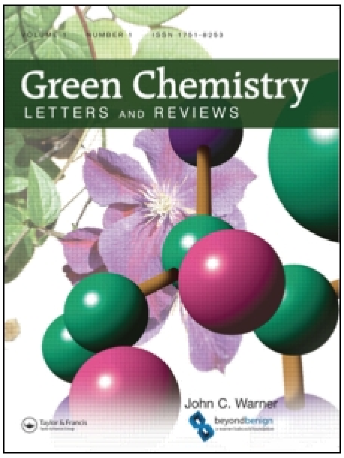

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An efficient green protocol for the synthesis of chalcones by a Claisen-Schmidt reaction using bismuth(III)chloride as a catalyst under solvent-free condition

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RESEARCH LETTER

An efficient green protocol for the synthesis of chalcones by a Claisen–Schmidt reaction using bismuth(III)chloride as a catalyst under solvent-free condition

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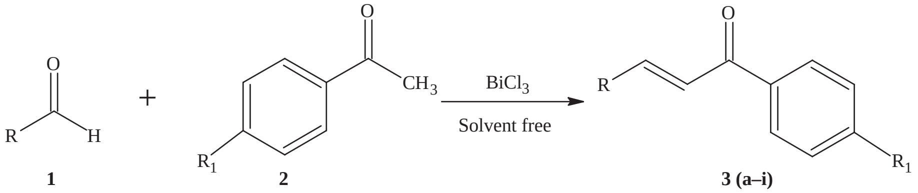
An environmentally benign protocol for the synthesis of chalcones by the Claisen–Schmidt condensation of aldehydes with ketones using eco-friendly non-toxic bismuth(III)chloride catalyst under solvent-free condition is reported. In this protocol, the reaction time is very short, yields are high, and there are no other pollutants formed.



Keywords: aldehydes; ketones; Claisen–Schmidt condensation; bismuth(III)chloride; chalcones; solvent free

Introduction

Chalcones are normally produced by the Claisen–Schmidt condensation of aldehydes with ketones. The chalcone motif is widely distributed in natural products (*1*) and they are crucial intermediates for the synthesis of a variety of pharmaceuticals. These molecules have a broad spectrum of biological activities, such as anti-bacterial (*2*), antioxidant (*3*), anti-inflammatory (*4*), antimalarial (*5*), antileshmanial (*6*), anticancer (*7*), and antitumor (*8*). In the synthesis of chalcones, various caustic, alkali, and clay catalysts have been used, including aqueous NaOH (*2,9*), KOH (*10–12*), $Ba(OH)_2$ (*13*) hydrotalcites, zeolites (*14*), LiHDMS (*15*), and calcined $NaNO_3$/natural phosphates (*16,17*), $AlCl_3$ (*18*), dry HCl (*19*), $Zn(bpy)(OAc)_2$ (*20*), $TiCl_4$ (*21*), $Cp_2ZrH_2/NiCl_2$ (*22*), $RuCl_3$ (*23*), $ZnCl_2$ (*24*), and Al_2O_3–$AlPO_4$ (*25*). Recently, $BF_3 \cdot Et_2O$ (*26,27*), $SOCl_2$/EtOH (*28*), ultrasound accelerated activated carbons (Na and Cs-Norit) (*29*), molecular I_2 (*30*), and Bronsted acidic ionic liquid catalysts (*31*). Because of the non-toxic nature and mild Lewis acid activity of bismuth(III)chloride, we and others have been using this as an efficient green catalyst for the production of vital organic compounds (*32–40*). In this communication, described herein is the synthesis of chalcones employing bismuth(III)chloride as a mild, green, and efficient catalyst (Scheme 1).

Results and discussion

We initiated our investigation with model experiments using 5 mol% $BiCl_3$ in the condensation of benzaldehyde (5 mmol) and acetophenone (5 mmol) under solvent-free conditions at 140°C (it was found that lower and higher temperatures were not suitable). It was found that any reduction in the amount of catalyst used resulted in a decrease in yield. In order to optimize the yields, experiments were carried out with varying levels of catalyst. It was established that 10 mol% of $BiCl_3$ is the optimum concentration. In a typical procedure, benzaldehyde, acetophenone, and $BiCl_3$ (1:1:0.1) were mixed thoroughly and stirred at the appropriate temperature under solvent-free conditions for 20 minutes to obtain the product **3** in high yields. To check the efficacy and applicability of this catalyst, the reaction was generalized using various aldehydes and acetophenones (Table 1). As is clear from Table 1, the reaction has wide applicability and the reaction times are only 10–20 minutes.

