

Solvent-Free Synthesis of Chalcones

Daniel R. Palleros

Department of Chemistry and Biochemistry, University of California Santa Cruz, Santa Cruz, CA 95064; palleros@chemistry.ucsc.edu

SUPPLEMENTAL MATERIAL

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1) Experimental Procedure

In a typical reaction, 5 mmol of the benzaldehyde and 5 mmol of the acetophenone (all commercially available) were added to a 3-inch porcelain mortar, 200 mg of solid NaOH (about a pellet) was added and the mixture ground with a pestle for about 5-10 minutes. In most cases, after a few seconds of grinding, the reaction mixture turned yellow and became pasty. Grinding was continued until the mixture solidified and the solid broke up in small particles. All mixtures solidified upon grinding except for chalcones 8, 17 and 20 which became rubbery instead. In the synthesis of chalcones 14 and 15, the starting materials were all solids. It was observed, however, that after a few seconds of mixing, these solid mixtures liquefied and then, upon continued grinding with NaOH, became pasty and finally solidified. In all cases, 10 mL of distilled water was added at the end of the grinding period and the product mixed well with the water, with the pestle and a spatula used to dislodge the solid from the mortar's wall. The suspension was vacuum filtered using a Buchner funnel. Mortar and pestle were rinsed with 5 mL of water and the rinses collected on the same filter. The product was washed on the filter with an additional 5-mL aliquot of water and it was allowed to air-dry on the filter. It was then weighed and analyzed by melting point and NMR spectroscopy (solutions were made in CDCl_3 and the spectra obtained using a 500-MHz instrument). The crude products were recrystallized from 95% ethanol, toluene-ethanol, or ethanol-water, as indicated in Table 2, and the melting points of the purified products were determined. It is worth mentioning that in most cases the recrystallization step can be skipped as the crude material consists of more than 90% chalcone.

2) Results

Each cell in Table 2 shows an assigned chalcone (and reaction) number, the literature melting point (when available), the melting points of the crude and recrystallized products, and the % yield of the crude material, as indicated below in Figure 2 (using chalcone 4 as an example). Each cell also shows the proportions of chalcone, ketol, and Michael addition product found in the crude material and discussed in the next section. Water and other minor impurities in the crude materials were not considered for the calculations.

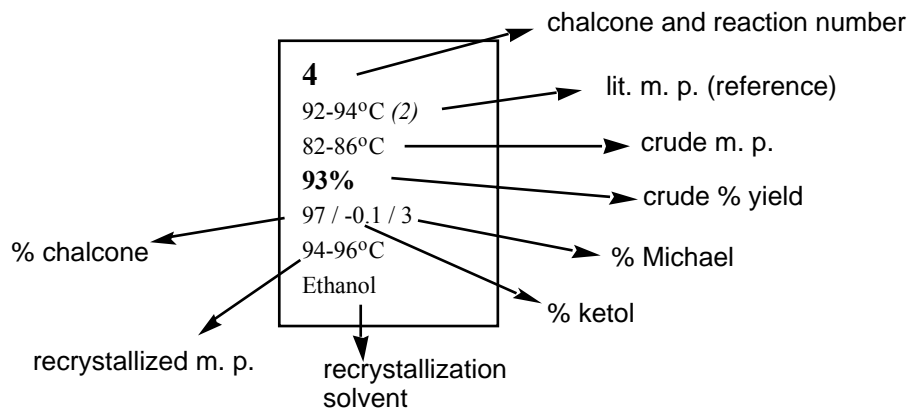
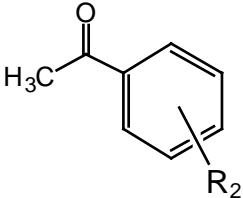
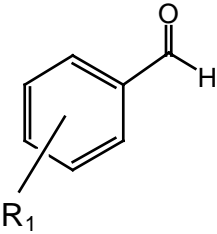


Figure 2. Explanation of Table 2 cells (using chalcone 4 as an example).

