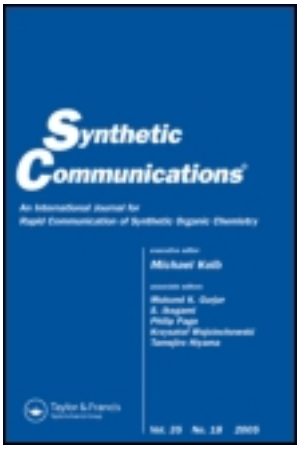

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Convenient One-Pot Synthesis of Chromone Derivatives and Their Antifungal and Antibacterial Evaluation

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CONVENIENT ONE-POT SYNTHESIS OF CHROMONE DERIVATIVES AND THEIR ANTIFUNGAL AND ANTIBACTERIAL EVALUATION

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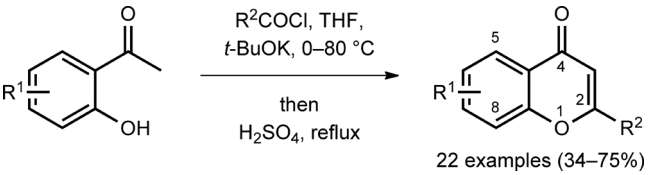
GRAPHICAL ABSTRACT



Abstract *A one-pot method for the synthesis of chromone derivatives from the reaction of 2-hydroxyacetophenones with aliphatic or aromatic acid chlorides is reported. Esterification and Baker–Venkataraman rearrangement were promoted by t-BuOK, which was followed directly by acid-catalyzed cyclization in one pot. Some of 2-cyclohexyl- and 2-cyclohexylmethyl-substituted chromones displayed activity against plant pathogenic fungal strains.*

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Keywords Antifungal activity; chromones; flavonoids; heterocycles

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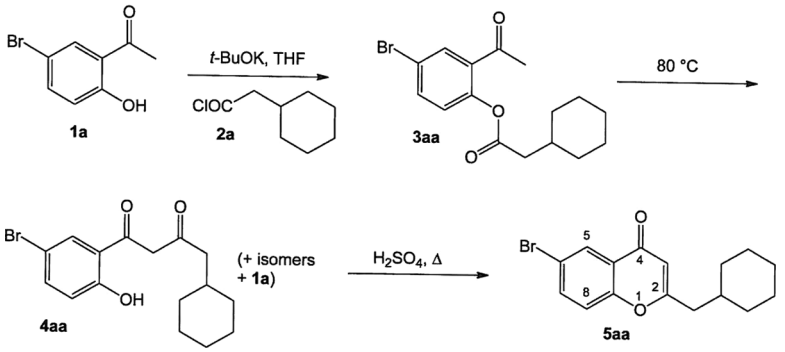
INTRODUCTION

The application of synthetic pesticides has undoubtedly played a vital role in delivering enhanced yields of crops and securing food supplies in developed countries. However, there has been concern for many years regarding the persistence of pesticides in the environment and their effect on human health and ecosystems,[1] leading to restrictions in the use of synthetic pesticides.[2] In addition, increasing resistance has challenged the efficacy of some available pesticides, fueling the search for new classes of active compounds.[3–5] Natural products have proved to be a source of many compounds applied in crop protection,[6,7] and their derivatives are likely to deliver additional novel leads in the future. Flavonoids are widely distributed compounds in plants and are some of the most studied natural products.[8] A variety of bioactivities has been reported for flavonoid derivatives including antifungal,[9,10] antibacterial,[9,11–14] and insecticidal[15–18] activity. In a previous article, we described the synthesis of some flavones and chromones and their preliminary antibacterial and antifungal evaluation.[9] Of the compounds tested, we found those where the ring B in the flavone was replaced with a cyclohexyl group gave enhanced activity against Gram-positive bacteria as well as promising results against *Aspergillus niger*. In this article, we describe the synthesis of chromone derivatives using a convenient one-pot procedure and the evaluation of selected compounds for antifungal and antibacterial activities.

