Iodine-catalyzed efficient synthesis of chalcones by grinding under solvent-free conditions

Hongshe Wang and June Zeng

Abstract: Chalcones are useful intermediates in organic synthesis and exhibit a large number of different biological activities. Chalcones have been synthesized in high yields by Claisen–Schmidt condensation of substituted acetophenones with various aromatic aldehydes in the presence of 10 mol% of iodine at room temperature by grinding under solvent-free conditions.

Key words: iodine, chalcones, Claisen–Schmidt condensation, grinding, solvent-free.

Résumé : Les chalcones sont des intermédiaires importants en synthèse organique et elles présentent un grand nombre d'activités biologiques diverses. On a réalisé la synthèse de chalcones avec des rendements élevés, par le biais d'une condensation de Claisen–Schmidt d'acétophénones substituées avec divers aldéhydes aromatiques, en présence de 10 moles % d'iode, à la température ambiante, par simple broyage dans des conditions sans solvant.

Mots-clés : iode, chalcones, condensation de Claisen–Schmidt, broyage, sans solvant.

[Traduit par la Rédaction]

Introduction

Chalcones and their derivatives are useful intermediates in organic synthesis.[1] Many chalcone derivatives display interesting pharmacological and biological activities.[2] Therefore, much attention has been paid to the synthesis of chalcones. Traditionally, chalcones are obtained via Claisen–Schmidt condensation carried out using alkaline hydroxides as catalysts.[3] However, the poor selectivity, generation of wastes, and laborious separation techniques make these catalysts practically inconvenient. Thus, more efficient methods have been developed for the synthesis of chalcones, which include the use of NaOH,[4] $FeCl_3 \cdot 6H_2O$,[5] $SOCl_2$/EtOH,[6] $BF_3 \cdot Et_2O$,[7] sulfonic-acid-functionalized organosilica materials,[8] $ZrCl_4$,[9] bamboo char sulfonic acid,[10] and ionic liquid[11] microwave[12] and ultrasonic irradiation.[13] However, some of the previously reported procedures have various disadvantages, such as long reaction times, special efforts needed to prepare the catalysts, high temperatures, and the use of expensive reagents and hazardous solvents. Thus, there is scope for further improvement involving more environment-friendly and milder reaction conditions.

With the increasing public concern over environmental pollution, it is of great importance for chemists to come up with new approaches that are less hazardous to human health and environment. The use of environmentally benign solvents, like water, and solvent-free reactions represent very powerful green chemical technology procedures from both the economical and synthetic points of view.[14] Grinding under solvent-free conditions is an environment-friendly method for the organic synthesis reactions.

In recent years, molecular iodine has been considered as an inexpensive and readily available catalyst for a variety of organic transformations.[15] In continuation to our work on studying iodine-catalyzed reactions,[16] we report herein an efficient and convenient procedure for the synthesis of chalcones from substituted acetophenones and various aromatic aldehydes via Claisen–Schmidt condensation in the presence of a catalytic amount of iodine at room temperature by grinding under solvent-free conditions (Scheme 1).

Results and discussion

To determine the efficiency of this procedure, we carried out the reaction of acetophenone with benzaldehyde using various other Lewis acids, such as $InCl_3$, $FeCl_3$, $ZnCl_2$, $(NH_4)_2Fe(SO_4)_2$, $Bi(NO_3)_3$, $Al_2(SO_4)_3$, and $Mg(ClO_4)_2$ at room temperature by grinding under solvent-free conditions (Table 1). Among these catalysts, I_2 was found to be the most effective catalyst for this conversion. As for the amount of the catalyst used, we found that 10 mol% of I_2 is sufficient to promote reaction efficiently (Table 2). No reaction was observed when acetophenone was reacted with benzaldehyde under similar conditions in the absence of I_2 even after grinding for 180 min. Any excess of I_2 beyond this loading did not show any further increase in conversion and yield. Use of less than the required catalyst loading resulted in low yields.

Received 14 March 2009. Accepted 8 June 2009. Published on the NRC Research Press Web site at canjchem.nrc.ca on 4 August 2009.

H. Wang[1] and J. Zeng. Shaanxi Key Laboratory for Phytochemistry, Department of Chemistry and Chemical Engineering, Baoji University of Arts and Sciences, Baoji 721013, P. R. China.

[1]Corresponding author (e-mail: hongshewang@126.com).

Scheme 1.

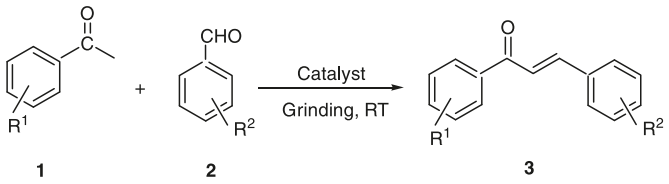

Table 1. Claisen–Schmidt condensation of acetophenone with benzaldehyde catalyzed by different catalysts.