Table 2. Properties of chalcones (detailed version). For explanation of table see Figure 2

					
	R ₂	4-CH ₃ (liquid)	4-Br (solid)	4-OCH ₃ (solid)	H (liquid)
	4-CH ₃ (liquid)	1 127 °C (1) 118-127 °C 81% 98/0.5/1.5 126-127.5 °C Ethanol	2 159-160 °C (2) 153-158 °C 83% 95/2/3 163-164 °C Toluene-Ethanol	3 126 °C (3) 115-120 °C 94% 97/2.5/0.5 127-127.5 °C Ethanol	4 92-94 °C (2) 82-86 °C 93% 97/≈0.1/3 94-96 °C Ethanol
	4-OCH ₃ (liquid)	5 98 °C (4) 79-84 °C 94% 96.5/0.5/3 94-96 °C Ethanol	6 145-146 °C (5) 135-138 °C 91% 95.5/0.5/4 145-146 °C Toluene-Ethanol	7 100-101 °C(5) 88-92 °C 87% 97/≈0.1/3 100-101.5 °C Ethanol	8 73-74 °C (2) 43-53 °C - a 90/- /10 69-71 °C Ethanol
	3-Cl (liquid)	9 109 °C (1) 95-98 °C 83% 94/2/4 109-110.5 °C Ethanol	10 - 80-99 °C 87% 91/1/8 113-113.5 °C Toluene-Ethanol	11 - 100-106 °C 84% 94/4.5/1.5 118-119 °C Ethanol	12 73-74 °C (2) 55-61 °C 89% 94/- /6 70-72 °C Ethanol
	4-Cl (solid)	13 147-149 °C (2) 135-138 °C 86% 93/5/2 145-147 °C Ethanol	14 168-169 °C (6) 150-154 °C 83% 91/7/2 166-167 °C Toluene-Ethanol	15 130-131 °C (7) 89-95 °C 88% 56/42/2 126-128 °C Ethanol	16 112-113 °C (2) 100-103 °C 83% 94/5/1 111-113 °C Ethanol
	H (liquid)	17 56.5 °C (8) ≈35 °C - a 93/- /7 42-47 °C Ethanol-Water	18 100-102 °C (2) 94-100 °C 88% 94/0.5/5.5 101-103 °C Ethanol	19 106-107 °C (2) 73-78 °C 92% 75/24/1 104-105 °C Ethanol	20 55-56 °C (2) ≈35 °C - a 91/- /9 42-46 °C Ethanol-Water

The state of the starting materials is indicated in parenthesis. **a** Crude product was rubbery.

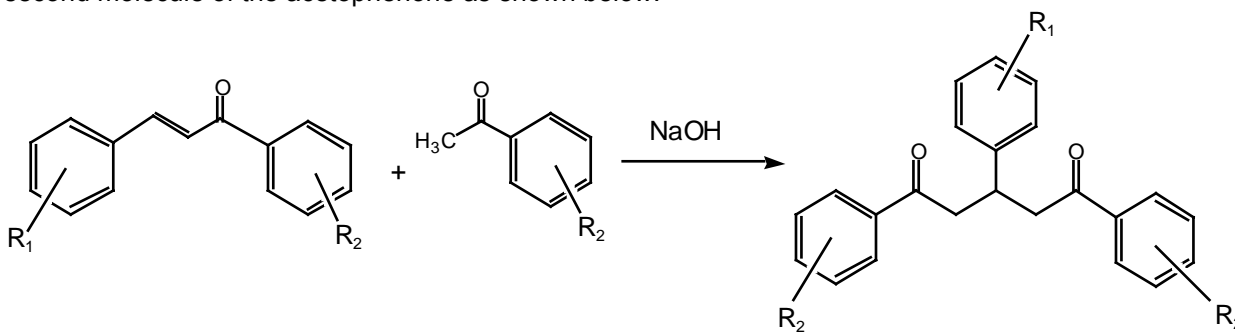
Crude chalcone 8 was recrystallized from 95% ethanol and yielded short needles with a melting point close to the literature value, see Table 2. The overall yield after the recrystallization

was 31%. The crude products of reactions 17 and 20 were dissolved in about 5 mL of 95% ethanol (they dissolved almost completely at room temperature) and then precipitated by the addition of water. The yields were very low (as low as 10%) and the products were still contaminated as their low melting points indicated, Table 2.