RESULTS AND DISCUSSION

To facilitate our studies of the antifungal and antibacterial potential of chromone derivatives, we required an effective synthesis of the chromone core that would deliver the compounds for testing as well as chromone intermediates suitable for further diversification. In an earlier work, we employed a modification of the well-known Baker–Venkataraman rearrangement reported by Riva et al. using pyridine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to synthesize chromone derivatives.[19] Overall, the process was performed in two steps, with the isolation and purification of the β-diketone followed by an acid-catalyzed dehydrative cyclization that was conducted under microwave irradiation.[9] Although this protocol worked well, we wished to develop a one-pot preparation while minimizing the use of toxic and costly reagents. Ares et al. had shown potassium *tert*-butoxide to be effective for both acylation and subsequent acyl transfer (Baker–Venkataraman) reactions,[20] although cyclization of the diketone was performed as a separate step. Herein we describe the application of a simple synthesis of chromones using potassium *tert*-butoxide followed by acid treatment and cyclization in one pot. We also report antifungal and antibacterial activity data for selected products.

Treatment of 2-hydroxy-5-bromoacetophenone (**1a**) and cyclohexanecarboxylic acid (**2a**) with 2 equivalents of *t*-BuOK in tetrahydrofuran (THF) at ambient temperature resulted in rapid and clean conversion to the ester **3aa** (Scheme 1). Alternatively, the reaction mixture was heated under reflux for 1 h and rearrangement of the intermediate ester to the β-diketone **4aa** was observed. The β-ketoester was obtained as a mixture of isomers including the enol tautomers. Analysis of the reaction mixture indicated the presence of several compounds including structural isomers of **4aa** and some 2-hydroxyacetophenone due to cleavage of the intermediate ester. Nonetheless,



Scheme 1. One-pot synthesis of chromones.

cyclization of the crude reaction mixture was conveniently achieved by acidification of the crude mixture with H_2SO_4 (final concentration of 2.3 M) and heating under reflux to give the chromone **5aa**. Following column chromatography, chromone **5aa** was isolated in 44% overall yield from the 2-hydroxyacetophenone **1a**.

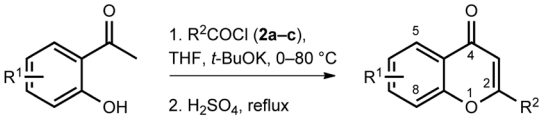
Under the relatively strongly acidic conditions employed for the cyclization, by-products originating from acid-catalyzed ring-opening reactions of the reaction solvent THF were observed. In some cases, these were difficult to remove by column chromatography. Replacing the solvent with 1,4-dioxane led to inferior yields of chromones. However, simply reducing the amount of H_2SO_4 (final solution concentration of 0.2 M in THF) used in the cyclization step reduced the side reaction, providing an enhanced yield of **5aa** (58%, entry 1, Table 1). The one-pot synthetic protocol was then applied to a variety of chromone derivatives **5aa**–**5ec**, in satisfactory to good yields (Table 1). A series of flavones (2-arylchromones) **5ad**–**5eg** were also synthesized in 46–75% yields using the one-pot protocol (Table 2).

Selected synthetic chromones were tested against *Drechselera oryzae*, *Alternaria alternate*, *Fusarium oxysporium*, *Aspergillus niger*, and *Macrophomina phaseolina* (Table 3).[21] Most of the tested compounds showed significant growth inhibition of the tested fungal species, with the exception of the 7-fluorochromones, which showed no inhibition at concentrations up to 42 $\mu g/cm^2$. The previously reported cyclohexyl-derivatives **5ac** and **5bc** (entries 4 and 5) were tested concurrently with the newly synthesized analogs for comparison.

Drechselera oryzae was the most sensitive fungus among the tested fungi, with compounds **5ac**, **5bc**, and **5bf** displaying the most effective inhibition with IC_{50} values of 0.007, 0.002, and 0.009 $\mu g/cm^2$ respectively (entries 4, 5, and 7). Compounds **5ba** and **5da** were the most potent inhibitors against *Alternaria alternata*, with IC_{50} values of 2.27 and 2.67 $\mu g/cm^2$ respectively (entries 2 and 3). In the case of *Fusarium* and *Aspergillus* the similar inhibitory potency was observed for most of the tested compounds with IC_{50} values in the range 2.20–3.12 $\mu g/cm^2$ (entries 1–7), with the exception of compounds **5da** and **5bf**, which showed reduced potency toward *Aspergillus* (IC_{50} values 8.7 and 37.39 $\mu g/cm^2$ respectively). For the fungus *Macrophomina*, broadly similar activity of the compounds in entries 1–7 was observed.

