cl	13 86% 93/5/2 145–147 °C	14 83% 91/7/2 166–167 °C	15 88% 56/42/2 126–128 °C	16 83% 94/5/1 111–113 °C	
-H	17 – ^f 93/–/7 42–47 °C	18 88% 94/0.5/5.5 101–103 °C	19 92% 75/24/1 104–105 °C	20 – ^f 91/–/9 42–46 °C	

^aA more detailed version of this table (including literature mp) is found in the Supplemental Material.^W

^bReaction number. ^cYield of the crude product. ^dPercents of chalcone/ketol/Michael products found in the crude material.

^eMelting point of the recrystallized product. ^fCrude product was rubbery.

which can be an eutectic mixture formed upon mixing the reactants or, in general, one of the reactants, itself, is a prerequisite for reaction to occur. The high concentration of reactants in these solvent-free but liquid environments would be responsible for the observed acceleration of reaction rates. Our results are in agreement with these authors' findings. Most of the reactions studied here involved at least one liquid reactant. In the two reactions where all solid reagents were used (reactions 14 and 15) it was observed that upon mixing the benzaldehyde and the acetophenone, the mixture melted even before adding the NaOH. Upon grinding the solid NaOH, the liquid mixtures became pasty as the solid product formed and separated from solution. At the end, all mixtures were solid with the exception of reactions 8, 17, and 20, as previously mentioned.

Rothenberg and co-workers, who studied ten different solvent-free aldol condensations including the formation of

one chalcone, proposed that the separation of the solid product from the liquid reaction mixture is responsible for driving these condensations to completion (11). Our results seem to confirm this hypothesis since the reactions that failed to produce the desired chalcones in good yields were the reactions that did not solidify at the end (reactions 8, 17, and 20). A plausible explanation for this observation is that the melting points of chalcones 8, 17, and 20 are relatively low and therefore, these chalcones would have more tendency to remain liquefied owing to the presence of side-products, such as water and the Michael addition product, which act as impurities and lower their melting points.

Our results also indicate that a relatively low melting point for the chalcone does not necessarily mean that the reaction would fail, as the good % yield for reaction 12 (89%) indicates, even though the melting point for the corresponding chalcone is relatively low (70–72 °C). It is not surprising

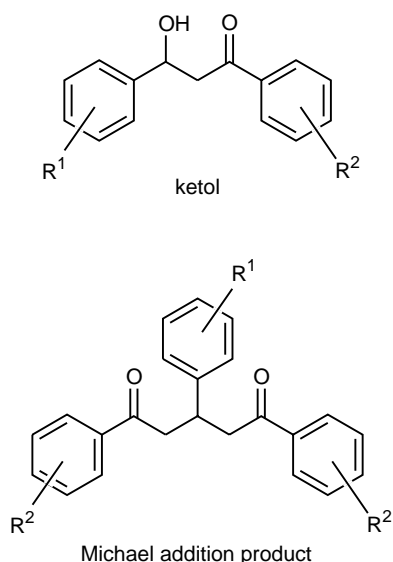


Figure 1. Ketol and Michael addition products found as side-products in the synthesis of chalcones.

that the melting point of the chalcone is not the only factor determining the outcome of these reactions since each reaction involves at least six different chemicals (the benzaldehyde, the acetophenone, NaOH, the ketol, the chalcone, and water) and thus, a rather complex multi-chemical phase diagram is in operation. The rate of formation and disappearance of the ketol, the melting point of the ketol, the mutual miscibilities of reactants and products, their solubilities in water, their melting points, as well as the electronic effects of the substituents are all factors that can affect the outcome of these reactions.

Hazards

Instructors and students should familiarize themselves with the hazards and toxicity of the chemicals involved. None of the acetophenones chosen are lachrymators (a common hazard in this type of compound). The starting materials are irritants and NaOH is caustic. The toxicity of many of the chalcones has not been studied. Chalcones **11** and **20** are strong irritants. Skin and eye contact should be avoided. The experiments should be performed in a well-ventilated space, and the use of gloves when performing the reactions is rec-

ommended. Gloves should be changed often and removed immediately after completion of the chemical operations. Waste disposal should be done following local, state, and federal regulations.

Acknowledgments

I would like to thank my students in Chemistry 112N who tested different parts of this experiment. I would also like to express gratitude to the reviewers and especially Mary M. Kirchhoff, *JCE Green Chemistry* editor, for their insightful suggestions.

Supplemental Material

Experimental procedure, results, conclusions, hazards, instructor's and students' notes, and equipment needed are available in this issue of *JCE Online*.

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