3) Comments and Conclusions

It had been previously reported that the synthesis of chalcone 20 in the absence of solvent proceeded with very low yield (10%) and afforded the corresponding ketol and no chalcone (9). Our results confirmed that the reaction takes place with very low overall yield (about 10%) but we found that the main product was the expected chalcone (about 91% of the crude product), and surprisingly, the minor product was not the ketol but the Michael addition product (about 9% of the crude product).

The Michael addition product is obtained by the condensation of the chalcone with a second molecule of the acetophenone as shown below.



It seems that the electronic effects of substituents R₁ and R₂, which are important factors in the outcome of these reactions in solution (9), are not very decisive for the success of these solvent-free reactions. No clear patterns in yields and side-products emerged from the analysis of the twenty reaction mixtures where electron-withdrawing as well as electron-donating substituents were attached to both the benzaldehyde and the acetophenone.

Reactions 15 and 19 yielded large amounts of the corresponding ketols (42 and 24%, respectively). However, upon recrystallization of the crude products from 95% ethanol the chalcones were obtained with high purity as determined by NMR and melting point. The formation of the Michael addition product was significant (> 5%) in reactions 8 (10%), 10 (8%), 12 (6%), 17 (7%), 18 (5.5%), and 20 (9%). In all cases the side products were easily eliminated by recrystallization.

This experiment brings to the forefront one of the principles of green chemistry, namely the elimination of the reaction solvent, and in doing so poses new and challenging questions: What are the factors controlling a chemical reaction under solvent-free, high-concentration conditions? What parameters should be considered in trying to predict the outcome of such reactions?

By eliminating the solvent, we create a much more complex environment for the reaction to occur, an environment where interactions that are normally ignored in solution chemistry, such as product-reactant interactions, may now play important roles in the final outcome (such as the Michael addition in our case). The solubilities of reactants and products in a given solvent, important considerations when doing solution chemistry, must now give way to the analysis of multidimensional temperature-composition phase diagrams which are complex and usually unavailable. Even with these limitations, that we hope future research will abate, the use of solvent-free reactions for organic synthesis is a fruitful and promising approach.

4) Hazards

Instructors and students should familiarize themselves with the hazards/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 recommended. Gloves should be changed often and removed immediately after completion of the chemical operations. Safety goggles must be worn at all times in the laboratory. Waste disposal should be done following local, state, and federal regulations.

5) Instructor's Notes

- 1) All starting materials are commercially available and can be purchased from Aldrich.
- 2) Given the high yields and easy purifications involved, the scale of these reactions can easily be increased or decreased to suit the school's needs.
- 3) These reactions can be performed in one 3-4-hour laboratory period. Our students were able to perform the synthesis of two or three chalcones in one 4-hour laboratory period with very good results.
- 4) If a comparison with the synthesis of chalcones in solution is desired, the students can follow the procedure described by Kohler and Chadwell (10). This is a macroscale synthesis that can be

scaled down by a factor of 1000. This will give the students a chance to learn about scaling-down a published procedure. In general, our students observed that better results were obtained by the solvent-free method. The yields were higher and the preparation times shorter.

5) An added bonus to this experiment is that the recrystallized chalcones usually separate in attractive crystalline forms with the appearance of needles or flakes that the students always enjoy watching.