Entry	Catalyst (mol%)	Time (min)	Yield[a] (%)
1	$InCl_3$ (50)	20	30
2	$FeCl_3$ (50)	20	30
3	$ZnCl_2$ (50)	20	20
4	$(NH_4)_2Fe(SO_4)_2$ (50)	20	20
5	$Bi(NO_3)_3$ (50)	20	40
6	$Al_2(SO_4)_3$ (50)	20	55
7	$Mg(ClO_4)_2$ (30)	10	72
8	I_2 (10)	5	91

Note: The reaction was performed with 1 mmol of benzaldehyde and 1 mmol of acetophenone by grinding at room temperature.

[a]Isolated yield.

To explore the generality of this method, a series of chalcones were prepared under the optimized reaction conditions. By this method, the reactions were carried out simply by mixing a variety of substituted acetophenones and substituted benzaldehydes in the presence of a catalytic amount (10 mol%) of iodine at room temperature by grinding under solvent-free conditions, and the results are summarized in Table 3. The components of the mixture were ground together in a mortar with a pestle for several minutes. In all the cases, the reactions proceeded smoothly to afford the corresponding products in good-to-excellent yields using ethanol recrystallization. Their physical properties were determined, and the structures were confirmed by ^1H and ^{13}C NMR, IR, and MS. All acetophenones and benaldehydes with either electron-withdrawing or electron-donating substitutes, such as nitro, and methoxy groups on aromatic rings produced a satisfactory yield ranging from 83% to 95%. It was found from ^1H NMR spectral data that all chalcones were with trans configuration.

In conclusion, we have developed a new methodology to prepare a variety of chalcones in the presence of a catalytic amount of iodine at room temperature by grinding under solvent-free conditions. The advantages, such as the easy procedure, shorter reaction times, green and clean to the environment, mild reaction conditions, and high yields, make our method an attractive alternative to the preparation of chalcones.

Experimental

Melting points were determined on an XT4A electrothermal apparatus equipped with a microscope. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer (^1H: 400 MHz, ^{13}C: 100 MHz) in $CDCl_3$ with TMS as an internal standard. Mass spectra were measured by HP5973 spectrometer. IR spectra were measured on a Nicolet FTIR-750 spectrometer. The benzaldehyde was distilled prior to use. All other reagents were commercially available products and were used without further purification.

Table 2. Effect of different amounts of iodine on the reaction of benzaldehyde with acetophenone.

Entry	I_2 (mol%)	Time (min)	Yield[a](%)
1	0	180	0
2	1	20	46
3	5	10	73
4	10	5	91
5	15	5	92
6	20	5	91

Note: The reaction was carried out at room temperature by grinding under solvent-free conditions.

[a]Isolated yield.

General procedure for the synthesis of chalcones

A mixture of acetophenone (1 mmol), benzaldehyde (1 mmol), and iodine (0.1 mmol) was ground in a mortar with a pestle (the mortar and pestle are thoroughly cleaned between runs) at room temperature until the reaction was completed (monitored by TLC). The reaction mixture was treated with 5% aqueous sodium thiosulfate. The precipitated products were then separated, washed with water, and recrystallized from ethanol to afford the pure products.

Except for compounds **3d**, **3e**, **3h**, and **3l**, all the products are known compounds. The spectroscopic and physical data for all known compounds corresponded to those given in the literatures.

*3-(4-*N,N*-Dimethylaminophenyl)-1-phenyl-2-propen-1-one (3d)*

IR (KBr) ν: 2922, 1649, 1565, 1529 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 3.05 (s, 6H), 6.73 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 16.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.55 (m, 3H), 7.80 (d, J = 16.0 Hz, 1H), 8.00 (d, J = 5.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 42.31, 110.13, 111.06, 119.11, 123.24, 128.23, 129.06, 133.10, 139.07, 145.19, 162.16, 190.08. MS (EI) m/z (%): 251 (M^+, 100), 250 (34), 236 (2), 222 (11), 207 (11), 174 (43), 105 (16). Anal. calcd. for $C_{17}H_{17}NO$: C, 81.27; H, 6.77; N, 5.59. Found: C, 81.16; H, 6.86; N, 5.67.

