

## Atom-Efficient, Solvent-Free, Green Synthesis of Chalcones by Grinding

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**Abstract:** An improved Claisen–Schmidt condensation reaction of methyl ketones and aromatic aldehydes can be achieved by grinding at room temperature in the absence of solvents. This process is simple, efficient, economical, and environmentally benign compared to classical reactions.

**Keywords:** Chalcones, Claisen–Schmidt condensation, green chemistry, grinding, solvent-free synthesis

Green chemistry focuses on research that attempts to reduce or eliminate negative environmental impacts. Green chemistry<sup>[1]</sup> aims to prevent waste and generate substances with little or no toxicity to humans and the environment, thereby maximizing atom economy. This is achieved by assuring that the final product contains the greatest possible proportion of the starting materials and avoiding the use of harmful solvents, or even better, any solvents at all.

Chalcones represent an important class of natural compounds with a variety of biological activities.<sup>[2]</sup> Recent studies on biological evaluation of chalcones revealed some to be antibacterial, antifungal, anticancer, anti-inflammatory, antitubercular, antihyperglycemic,<sup>[3]</sup> and antimalarial agents.<sup>[4]</sup> Chalcones are very common in natural products chemistry.<sup>[5]</sup> Some derivatives are used as sweeteners, drugs, and sunscreen agents.<sup>[5]</sup> Chalcones are also well-known intermediates in the synthesis of various

Received October 7, 2008.

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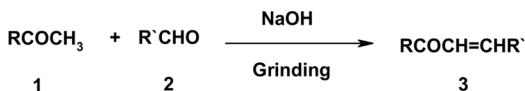
heterocyclic compounds.<sup>[6,7]</sup> Some halo derivatives of chalcones are useful synthons in the synthesis of a large number of bioactive molecules.<sup>[6]</sup>

Several methods have been developed for the preparation of chalcone derivatives. The most common method is the base-catalyzed Claisen–Schmidt reaction, in which the condensation of a methyl ketone with an aldehyde is carried out in the presence of aqueous sodium hydroxide.<sup>[3,8,9]</sup> Some other derivatives were prepared by condensation in chloroform<sup>[10]</sup> in the presence of a catalytic amount of piperidine at 80°C. Also, the Claisen–Schmidt reaction was improved by using KOH·Al<sub>2</sub>O<sub>3</sub> as a catalyst in alcoholic solvent under ultrasound irradiation.<sup>[5]</sup> In addition, another method was described for the synthesis of chalcones using borontrifluoride-etherate as a catalyst at room temperature.<sup>[3]</sup> However, in spite of their utility, some methods suffer disadvantages such as long reaction times (3–4 h) with high probability of side reactions<sup>[3]</sup> (as Cannizzaro or aldol condensation), small yields, chemical hazards, and environmental pollution.

Toda et al.<sup>[11]</sup> has reported that many reactions can be conducted with good yields by just grinding solids (or liquid and solids) together. Because green chemistry has attracted great attention in recent years, we report herein a simple approach for the preparation of chalcone derivatives.

Most chalcones reported herein have been previously prepared using classical methods. Several chalcones, **3a–q**, were prepared (Scheme 1) by grinding together equivalent amounts of the appropriate methyl ketones and different aldehydes in the presence of solid sodium hydroxide in a porcelain mortar under solvent-free conditions. Grinding for about 3–5 min led to a yellow-colored solid mass, which proved to be the target chalcone. Grinding continued for another 5–10 min. The crude products were easily separated by washing with cold water and simple Buchner filtration; final purification was achieved by crystallization from the appropriate solvents (Table 1).

The method reported here for the synthesis of chalcones is simple and effective in terms of short reaction time, excellent yields, and the



**Scheme 1.** 3a–e, R = 2-furyl: 3a, R' = 2-furyl; 3b, R' = 2-thienyl; 3c, R' = C<sub>6</sub>H<sub>5</sub>; 3d, R' = 4-FC<sub>6</sub>H<sub>4</sub>; 3e, R' = 4-ClC<sub>6</sub>H<sub>4</sub>. 3f–j, R = phenyl: 3f, R' = C<sub>6</sub>H<sub>5</sub>; 3g, R' = 4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>; 3h, R' = 4-FC<sub>6</sub>H<sub>4</sub>; 3i, R' = 4-ClC<sub>6</sub>H<sub>4</sub>; 3j, R' = 2-thienyl. 3k–o, R = 2-naphthyl: 3k, R' = C<sub>6</sub>H<sub>5</sub>; 3l, R' = 4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>; 3m, R' = 4-FC<sub>6</sub>H<sub>4</sub>; 3n, R' = 4-ClC<sub>6</sub>H<sub>4</sub>; 3o, R' = 2-thienyl. 3p,q, R = 4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>: 3p, R' = 4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>; 3q, R' = 4CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>.