6) The chalcones can be easily characterized by $^1\text{H-NMR}$. A 60-MHz spectrometer will give satisfactory spectra. The chalcones are easily identified by the doublets of the alkene hydrogens between 7.4 and 7.8 ppm. Students can easily determine that the chalcones are trans by measuring the coupling constants of the alkene hydrogens (about 15 Hz). If a higher resolution spectrometer (250-500 MHz) is used, then the ketol and Michael addition product can also be studied. The ketol can be identified by a multiplet, corresponding to the methine hydrogen, around 5.3 ppm. The Michael addition product shows two double-doublets for the diastereotopic methylene hydrogens (between 3.3 and 3.5 ppm) and a multiplet (a quintet in most cases) for the methine hydrogen around 4 ppm. As a typical example, the $^1\text{H-NMR}$ spectrum of the crude product for reaction 14 is shown in Figure 3. The high-resolution $^1\text{H-NMR}$ can be used to calculate the proportions of chalcone, ketol, and Michael addition product as explained below. This is a challenging exercise that the instructor may want to reserve for a more advanced group of students.

7) The use of $^1\text{H-NMR}$ to determine the proportions of chalcone, ketol, and Michael addition product illustrates a less commonly examined aspect of NMR: Its application as a quantitative tool. The calculation of the percentages of chalcone, ketol, and Michael addition product for reaction 14, Figure 3, is shown below.

