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A simple and highly efficient method for the synthesis of chalcones by using borontrifluoride-etherate☆

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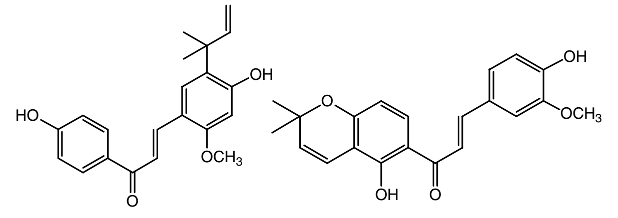
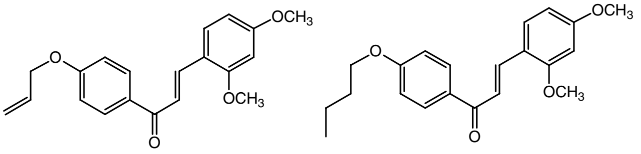
Abstract—Chalcones are secondary metabolites of terrestrial plants, precursors for the biosynthesis of flavonoids and exhibit various biological activities. Condensation of substituted acetophenones (**2a**–**12a**) with various aromatic aldehydes (**1b**–**7b**) in the presence of BF_3–Et_2O at room temperature gave chalcones in 75–96% yield.

Chalcones are the main precursors for the biosynthesis of flavonoids, which are frequent components of the human diet. Licochalcone A isolated from the roots of *Glycyrrhiza inflata* (licorice) has in vitro and in vivo antimalarial[1] and antileishmanial activity,[2] 3-methoxy-4-hydroxyloncocarpin isolated from the roots of *Lonchocarpus utilis* inhibits NADH:ubiquinone oxidoreductase activity[3] and synthetic chalcones such as 2,4-dimethoxy-4′-allyloxychalcone and 2,4-dimethoxy-4′-butoxychalcone have been reported as antileishmanial agents[4] (Fig. 1). Recent studies on biological evaluation of chalcones revealed some to be anti-cancer,[5] anti-inflammatory,[6] antimitotic,[7] anti-tubercular,[8] cardiovascular,[9] cell differentiation inducing,[10] nitric oxide regulation modulatory[11] and anti-hyperglycemic agents.[12]



Licochalcone A

3-methoxy-4-hydroxyloncocarpin



2,4-dimethoxy-4'-allylchalcone

2,4-dimethoxy-4'-butoxychalcone

Figure 1. Naturally occurring chalcones (licochalcone A and 3-methoxy-4-hydroxyloncocarpin) and synthetic chalcones (2,4-dimethoxy-4′-allyloxychalcone and 2,4-dimethoxy-4′-butoxychalcone).

Of the many methods available for the synthesis of chalcones, the most widely used is the base catalysed Claisen–Schmidt reaction in which the condensation of a ketone with an aldehyde is carried out in the presence of aq NaOH,[13] KOH,[14] $Ba(OH)_2$,[15] hydrotalcites,[16] LiHDMS[17] and calcined $NaNO_3$/natural phosphates.[18] The acid catalyzed methodologies include the use of $AlCl_3$,[19] dry HCl,[20] $Zn(bpy)(OAc)_2$,[21] $TiCl_4$,[22] $Cp_2ZrH_2/NiCl_2$,[23] Zeolites[16] and $RuCl_3$.[24]

To our knowledge, BF_3–Et_2O has not been used for the Claisen–Schmidt reaction, however in 1940, Breslow and Hauser[25] described the use of BF_3 gas for one example, the condensation of acetophenone with benzaldehyde. This method has several disadvantages such as the special efforts needed to pass BF_3 gas into the reaction mixture (commercial BF_3 gas was passed through a solution of boric oxide in concd H_2SO_4 to remove hydrogen fluoride), or a special experimental set up for BF_3 gas generation, the high cost of BF_3 gas and a laborious work-up.

To generalize our methodology we synthesized several chalcones **1c**–**15c** (Table 1) by reacting various substituted acetophenones (**2a**–**12a**) and substituted benzaldehydes (**1b**–**7b**) using 0.5 equiv of BF_3–Et_2O

Keywords: Chalcone; Synthesis; BF_3–Et_2O; Claisen–Schmidt reaction.