3-(2-Hydroxyphenyl)-1-phenyl-2-propen-1-one (3e)

IR (KBr) ν: 3386, 1662, 1591, 1562, 1498, 1392, 800, 762 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.60 (m, 3H), 7.23 (d, J = 16.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.54 (m, 3H), 7.71 (d, J = 16.0 Hz, 1H), 8.01 (d, J = 8.0 Hz, 2H), 9.68 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 110.96, 111.63, 119.79, 123.91, 128.62, 129.32, 129.86, 131.05, 133.53, 138.61, 145.11, 162.84, 166.17, 190.87. MS (EI) m/z (%): 224 (M^+, 66), 207 (100), 206 (2), 222 (16), 147 (71), 119 (31), 105 (65). Anal. calcd. for $C_{15}H_{12}O_2$: C, 80.36; H, 5.36. Found: C, 80.23; H, 5.45.

Table 3. Synthesis of chalcones catalyzed by iodine.

Entry	Product	R^1	R^2	Time (min)	Yield[a] (%)	Mp (lit.) (°C)
1	**3a**	H	H	5	91	57–58 (56–57)[7]
2	**3b**	H	4-CH_3	5	90	94–95 (93–94)[5]
3	**3c**	H	3-NO_2	5	92	143–144 (144–145)[5]
4	**3d**	H	4-$N(CH_3)_2$	8	88	102–103
5	**3e**	H	2-OH	5	89	142–143
6	**3f**	4-CH_3	H	5	90	54–55 (53–54)[17]
7	**3g**	4-NO_2	H	5	95	118–119 (117–119)[13]
8	**3h**	2,4-$(OCH_3)_2$	3-NO_2	10	87	168–170
9	**3i**	4-Br	4-OH	8	92	179–181 (180–182)[13]
10	**3j**	3-OCH_3	2-NO_2	10	91	88–90 (99–90)[13]
11	**3k**	2,4-$(OH)_2$	4-$N(CH_3)_2$	10	85	181–183 (180–182)[13]
12	**3l**	2,4-$(OCH_3)_2$	4-OCH_3	10	83	33–35

Note: All the reactions were performed with 10 mol% of iodine at room temperature by grinding under solvent-free conditions.

[a]Isolated yields.

1-(2,4-Dimethoxyphenyl)-3-(3-nitrophenyl)-2-propen-1-one (3h)

IR (KBr) ν: 3055, 2965, 2843, 1658, 1605, 1573, 1403, 813, 646 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 3.90 (s, 3H), 3.98 (s, 3H), 6.50 (m, 2H), 7.48 (m, 4H), 7.61 (d, J = 16.0 Hz, 1H), 7.82 (d, J = 16.0 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 55.96, 114.98, 120.66, 121.73, 125.06, 126.98, 129.09, 130.05, 134.64, 139.13, 142.60, 145.43, 164.44, 191.87. MS (EI) m/z (%): 313 (M^+, 58), 296 (30), 285 (83), 165 (100), 151 (33). Anal. calcd. for $C_{17}H_{15}NO_5$: C, 65.18; H, 4.79; N, 4.40. Found: C, 65.11; H, 4.71; N, 4.55.

1-(2,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one (3l)

IR (KBr) ν: 3050, 1651, 1600, 1573, 1510, 1441, 1330, 1015, 980, 821, 772, 680 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 3.86 (s, 6H), 3.97 (s, 3H), 6.36 (m, 2H), 6.95 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 16.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 16.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 55.73, 114.01, 114.69, 119.43, 121.21, 128.75, 129.87, 130.11, 133.89, 140.03, 144.30, 161.64, 163.54, 190.77. MS (EI) m/z (%): 298 (M^+, 100), 283 (82), 255 (10). Anal. calcd. for $C_{18}H_{18}O_4$: C, 72.48; H, 6.04. Found: C, 72.33; H, 6.03.

Acknowledgments

This work was financially supported by the Educational Committee of Shaanxi Province (Nos. 08JZ09 and 09JK332) and Baoji University of Arts and Sciences (No. Zk064).

References

(1) (a) Ranu, B. C.; Hajra, A.; Jana, U. *Synlett* **2000**, 75; (b) Katritzky, A. R.; Abdel-Fattah, A. A.; Tymoshenko, D. O.; Essawy, S. A. *Synthesis* **1999**, *1999* (12), 2114–2118. doi:10.1055/s-1999-3637.

(2) (a) Liu, M.; Wilairat, P.; Go, M. L. J. *Med. Chem.* **2001**, *44* (25), 4443–4452. doi:10.1021/jm0101747.; (b) Kumar, S. K.; Hager, E.; Pettit, C.; Gurulingappa, H.; Davidson, N. E.; Khan, S. R. J. *Med. Chem.* **2003**, *46* (14), 2813–2815. doi:10.1021/jm030213+.

(3) (a) Edwards, M. L.; Stemerick, D. M.; Sunkara, P. S. J. *Med. Chem.* **1990**, *33* (7), 1948–1954. doi:10.1021/jm00169a021.; (b) Alcantara, A. R.; Marinas, J. K.; Sinisterra, J. V. *Tetrahedron Lett.* **1987**, *28* (14), 1515–1518. doi:10.1016/S0040-4039(01)81030-3.