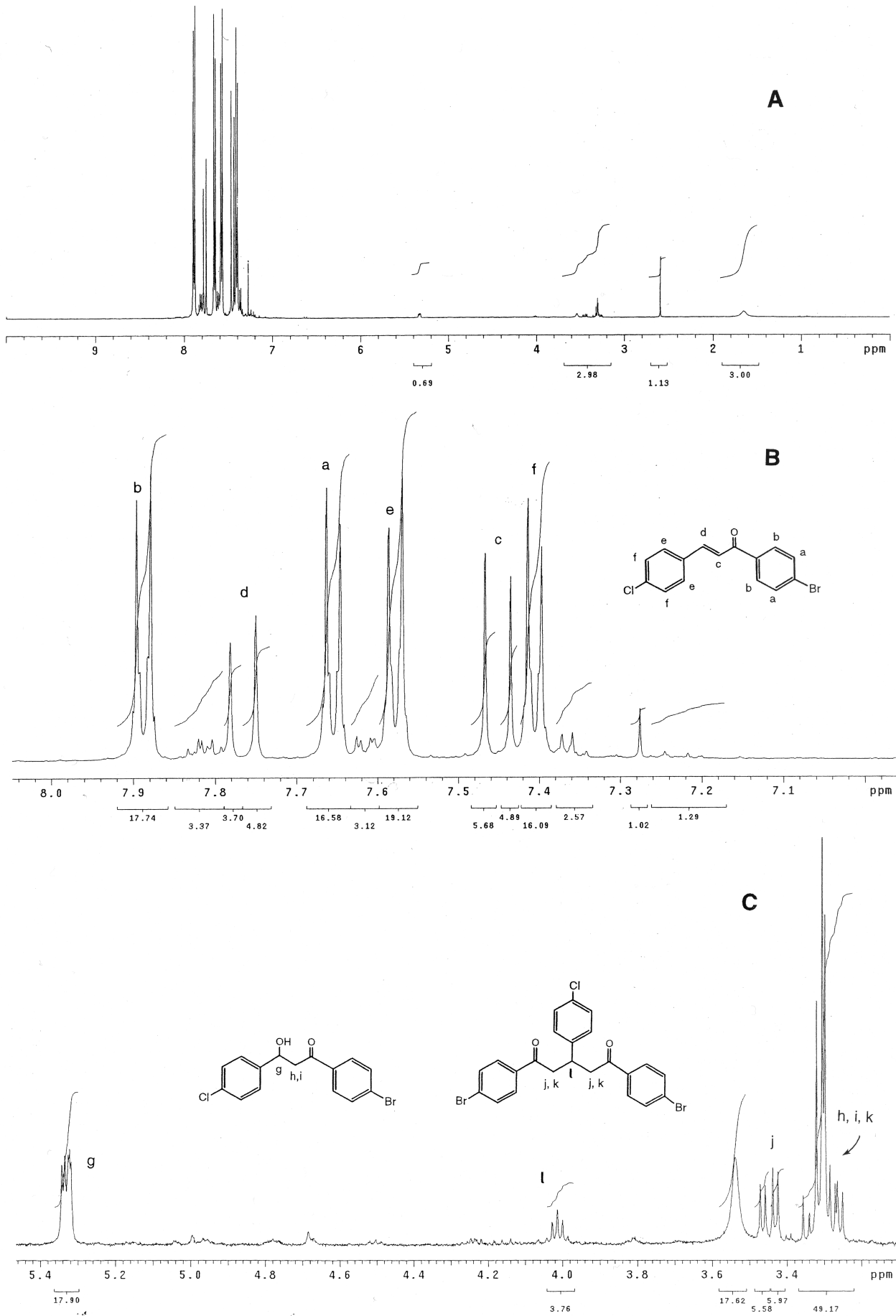


Figure 3. 500-MHz $^1\text{H-NMR}$ of crude reaction mixture 14 (CDCl_3). (A) Overall spectrum. (B) Detail showing the chalcone peaks. (C) Detail showing the ketol and Michael addition product peaks. The integration lines for parts A and B are on the same scale.

To calculate the percentages, we must first calculate the integration area that corresponds to one hydrogen atom in each of the molecules. Figure 3A shows the integration for the ketol and Michael addition product peaks. The peak around 5.35 ppm corresponds to the methine hydrogen of the ketol and is clearly integrated. The integration for the chalcone *on the same scale* is shown in Figure 3B. Figure 3C shows the integration of the ketol and Michael addition product peaks *on a different scale* than that of Fig. 3A and 3B. For the chalcone, we choose hydrogens c and d which are easy to identify as two doublets in Figure 3B:

$$\text{Total area for c and d} = 4.89 + 5.68 + 4.82 + 3.70 = 19.09$$

$$\text{Area per hydrogen of chalcone} = 19.09/2 = 9.55$$

For the ketol, we choose hydrogen g, which gives a multiplet around 5.35 ppm. In Figure 3A the integration value for this multiplet is 0.69:

$$\text{Area per hydrogen of ketol} = 0.69$$

It can also be observed that in Figure 3C, the integration for hydrogen g is 17.90. This means that the integration values of Figure 3C must be reduced by a factor of 0.69/17.90 to be comparable to the integration values of Figures 3A and 3B.

$$\text{Integration correction factor for Fig. 3C} = 0.69/17.90 = 0.0385$$

The integration for hydrogens j and l in Figure 3C is:

$$\text{Total area for j and l} = 5.97 + 5.58 + 3.76 = 15.31$$

This area corresponds to three hydrogens (two j, and one l), thus:

$$\text{Area per hydrogen of Michael addition product} = 15.31/3 = 5.10$$

Applying the correction factor:

$$\text{Corrected area per hydrogen of Michael addition product} = 5.10 \times 0.0385 = 0.20$$

$$\% \text{ chalcone} = 100 \times 9.55 / (9.55 + 0.69 + 0.20) = 91\%$$

$$\% \text{ ketol} = 100 \times 0.69 / (9.55 + 0.69 + 0.20) = 7\%$$

$$\% \text{ Michael} = 100 \times 0.20 / (9.55 + 0.69 + 0.20) = 2\%$$

6) Students' Notes

- 1) Briefly explain the advantages of eliminating the reaction solvent.
- 2) Can you think of any complications that may result as a consequence of eliminating the reaction solvent?
- 3) Propose a mechanism for the formation of chalcones from a benzaldehyde and an acetophenone in the presence of NaOH.
- 4) Propose a mechanism for the formation of the Michael addition product.

5) One of the principles of green chemistry is that of "maximum atom economy". Atom economy is an evaluation of the degree to which the reactants are incorporated into the product. If all the atoms from the reactants end up in the product, then the atom economy is 100%. Reactions with high atom economy are usually preferred because they are less wasteful. Discuss the atom economy for the formation of the ketol, the chalcone and the Michael addition product.