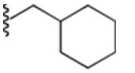
Following from the antifungal investigation, a small number of chromones were used to screen for antibacterial activity.[22] When examined against a methicillin-sensitive

Table 1. One-pot synthesis of chromones



1a (R^1=5-Br); **1b** (R^1=5-OMe);
1c (R^1=5-OH); **1d** (R^1=4-OMe);
1e (R^1=4-F)

5aa-5ec

	Reactants					
Entry	**1**	**2**	Product	R^1	R^2	Yield (%)[a]
1	**1a**	**2a**	**5aa**	6-Br	 a	58
2	**1b**	**2a**	**5ba**	6-OMe		57
3	**1c**	**2a**	**5ca**	6-OH		34
4	**1d**	**2a**	**5da**	7-OMe		35
5	**1a**	**2b**	**5ab**	6-Br	 b	48
6	**1b**	**2b**	**5bb**	6-OMe		41
7	**1a**	**2c**	**5ac**	6-Br	 c	62
8	**1b**	**2c**	**5bc**	6-OMe		72
9	**1d**	**2c**	**5dc**	7-OMe		54
10	**1e**	**2c**	**5ec**	7-F		54

[a]Indicates isolated yield of analytically pure material.

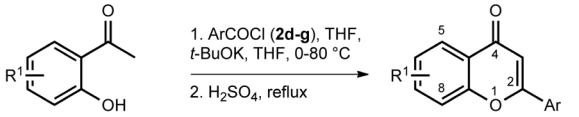
strain of the Gram-positive organism *Staphylococcus aureus* (MSSA), **5ba** was observed to have a moderate minimum inhibitory concentration (MIC) of 64 mg/mL. The only other compound with any notable activity was **5aa**, which yielded an MIC of 97.5 mg/mL against MSSA. Clearly, this antibacterial activity is somewhat strain-specific, as only **5ba** had any activity against a methicillin-resistant strain of this organism. When screened against the Gram-negative organism *Escherichia coli*, **5ba** was found to display only very weak activity. A stronger antibacterial action of **5ba** against Gram-positive organisms would suggest that the lipopolysaccharide (LPS) layer surrounding *E. coli* prevents access of the compound into the cell and in so doing limits activity. Lacking an LPS layer, Gram-positive cells with just a peptidoglycan cell wall may be more easily accessed by the chromones.

In summary, a simple and effective one-pot synthesis of chromones is described, which has been used to prepare a number of derivatives bearing cycloakyl and aryl substituents at the 2-position. This approach avoids the use of toxic and expensive amine bases such as pyridine and DBU. Preliminary investigations show some of these chromones to possess activity against plant pathogenic fungi and one compound, **5ba**, displayed activity against a methicillin-resistant strain of *Staphylococcus aureus*.

EXPERIMENTAL

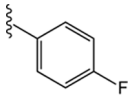
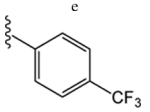
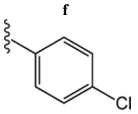
All reactions were carried out under an inert atmosphere of N_2 gas in oven- or flame-dried glassware. The solvents CH_2Cl_2 (from CaH_2) and tetrahydrofuran (THF) (from Na/benzophenone) were distilled prior to use. All other solvents

Table 2. One-pot synthesis of flavones



1a (R^1=5-Br); **1b** (R^1=5-OMe); **1d** (R^1=4-OMe); **1e** (R^1=4-F)

5ad-5eg

Entry	Reactants 1	Reactants 2	Product	R^1	Ar	Yield (%)[a]
1	**1a**	**2d**	**5ad**	6-Br	 d	46
2	**1b**	**2d**	**5bd**	6-OMe		62
3	**1d**	**2d**	**5dd**	7-OMe		54
4	**1e**	**2d**	**5ed**	7-F		60
5	**1a**	**2e**	**5ae**	6-Br	 e	49
6	**1b**	**2e**	**5be**	6-OMe		75
7	**1d**	**2e**	**5de**	7-OMe		52
8	**1a**	**2f**	**5af**	6-Br	 f	51 (68)[b]
9	**1b**	**2f**	**5bf**	6-OMe		67
10	**1d**	**2f**	**5df**	7-OMe		49
11	**1b**	**2g**	**5bg**	6-OMe	 g	61
12	**1e**	**2g**	**5eg**	7-F		56

