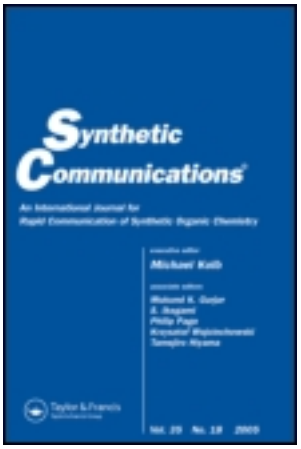

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Efficient Synthesis of 3-Methyl-2H-chromen-2-one: Classic Versus Microwave Conditions

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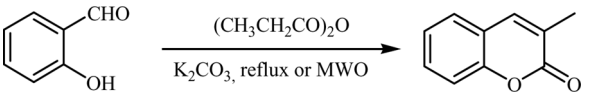
GRAPHICAL ABSTRACT



Abstract *The reaction of salicylaldehyde with propionic anhydride in the presence of anhydrous K_2CO_3 as catalyst afforded 3-methyl-2*H*-chromen-2-one (3-methylcoumarin) in good yields depending on the reaction conditions. The reaction was performed under classic thermal (55% yield) and microwave conditions (91–97% yield).*

Keywords Aldol condensation; 3-methylcoumarin; microwave; Perkin reaction

INTRODUCTION

Coumarin derivatives are well known as versatile molecules, not only for their interesting fluorescent properties, which change drastically with substituents and their introduced positions,[1] but also for their usefulness as precursors for many heterocyclic compounds.

3-Methyl-2*H*-chromen-2-one (3-methylcoumarin) **1** is an important building block in organic synthesis. A variety of synthetic methods for preparation of substituted 3-methylcoumarins are known, such as Baylis–Hillman reaction of *O*-benzylated salicylaldehydes,[2] thermal transformations (rearrangements) of α-aryloxymethylacrylic acids and their derivatives leading to the formation of "ene" dimers,[3] regioselective nucleophilic addition of organolithium, Grignard, and hydride reagents to α-phenylsulfanyl-α,β-unsaturated oxazolines,[4] rhodium-catalyzed cyclic carbonylation of 2-alkynylphenols,[5] Wittig–Horner reaction of β-hydroxyoxo compounds and phosphonopropionic acid,[6] and modified Perkin reaction of carboxylic acids and salicylaldehydes.[7] A majority of reported syntheses have disadvatages; they either suffer unsatisfactory yields or require multistep synthesis.[8] We needed to

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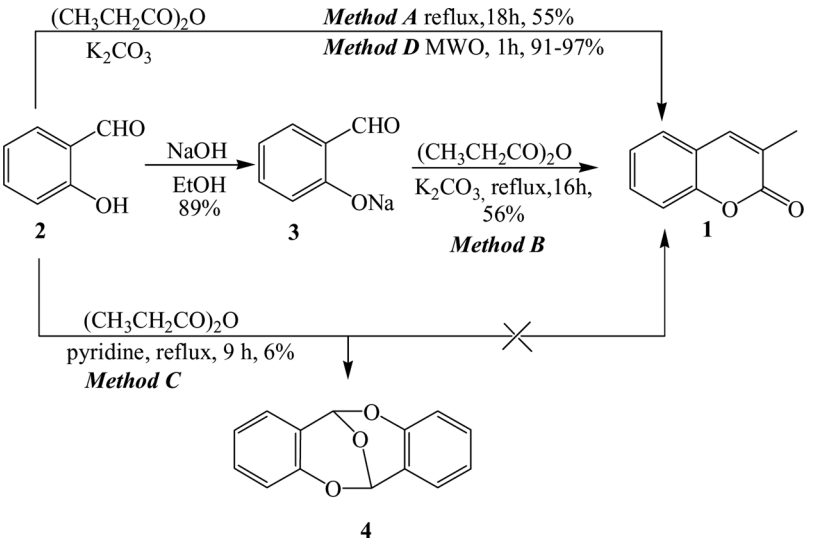
prepare 3-methyl-2*H*-chromen-2-one **1** in multigram quantities. Here we describe an efficient synthesis of coumarin **1** from readily available starting compounds.

RESULTS AND DISCUSSION

Synthesis Under Classic Conditions

The synthesis of 3-methyl-2*H*-chromen-2-one **1** was performed under modified conditions of the Perkin reaction. Reaction of salicylaldehyde **2** (method A) or its sodium salt **3** (method B) with propionic anhydride in the presence of anhydrous K_2CO_3 as catalyst afforded 3-methyl-2*H*-chromen-2-one **1** (Scheme 1). It is known that a larger amount of anhydride is required to give moderate yields in the Perkin reaction.[9] We used a large excess of propionic anhydride for the reaction under thermal conditions. The yields of both methods were comparable (Table 1, entries I and II). The poor yield of **1** was obtained probably because of the formation of *E*-phenylpropenoic acid, which does not cyclize to the lactone ring. The reaction of equimolar amounts of starting compounds resulted in poor and unsatisfactory yield of product.