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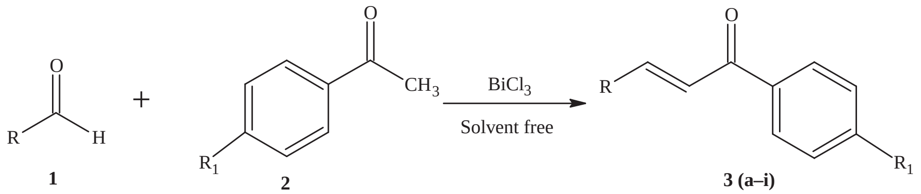
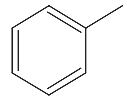
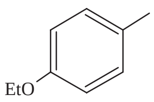
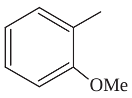
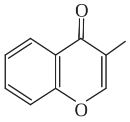
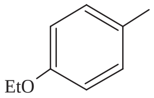
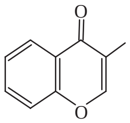
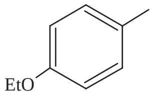
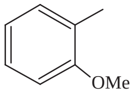
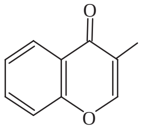


Scheme 1. Synthesis of chalcones.

The mechanism of the $BiCl_3$ catalyst is that it activates the methyl group of the ketones used by attaching itself to the carbonyl oxygen, as is typical in similar reactions. In comparison to earlier reported catalysts, the $BiCl_3$ catalyst is inexpensive, non-toxic, and uses mild reaction conditions. In this present

Table 1. $BiCl_3$ catalyzed condensation of aldehydes and ketones.

Product[a] (**3**)	***R***	R_1	Time (minutes)	Yield, lit. (ref.)	Yield[b] (%)	MP (°C)[c] (lit.) (ref.)
3a		H	20	85 (*24*)	85	54–55 (55) (*24*)
3b		H	18	88 (*30*)	88	51–52 (52–53) (*30*)
3c		H	16	88 (*30*)	86	52–53 (53–54) (*30*)
3d		H	10	70 (*11*)	90	167–168 (166–167) (*11*)
3e		CH_3	17	90 (*30*)	87	94–95 (95–96) (*30*)
3f		CH_3	13	72 (*11*)	88	174–175 (175) (*11*)
3g		Cl	16	86 (*30*)	86	125 (125–126) (*30*)
3h		Cl	17	85 (*30*)	86	75–76 (75–76) (*30*)
3i		Cl	13	74 (*11*)	86	168–169 (169) (*11*)

[a] The products were characterized by comparison of their melting points (MP) and spectral techniques (IR, ^1H NMR, ^{13}C NMR, and MS) data with those of authentic samples.

[b] Isolated yields after re-crystallization.

[c] Value in parenthesis indicates reference. MP also in brackets yields of earlier reports are shown.

protocol, a variety of chromonyl chalcones (**3d**, **3f**, and **3i**) have been synthesized and the obtained yields are very high in the comparison to previously reported processes (Table 1). In the case of compounds **3d**, **3f**, and **3i**, the reaction temperature was maintained at 110°C since at higher temperatures the chromone moiety breaks down.

Experimental

Melting points(MP) were determined in open capillaries and are uncorrected. Reagent-grade chemicals were purchased from commercial source and used without further purification. IR spectra were recorded in KBr discs on a Perkin–Elmer 240C analyzer. ^{1}H NMR spectra were recorded on Varian Gemini 300 (300-MHz) spectrometer using trimethyl silane as internal standard. The progress of the reaction was monitored by thin layer chromatography (TLC) using silica gel G (Merck).

General procedure for preparation of chalcones

A mixture of benzaldehyde (10 mmol, 1.06 g), acetophenone (10 mmol, 1.20 g), and $BiCl_3$ (0.1 mmol) was heated at 140°C for 20 minutes under solvent-free condition. The reaction was monitored via TLC using toluene:ethylacetate (9:1). After completion of the reaction, the reaction mixture is cooled to room temperature and product is isolated to obtain crude product, which is re-crystallized from absolute alcohol to afford the pure chalcone.

Physical and spectral data

In the case of 3-(3-aryl-3-oxo1-propenyl)-4*H*-1-benzopyran (**3d**), the yield is 90% and the absorption observed in IR region is 1682 cm^{-1} for O = C–C and 1638 cm^{-1} for pyronyl C = O, respectively. In the ^{1}H NMR spectra, a pair of doublets at δ 7.11 and δ 7.87 was found for the α and β protons of chalcone system, the hydrogen attached to C2 position of chromone appeared as a singlet at δ = 8.26, and other aromatic protons appeared as a complex multiplet pattern at δ = 7.22–8.12, respectively.