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Table 1. Synthetic chalcones (**1c**–**15c**) prepared using BF_3–Et_2O

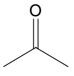
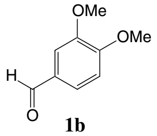
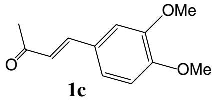
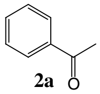
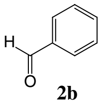
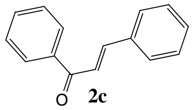
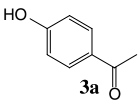
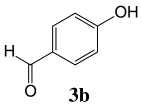
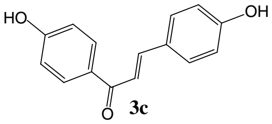
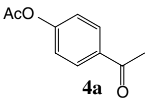
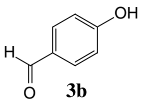
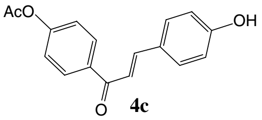
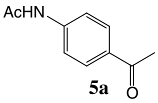
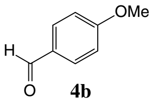
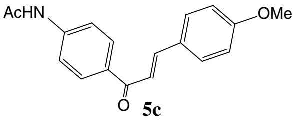
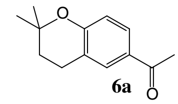
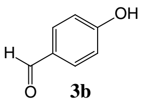
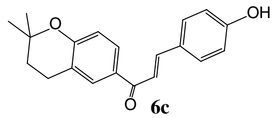
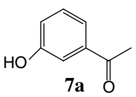
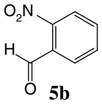
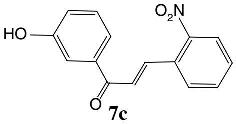
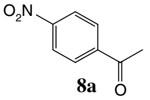
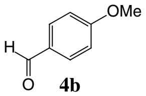
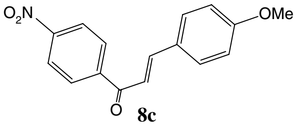
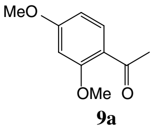
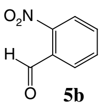
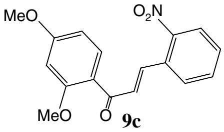
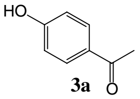
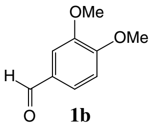
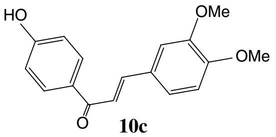
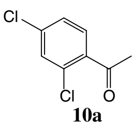
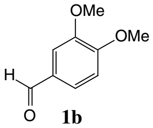
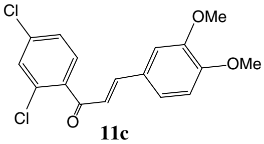
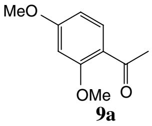
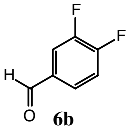
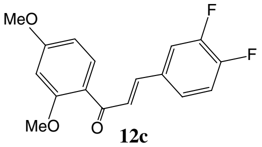
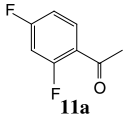
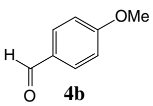
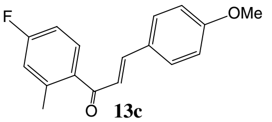
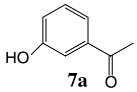
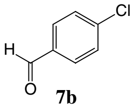
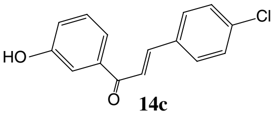
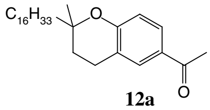
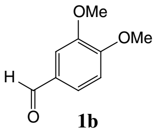
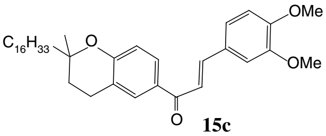
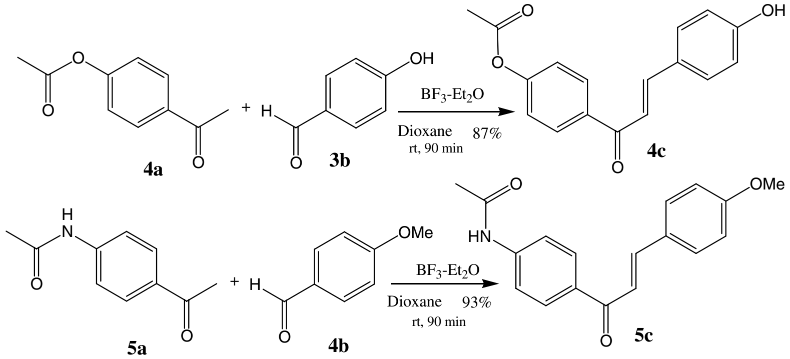
Entry	Ketone	Aldehyde	Chalcone (product)	Time (min)	Yield[a] (%)	Mp (°C)
1	 **1a**	 **1b**	 **1c**	30	94	85–87
2	 **2a**	 **2b**	 **2c**	15	90	56–57
3	 **3a**	 **3b**	 **3c**	150	80	196–198
4	 **4a**	 **3b**	 **4c**	90	87	168–170
5	 **5a**	 **4b**	 **5c**	90	93	197–198
6	 **6a**	 **3b**	 **6c**	120	96	160–162
7	 **7a**	 **5b**	 **7c**	150	93	187–189
8	 **8a**	 **4b**	 **8c**	60	92	192–194
9	 **9a**	 **5b**	 **9c**	30	88	128–130
10	 **3a**	 **1b**	 **10c**	150	90	194–196
11	 **10a**	 **1b**	 **11c**	150	75	134–136
12	 **9a**	 **6b**	 **12c**	90	81	130–132