There is a variety of catalysts suitable for the Perkin reaction.[10] Potassium carbonate proved to be a good catalyst for the synthesis of 3-substituted 2*H*-chromen-2-ones[11] and for the synthesis of 3-alkyl-2*H*-chromen-2-ones in ionic liquids.[12] It worked well also for synthesis of chromene **1**. When we used pyridine as catalyst instead of K_2CO_3 (method C), the reaction yielded 6*H*,12*H*-6,12-epoxidibenzo[*bf*][1,5]dioxocine **4**, and no 3-methyl-2*H*-chromen-2-one **1** was isolated in that case. We also have not isolated 2-formylphenyl propionate from the reaction mixture. It was not a component of liquid residuals distilled off from the reaction mixture. We expected the formation of this ester, as it can be prepared from salicylaldehyde **2** and



2 3 1 4

Scheme 1. Synthesis of 3-methyl-2*H*-chromen-2-one.

Table 1. Effect of reaction mixture composition and reaction time on yield of 3-methyl-2-oxo-2*H*-chromene **1**

Entry	Ratio of starting compounds aldehyde/anhydride/catalyst	$n_{aldehyde}$ (mol)	$n_{anhydride}$ (mol)	Reaction time	Method	Yield (%)
I	1:3:0.05	0.082	0.23	16 h	A	55
II	1:12:0.05	0.045	0.54	16 h	B	56
III	1:1:0.05	0.047	0.047	65 min	D	14
IV	1:1:0.05	0.288	0.288	70 min	D	62
V	1:1:0.03	0.192	0.192	70 min	D	51
VI	1:1.1:0.08	0.288	0.315	95 min	D	73
VII	1:1.6:0.05	0.047	0.076	65 min	D	91
VIII	1:0.76:0.13	0.029	0.022	65 min	D	55
IX	1:0.76:0.05	0.047	0.036	65 min	D	97
X	1:0.75:0.04	0.096	0.072	30 min	D	45

propionic anhydride in the presence of pyridine.[13] Formation of **4** under different reaction conditions was reported.[14]

Synthesis Under Microwave Conditions

Microwave irradiation has proved to be extremely useful for promoting and simplifying many condensation reactions, which can be carried out both under solvent and solvent-free conditions. The microwave irradiation shortened the reaction time of the Perkin reaction of benzaldehydes with acetic anhydride in the presence of cesium salts as catalysts by 60–80 times over classical heating.[15] The yield of unsubstituted 2*H*-chromen-2-one obtained this way (48%)[15] is comparable with the yield of 3-methyl-2*H*-chromen-2-one **1** obtained by method A (55%). The Perkin reaction of less reactive anhydrides (propionic and butyric) with benzaldehydes led to poor yields (11–14%).[15] Contrary to these reported data, the studied reaction of salicylaldehyde **2** with propionic anhydride in the presence of anhydrous K_2CO_3 as catalyst carried out under microwave conditions (method D) afforded 3-methyl-2*H*-chromen-2-one **1** in significantly greater yields (Table 1, entries IV, VI, VII, and IX). This yield is also greater in comparisom with yields of reactions performed under thermal conditions. Also the reaction time is considerably shorter, about 16-fold. Fast and uniform overheating of reaction mixture caused by microwave irradiation results in decreasing the content of polar low-boiling compounds (e.g., water) in reaction mixture; thus, the reaction equilibrium is shifted toward 3-methyl-2*H*-chromen-2-one **1**. The reaction in a microwave oven was performed at temperatures over 180 °C (to about 185 °C; measured by temperature sensor of the oven). Decrease of reaction temperatute to 170 °C led to a decrease in the yield of product by 15%.

Concentration of catalyst influences the yield of 3-methyl-2*H*-chromen-2-one **1**. We have found that the amount of catalyst of 5% of **2** led to the best yields. A greater amount of catalyst (Table 1, entry VI) caused sintering of reaction mixture, and the isolation of pure chromene was difficult, which resulted in lower yield of compound **2**. Lower amount of catalyst (Table 1, entry V) led to longer reaction time and poor yield.