(4) Toda, F.; Tanaka, K.; Hamai, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, (11): 3207. doi:10.1039/p19900003207.

(5) Zhang, X.; Niu, H.; Wang, J. *J. Chem. Res. Synop.* **2003**, 33.

(6) Petrov, O.; Ivanova, Y.; Gerova, M. *Catal. Commun.* **2008**, *9* (2), 315–316. doi:10.1016/j.catcom.2007.06.013.

(7) Narender, T.; Reddy, K. P. *Tetrahedron Lett.* **2007**, *48* (18), 3177–3180. doi:10.1016/j.tetlet.2007.03.054.

(8) Shylesh, S.; Samuel, P. P.; Srilakshmi, C.; Parischa, R.; Singh, A. P. *J. Mol. Catal. Chem.* **2007**, *274* (1-2), 153–158. doi:10.1016/j.molcata.2007.04.040.

(9) Kumar, A.; Akanksha. *J. Mol. Catal. Chem.* **2007**, *274* (1-2), 212–216. doi:10.1016/j.molcata.2007.05.016.

(10) Xu, Q.; Yang, Z.; Yin, D.; Zhang, F. *Catal. Commun.* **2008**, *9* (7), 1579–1582. doi:10.1016/j.catcom.2008.01.007.

(11) Fan, D.; Cheng, J.; Fei, Z.; Gong, K.; Liu, Z. *Catal. Commun.* **2008**, *9* (6), 1394. doi:10.1016/j.catcom.2007.11.039.

(12) Zhou, J. F.; Zhou, J. F. *Synth. Commun.* **2002**, *32* (21), 3289–3294. doi:10.1081/SCC-120014034.

(13) Huang, D.; Jiang, G. Q. *Chin. J. Org. Chem.* **2002**, *22*, 1057.

(14) (a) Rothenberg, G.; Downie, A. P.; Raston, C. L.; Scott, J. L. *J. Am. Chem. Soc.* **2001**, *123* (36), 8701–8708. doi:10.1021/ja0034388. PMID:11535074.; (b) Jeon, S. J.; Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127* (47), 16416–16425. doi:10.1021/ja052200m. PMID:16305227.

(15) (a) Sun, G.; Wang, Z. *Tetrahedron Lett.* **2008**, *49* (33), 4929–4932. doi:10.1016/j.tetlet.2008.05.146.; (b) Liu, B.; Ji, S. J. *Synth. Commun.* **2008**, *38* (8), 1201–1211. doi:10.1080/00397910701866254.; (c) Deb, M. L.; Bhuyan, P. J. *Synlett* **2008**, 325; (d) Zhang, X.; Rao, W.; Chan, P. W. H. *Synlett* **2008**, 2204; (e) Lucas, R.; Vergnaud, J.; Teste, K.; Zerrouki, R.; Sol, V.; Krausz, P. *Tetrahedron Lett.* **2008**, *49* (38), 5537–5539. doi:10.1016/j.tetlet.2008.07.058.; (f) Yadav, J. S.; Reddy, B. V. S.; Narasimhulu, G.; Satheesh, G. *Tetrahedron Lett.* **2008**, *49* (39), 5683–5686. doi:10.1016/j.tetlet.2008.07.085.; (g) Wang, J.; Xu, F. X.; Lin, X. F.; Wang, Y. G. *Tetrahedron Lett.* **2008**, *49* (35), 5208–5210. doi:10.1016/j.tetlet.2008.06.024.; (h) Yadav, J. S.; Reddy, B. V. S.; Gopal, A. V. H.; Kumar, G. G. K. S. N.; Madavi, C.; Kunwar,

A. C. *Tetrahedron Lett.* **2008**, *49* (28), 4420–4423. doi:10.1016/j.tetlet.2008.05.014.

(16) (a) Wang, H. S.; Zeng, J. E. *Chin. J. Chem.* **2008**, *26* (1), 175–178. doi:10.1002/cjoc.200890017.; (b) Wang, H. S.; Zhao, L. F.; Du, Z. M. *Chin. J. Chem.* **2006**, *24* (1), 135–137. doi:10.1002/cjoc.200690009.; (c) Wang, H. S.; Zeng, J. E. *Chin. Chem. Lett.* **2007**, *18* (12), 1447–1450. doi:10.1016/j.cclet.2007.10.024.

(17) Huang, D.; Wang, J.; Hu, Y.; Zhang, Y.; Tang, J. *Synth. Commun.* **2002**, *32* (7), 971–979. doi:10.1081/SCC-120003144.