6) How can you use $^1\text{H-NMR}$ to determine if the chalcone double bond is cis or trans?

7) Equipment Needed

Porcelain mortar (5-8 cm in diameter) with pestle; spatula; Pasteur pipets; 10-25 mL graduated cylinder; glass rod; 25-mL Erlenmeyer flask; Buchner funnel; filter flask; melting point apparatus; NMR spectrometer.

8) Literature Cited

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9) CAS Registry Numbers

Benzaldehyde: 100-52-7

4-Chlorobenzaldehyde: 104-88-1

3-Chlorobenzaldehyde: 587-04-2

4-Methoxybenzaldehyde (*p*-anisaldehyde): 123-11-5

4-Methylbenzaldehyde (*p*-tolualdehyde): 104-87-0

Acetophenone: 98-86-2

4'-bromoacetophenone: 99-90-1

4'-methoxyacetophenone: 100-06-1

4'-methylacetophenone: 122-00-9

Chalcone 1: (*E*)-1,3-bis(4-methylphenyl)-2-propen-1-one: 13565-37-2

Chalcone 2: (*E*)-1-(4-bromophenyl)-3-(4-methylphenyl)-2-propen-1-one: 22946-44-7
Chalcone 3: (*E*)-1-(4-methoxyphenyl)-3-(4-methylphenyl)-2-propen-1-one: 41564-65-2
Chalcone 4: (*E*)-3-(4-methylphenyl)-1-phenyl-2-propen-1-one; (*E*)-4-methylchalcone: 22252-14-8
Chalcone 5: (*E*)-3-(4-methoxyphenyl)-1-(4-methylphenyl)-2-propen-1-one: 50990-40-4
Chalcone 6: (*E*)-1-(4-bromophenyl)-3-(4-methoxyphenyl)-2-propen-1-one: 126443-12-7
Chalcone 7: (*E*)-1,3-bis(4-methoxyphenyl)-2-propen-1-one: 41564-67-4
Chalcone 8: (*E*)-3-(4-methoxyphenyl)-1-phenyl-2-propen-1-one; (*E*)-4-methoxychalcone: 22252-15-9
Chalcone 9: (*E*)-3-(3-chlorophenyl)-1-(4-methylphenyl)-2-propen-1-one: 13565-42-9
Chalcone 10: 1-(4-bromophenyl)-3-(3-chlorophenyl)-2-propen-1-one: 358655-87-5
Chalcone 11: 3-(3-chlorophenyl)-1-(4-methoxyphenyl)-2-propen-1-one: 52182-25-9
Chalcone 12: (*E*)-3-(3-chlorophenyl)-1-phenyl-2-propen-1-one; (*E*)-3-chlorochalcone: 22966-13-8
Chalcone 13: (*E*)-3-(4-chlorophenyl)-1-(4-methylphenyl)-2-propen-1-one: 13565-39-4
Chalcone 14: (*E*)-1-(4-bromophenyl)-3-(4-chlorophenyl)-2-propen-1-one: 126443-16-1
Chalcone 15: (*E*)-3-(4-chlorophenyl)-1-(4-methoxyphenyl)-2-propen-1-one: 41564-68-5
Chalcone 16: (*E*)-3-(4-chlorophenyl)-1-phenyl-2-propen-1-one; (*E*)-4-chlorochalcone: 22252-16-0
Chalcone 17: (*E*)-1-(4-methylphenyl)-3-phenyl-2-propen-1-one; (*E*)-4'-methylchalcone: 14802-30-3
Chalcone 18: (*E*)-1-(4-bromophenyl)-3-phenyl-2-propen-1-one; (*E*)-4'-bromochalcone: 22966-23-0
Chalcone 19: (*E*)-1-(4-methoxyphenyl)-3-phenyl-2-propen-1-one; (*E*)-4'-methoxychalcone: 22966-19-4
Chalcone 20: (*E*)-1,3-diphenyl-2-propen-1-one; (*E*)-chalcone: 614-47-1