**Table 1.** Synthesis of chalcones by grinding

Product	R	R'	Time (min)	Solvent of crystallization	Found		Reported	
					Mp (°C)	Yield (%)	Mp (°C)	Yield (%)
<b>3a</b>	2-Furyl	2-Furyl	15	MeOH	88–90	75	88–90 <sup>[7]</sup>	48
<b>3b</b>	2-Furyl	2-Thienyl	10–15	MeOH	68–70	70	82–83 <sup>[13]</sup>	72
<b>3c</b>	2-Furyl	C <sub>6</sub> H <sub>5</sub>	15	Benzene	89	78	88 <sup>[12]</sup>	50
<b>3d</b>	2-Furyl	4-FC <sub>6</sub> H <sub>4</sub>	3–6	MeOH	114	85	116 <sup>[12]</sup>	82
<b>3e</b>	2-Furyl	4-ClC <sub>6</sub> H <sub>4</sub>	3–4	MeOH	125	90	127 <sup>[12]</sup>	88
<b>3f</b>	Phenyl	C <sub>6</sub> H <sub>5</sub>	10–15	EtOH	52	85	55–56 <sup>[5]</sup>	80
<b>3g</b>	Phenyl	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	5–10	EtOH	90–92	95	96 <sup>[5]</sup>	93
<b>3h</b>	Phenyl	4-FC <sub>6</sub> H <sub>4</sub>	5–10	Dilute ethanol	75–78	92	87 <sup>[14]</sup>	—
<b>3i</b>	Phenyl	4-ClC <sub>6</sub> H <sub>4</sub>	3–4	EtOH	105–107	93	112 <sup>[5]</sup>	91
<b>3j</b>	Phenyl	2-thienyl	15	Ethanol	49–52	71	—	—
<b>3k</b>	2-Naphthyl	C <sub>6</sub> H <sub>5</sub>	10–15	Dilute ethanol	98–100	96	106 <sup>[15]</sup>	96
<b>3l</b>	2-Naphthyl	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	3–5	Dilute dioxane	128–130	94	146 <sup>[16]</sup>	48
<b>3m</b>	2-Naphthyl	4-FC <sub>6</sub> H <sub>4</sub>	5–10	Dilute dioxane	110–113	96	—	—
<b>3n</b>	2-Naphthyl	4-ClC <sub>6</sub> H <sub>4</sub>	3–5	Dioxane	155–157	95	146 <sup>[16]</sup>	81
<b>3o</b>	2-Naphthyl	2-thienyl	10–15	Ethanol	80–82	75	—	—
<b>3p</b>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	3–5	Ethanol	98–100	86	95–96 <sup>[17]</sup>	—
<b>3q</b>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	4-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	4–6	Ethanol	87–90	83	93–94 <sup>[17]</sup>	—

formation of one product as measured by thin-layer chromatography (TLC). It is also consistent with the green chemistry approach because it does not need heating or microwave irradiation. It occurs at room temperature and is completely free from organic solvents during both the reaction and separation of the product (except for recrystallization).

## EXPERIMENTAL

Melting points were measured on an Electrothermal melting-point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu Fourier transform (FT)-IR 8101 PC IR spectrophotometer. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University.

### General Procedure

A mixture of the appropriate methyl ketones **1** (5 mmol), aromatic aldehyde **2** (5 mmol), and sodium hydroxide (7 mmol) was thoroughly ground with a pestle in an open mortar at room temperature for 2–3 min until the mixture turned into a melt. The initial syrupy reaction mixture solidified within 3–5 min. Grinding continued for 5–10 min more, and the reaction was monitored by TLC. The solid was washed with cold water to remove the sodium hydroxide and recrystallized from the appropriate solvent to give the corresponding chalcone derivatives. The yields and melting points are reported in Table 1.

### Spectral and Analytical Data of Some Compounds

Compound **3j**: mp 49–52°C; MS:  $m/z = 214$ . Anal. calcd.  $C_{13}H_{10}OS$ : C, 72.87; H, 4.70; S, 14.96. Found: C, 72.77; H, 4.79; S, 15.11. IR (KBr):  $\nu/cm^{-1}$  1651 (CO).

Compound **3m**: mp 110–113°C; MS:  $m/z = 276$ . Anal. calcd.  $C_{19}H_{13}FO$ : C, 82.59; H, 4.74. Found: C, 82.55; H, 4.62. IR (KBr):  $\nu/cm^{-1}$  1662 (CO).

Compound **3o**: mp 80–82°C; MS:  $m/z = 264$ . Anal. calcd.  $C_{17}H_{12}OS$ : C, 77.24; H, 4.58; S, 12.13. Found: C, 77.30; H, 4.49; S, 12.0. IR (KBr):  $\nu/cm^{-1}$  1654 (CO).

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