[a]Indicates isolated yield of analytically pure material.
[b]Isolated yield obtained under modified conditions for the cyclisation step (0.2 M H_2SO_4).

and reagents were used as received. Thin-layer chromatography (TLC) was performed on aluminium-precoated plates of silica gel 60, and chromatograms were visualized under ultraviolet (UV) light and/or by staining with potassium permanganate solution. Flash chromatography was performed using 35 to 70-μm

Table 3. IC_{50} data[a] for chromone derivatives[b] **5aa**, **5ba**, **5da**, **5ac**, **5bc**, **5af**, and **5bf**

Entry	Compound	*Drechslera oryzae*	*Alternaria alternate*	*Fusarium oxysporium*	*Aspergillus niger*	*Macrophomena* spp.
1	**5aa**	0.145 ± 0.047	3.450 ± 0.209	2.992 ± 0.145	2.815 ± 0.112	3.889 ± 0.167
2	**5ba**	1.753 ± 0.058	2.275 ± 0.254	2.812 ± 0.065	3.118 ± 0.036	5.051 ± 0.157
3	**5da**	0.397 ± 0.036	2.679 ± 0.147	2.603 ± 0.147	8.736 ± 0.77	3.967 ± 0.532
4	**5ac**	0.007 ± 0.006	4.89 ± 0.71	2.26 ± 0.088	2.81 ± 0.17	4.67 ± 0.48
5	**5bc**	0.002 ± 0.007	4.69 ± 1.28	2.20 ± 0.066	2.59 ± 0.88	3.79 ± 3.60
6	**5af**	0.186 ± 0.031	2.842 ± 0.049	2.455 ± 0.073	2.778 ± 0.76	3.023 ± 0.35
7	**5bf**	0.009 ± 0.009	4.488 ± 0.142	3.052 ± 0.363	37.392 ± 3.424	4.362 ± 0.443

[a]IC_{50} values are reported in μg/cm^2.
[b]Compounds **5ec, 5ef**, and **5eg** did not display activity in the assays up to 42 μg/cm^2.

silica gel. ^{1}H spectra were recorded at 300 MHz while ^{13}C NMR spectra were recorded at 75 MHz or 100 MHz, in $CDCl_3$ (unless otherwise stated) with $CHCl_3$ ($\delta = 7.27$ ppm ^{1}H, $\delta = 77.0$ ppm ^{13}C) as the internal standard. Infrared (IR) spectra were obtained using the neat compounds and are reported in wave numbers (cm^{-1}). Melting points were obtained in open-ended capillary tubes and are uncorrected. All electrospray positive (ES^+) low-resolution mass spectra (LRMS) were recorded on a Waters ZMD quadrupole spectrometer. High-resolution electrospray positive (ES^+) was performed on a FT-ICR Bruker Apex III spectrometer. Physical and spectroscopic data for known compounds were consistent with reported values: **5ac**,[9] **5bc**,[9] **5dc**,[23] **5ad**,[9] **5bd**,[18] **5dd**,[18] **5ae**,[9] **5de**,[20] **5df**,[24] and **5bg**.[9] Compound **5ed** has also been reported previously,[25] although our data are not consistent with the partial data reported. Our full characterization data for **5ed** are therefore provided herein.

Procedure for the Synthesis of Chromones: 6-Bromo-2-(cyclohexylmethyl)-4*H*-chromen-4-one (5aa)