Table 1 (*continued*)

Entry	Ketone	Aldehyde	Chalcone (product)	Time (min)	Yield[a] (%)	Mp (°C)
13	 **11a**	 **4b**	 **13c**	150	82	97–99
14	 **7a**	 **7b**	 **14c**	30	87	148–150
15	 **12a**	 **1b**	 **15c**	60	92	Oil

[a] Isolated yields.



Scheme 1. Synthesis of O-acylated and N-acylated chalcones by using BF_3–Et_2O.

(Scheme 1).[26] Most of the products were formed within 15–150 min and the trans double bond was obtained exclusively. The reaction mixture was washed with water to remove BF_3 complexes, concentrated and recrystallized to give pure chalcones (**1c**–**15c**) in high yields without column chromatography in most cases.

In aq KOH or NaOH assisted reactions, reaction times were much longer (2–4 days), with high probability of side reactions such as the Cannizzaro reaction or aldol condensation. By using BF_3–Et_2O we obtained chalcones exclusively, within 15–150 min and moreover, we did not observe any side reactions.

It is important to note that BF_3–Et_2O can be used in the presence of ester and amide functional groups. To demonstrate this we carried out a condensation reaction between O-acylated **4a** or N-acylated acetophenone **5a** and aromatic aldehydes (**3b**, **4b**) and synthesized O-acylated **4c** or N-acylated chalcones **5c** in high yields (Scheme 1) by using BF_3–Et_2O. These types of reactions cannot be carried out using KOH or NaOH since hydrolysis of the ester or amide would occur.

In summary, we have developed a new methodology and synthesized several substituted chalcones by using BF_3–Et_2O, for the first time. Our method has many advantages over existing methods such as high yields, simple work-up, short reaction times, no side reactions, no column-chromatography in most cases, a convenient source of BF_3, solvent-free reactions in the case of liquid reactants and tolerance of base sensitive functional groups (esters, amides).

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Supplementary data

Spectral data of all the synthetic compounds are available in the supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.03.054.

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26. *Representative procedure for preparation of chalcones by condensation between acetophenone and benzaldehyde:* To a stirred solution of acetophenone **2a** (1.2 g, 10 mmol) and benzaldehyde **2b** (1.1 g, 10 mmol) was added gradually BF_3–Et_2O (0.6 mL, 5 mmol) at room temperature. (If the reactants were solids, a little dry dioxane was used as a solvent). The solution was stirred for 15 min at room temperature. After dilution with moist ether (100 mL), the solution was washed with water (3×50 mL) to discharge the colour and the BF_3–Et_2O complex. The ethereal solution obtained after extraction was dried over anhyd. Na_2SO_4 and evaporated under reduced pressure. The crude mixture was passed through a silica gel column chromatography to afford desired chalcone **2c** (1.85 g, 90%).