3-(4-Ethoxyphenyl)-1-phenylpropenone

MP 52°C (52–53)[30]; IR (KBr): 3021, 2927, 1656, 1596, 1216, and 760 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 7.2 Hz, 2H), 7.79 (d, *J* = 15.9 Hz, 1H), 7.57–7.38 (m, 6H), 6.89 (d, *J* = 7.9 Hz, 2H), 4.01 (q, *J* = 7.5, 6.8 Hz, 2H), and 1.40 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz): δ = 190.48, 161.20, 144.74, 138.52, 132.66, 130.30, 128.59, 128.43, 127.37, 119.50, 114.93, 63.52, and 14.54; ESI (*m*/*z*) 252 [M + H]$^{+}$ (Table 1, product **3b**).

3-(2-Methoxyphenyl)-1-phenylpropenone

MP 52–53°C (53–54)[30]; IR (KBr): 3061, 2956, 2837, 1659, 1597, 1340, 1248, 1209, 1018, and 753 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.17 (d, *J* = 15.4 Hz, 1H), 8.04 (d, *J* = 7.7 Hz, 2H), 7.67–7.45 (m, 5H), 7.34 (t, *J* = 7.7 Hz, 1H), 6.99–6.94 (t, *J* = 7.7 Hz, 1H), 6.89 (d, *J* = 9.0 Hz, 1H), and 3.84 (s, 3H); ^{13}C NMR (75 MHz): δ = 191.01, 158.96, 140.51, 138.55, 132.79, 132.01, 129.26, 128.61, 128.53, 123.90, 122.72, 120.89, 111.34, and 55.62; ESI (*m*/*z*) 239 [M + H] $^{+}$ (Table 1, product **3c**).

3-(4-Ethoxyphenyl)-1-p-tolylpropenone

MP 94–95°C (95–96)[30]; IR (KBr): 3030, 2977, 1648, 1563, and 1217 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.94 (d, *J* = 7.6 Hz, 2H), 7.79 (d, *J* = 15.2 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 2H), 7.41 (d, *J* = 15.2 Hz, 1H), 7.27 (d, *J* = 7.6 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 4.02 (q, *J* = 7.5, 6.8 Hz, 2H), 1.40 (t, *J* = 7.6 Hz, 3H), and 2.1 (s, 3H); ^{13}C NMR (75 MHz): δ = 189.87, 161.11, 144.33, 143.33, 135.90, 130.18, 129.28, 128.61, 127.47, 119.46, 114.84, 63.70, 21.71, and 14.85; ESI (*m*/*z*) 267 [M + H]$^{+}$ (Table 1, product **3e**).

1-(4-Chlorophenyl)-3-(4-ethoxyphenyl)-propenone

MP 125°C (125–126)[30]; IR (KBr): 3019, 1657, 1601, 1216, 1028, and 759 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.95 (d, *J* = 9.0 Hz, 2H), 7.77 (d, *J* = 15.7 Hz, 1H), 7.56 (d, *J* = 7.9 Hz, 2H), 7.44 (d, *J* = 7.8 Hz, 2H), 7.35 (d, *J* = 15.8 Hz, 1H), 7.31 (d, *J* = 8.9 Hz, 2H), 4.05 (q, *J* = 7.5, 6.8 Hz, 2H), and 1.42 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (50 MHz): δ = 189.79, 162.06, 146.03, 139.32, 137.26, 130.8, 130.29, 129.3, 127.65, 119.31, 115.35, 64.15, and 15.17; ESI (*m*/*z*) 287 [M + H]$^{+}$ (Table 1, product **3g**).

1-(4-Chlorophenyl)-3-(2-methoxyphenyl)-propenone

MP 75–76°C (75–76)[30]; IR (KBr): 3017, 2935, 1655, 1599, 1501, 1218, 1168, 1026, and 758 cm^{-1}; ^{1}H NMR($CDCl_3$, 300 MHz): δ = 8.13 (d, *J* = 14.8 Hz, 1H), 7.94 (d, *J* = 9.2 Hz, 2H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.54 (s, 1H), 7.42 (d, *J* = 7.3 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 6.99–6.89 (m, 2H), and 3.88 (s, 3H); ^{13}C NMR (50 MHz): δ = 190.06, 159.44, 141.23, 139.29, 137.18, 132.47, 130.4, 129.69, 129.25, 124.06, 122.56, 121.24, 111.68, and 55.93; ESI (*m*/*z*) 273 [M + H]$^{+}$ (Table 1, product **3h**).

Conclusion

In summary, the present method employing $BiCl_3$ is mild, efficient, and environment benign green protocol for the synthesis of chalcones. The products are obtained in high yields and the reaction time is short. The present protocol employs a catalyst that is inexpensive and a well-known non-toxic inorganic salt. Furthermore, the process is carried out with operational simplicity and simple work-up procedures. These features place this protocol at an advantage to the existing processes.

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