Cyclohexylacetyl chloride (**2a**, 0.657 mL, 4.20 mmol) was added dropwise to a stirred solution of 5-bromo-2-hydroxy-acetophenone (**1a**, 900 mg, 4.20 mmol) and *t*-BuOK (988 mg, 8.80 mmol) in THF (50 mL), and then the mixture was heated at 80 °C for 5 h to afford the crude β-diketone. The reaction mixture was allowed to cool to rt, concentrated H_2SO_4 (7.5 mL, 135 mmol) was added dropwise, and the mixture was heated at 90 °C for 3 h. The mixture was cooled to rt, diluted with EtOAc, and then poured into aqueous 2 N NaOH (60 mL). The organic layer was separated, re-extracting the aqueous solution with EtOAc. The combined organic extract was washed sequentially with aqueous HCl (5%), $NaHCO_3$ (5%), and brine and then dried ($MgSO_4$). Solvent was removed under reduced pressure to afford a brown-orange oil (2.50 g). Purification by column chromatography (SiO_2) eluting with EtOAc/hexane (2.5:97.5 → 20:80) afforded the title compound **5aa** (780 mg, 2.41 mmol, 58%) as a pale orange solid.

Modified Procedure for the Synthesis of Chromones: 6-Bromo-2-(4-(trifluoromethyl)phenyl)-4*H*-chromen-4-one (5af)

4-Trifluoromethylbenzoyl chloride (**2f**, 600 μL, 4.0 mmol) was added dropwise to a stirred solution of 5-bromo-2-hydroxy-acetophenone (**1a**, 860 mg, 4.0 mmol) and *t*-BuOK (942 mg, 8.4 mmol) in THF (50 mL). The mixture was heated at 80 °C for 3 h to afford the crude β-diketone. The reaction mixture was allowed to cool to rt, concentrated H_2SO_4(0.5 mL, 9.0 mmol) was added, and the mixture was heated at 90 °C for 2 h. The mixture was diluted with EtOAc (50 mL), washed sequentially with aqueous $NaHCO_3$ (5%) and brine, and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford an orange solid. Purification by column chromatography eluting with EtOAc/hexane (5:95 → 30:70) afforded the title compound **5af** (1.01 g, 2.74 mmol, 68%) as an orange-yellow solid.

6-Bromo-2-(Cyclohexylmethyl)-4*H*-chromen-4-one (5aa). Yield 58%; pale orange solid; mp 99–101 °C; IR (neat) ν_{max} 1651 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (1H, d, $J = 2.4$ Hz, Ar-H5), 7.72 (1H, dd, $J = 9.0$,

2.4 Hz, Ar-H7), 7.33 (1H, d, $J = 9.0$ Hz, Ar-H8), 6.16 (1H, s), 2.49 (2H, d, $J = 7.0$ Hz, CH_2), 1.90–1.66 (6H,m), 1.36–1.05 (5H, m) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6 (C), 168.8 (C), 155.1 (C), 136.1 (CH), 128.1 (CH), 124.9 (C), 119.7 (CH), 118.1 (C), 110.7 (CH), 42.0 (CH_2), 36.1 (CH_2), 32.8 (CH), 25.9 (CH_2), 25.8 (CH_2) ppm; LRMS (ES^+) m/z 321.1 (& 323.1) $[M + H]^+$. HRMS (ES^+) m/z $C_{16}H_{18}BrO_2$ requires 321.0485; found 321.0491.

6-Bromo-2-(4-(trifluoromethyl)phenyl)-4*H*-chromen-4-one (5af). Yield 51%; orange-yellow solid; mp 174–176 °C; IR (neat) ν_{max} 1659 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.37 (1H, d, $J = 2.6$ Hz, Ar-H5), 8.04 (2H, d, $J = 8.9$ Hz), 7.82 (1H, dd, $J = 8.9$, 2.6 Hz, Ar-H7), 7.81 (2H, d, $J = 8.9$ Hz), 7.50 (1H, d, $J = 8.9$ Hz, Ar-H8), 6.88 (1H, s, H3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7 (C), 161.9 (C), 154.9 (C), 137.0 (CH), 134.8 (C), 133.4 (q, $J_{CF} = 33$ Hz), 128.5 (CH), 126.7 (CH), 126.1 (2 C, q, $J_{CF} = 4$ Hz, CH), 125.2 (C), 124.9 ($J_{CF} = 271$ Hz, C), 120.0 (CH), 119.0 (C), 108.7 (CH) ppm; LRMS (ES^+) m/z 761.1 (& 763.2) $[2M + Na]^+$. HRMS (ES^+) m/z C_{32} H_{16} $Br_2F_6O_4Na$ requires 760.9212; Found 760.9164.

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