Ratio of starting compounds also influences the yield of the reaction. There are two proposed mechanisms for the Perkin reaction.[16,17] The first proposes a formation of enolate from anhydride,[16] and thus an excess[9] of anhydride is necessary. We have found that the molar ratio of aldehyde/anhydride 1:1.6 gives the best results (Table I, entry VII). This finding is the same as for synthesis of unsubstituted coumarin under thermal conditions.[18] The second mechanism proposes a formation of *gem*-dicarboxylate,[17] when the use of an excess of aldehyde results in better yield. We performed the condensation reaction with 25% excess of salicylaldehyde, and we have obtained 97% yield of 3-methyl-2*H*-chromen-2-one **1** (Table 1, entry IX). The reaction with equimolar ratio of reactants under microwave conditions resulted in greater yield (Table 1, entry IV) than the the reaction performed with excess of anhydride under thermal conditions.

CONCLUSION

To conclude, we have found suitable reaction condition for synthesis of 3-methyl-2*H*-chromen-2-one **1** in multigram amounts. The reaction of salicylaldehyde **2** with propionic anhydride in the presence of anhydrous K_2CO_3 as catalyst under microwave condition, depending on the ratio of starting compounds, afforded 3-methyl-2*H*-chromen-2-one **1** in 91–97% yield.

EXPERIMENTAL

Melting points (uncorrected) were measured on a Kofler hot stage. The spectra were recorded on a 300-MHz Varian Gemini 200 spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as internal standard. All microwave-assisted reactions were carried out in a Prolabo Synthewave 402 microwave oven in the single-mode cavity reactor. Reaction course was monitored using thin-layer chromatography (TLC) (silica gel; eluent ethyl acetate/hexane 3:1).

Materials

Commercial chemicals and solvents were purchased from the major chemical suppliers as highest purity grade.

Method A

Mixture of salicylaldehyde **2** (81.89 mmol), propionic anhydride (230.5 mmol), and K_2CO_3 (4 mmol) was refluxed until the color of the reaction mixture became brown (16 h). The excess of propionic anhydride was distilled off. The residue was poured into crushed ice, and the pH was adjusted to 7 using $NaHCO_3$. The precipitate was filtered off, washed with water, dried, and recrystallized from a mixture of hexane/ethyl acetate (4:1) to give 7.18 g (55%) of 3-methyl-2*H*-chromen-2-one **1** as white needles: mp 90–91 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22 (d, 3H, $J = 1.47$ Hz, CH_3), 7.22–7.33 (m, 2H, Ar-H), 7.40–7.49 (m, 2H, Ar-H), 7.52 (s, 1H, H-4).

Method B

Salicylaldehyde **2** (70.42 mmol) was added to the solution of NaOH (125 mmol) in EtOH (50 ml). A precipitate was formed immediately. The salt was filtered off and dried to give 8.98 g (89%) of sodium 2-formylphenoxide **3**. Consequently, the solution of sodium 2-formylphenoxide **3** (45.13 mmol), propionic anhydride (0.54 mol), and K_2CO_3 (2.25 mmol) was refluxed for 16 h. After cooling, the excess of propionic anhydride was distilled off. The residue was poured into crushed ice, and the pH was adjusted to 7 using $NaHCO_3$. The precipitate was filtered off, washed with water, dried, and recrystallized from a mixture of hexane/ethyl acetate 4:1 to give 4.04 g (56%) of 3-methyl-2H-chromen-2-one **1** as white needles: mp 90–91 °C.

Method C

The mixture of salicylaldehyde **2** (4.7 mmol), propionic anhydride (16.9 mmol), and a drop of pyridine was refluxed until the color of the solution turned brown (9 h). After cooling, the unreacted starting material was distilled off. The residue was purified by column chromatography (hexane/chloroform 1:3) to give 0.04 g (6%) of 6*H*,12*H*-6,12-epoxido-dibenzo[*bf*][1,5]dioxocine **4** as white needles: mp 129–130 °C (mp[7] = 130–131 °C).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.34 (s, 2H, CH), 6.86 (d, 1H, $J = 8.26$ Hz, Ar-H), 6.94–6.99 (dt, 2H, $J = 6.43$, 1.08 Hz, Ar-H), 7.21–7.31 (m, 4H, Ar-H).

Method D: General Procedure

The mixture of salicylaldehyde **2**, propionic anhydride, and K_2CO_3 was heated under microwave irradiation to 180 °C for the time given in Table 1. The solution was poured into crushed ice, and the pH was adjusted to 7 using $NaHCO_3$. The precipitate was filtered off, washed with water, dried, and recrystallized from ethanol to give 3-methyl-2H-chromen-2-one **1** as white needles in yields given in Table 1, mp 90–91 °C.

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