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Polyphosphoric acid-promoted synthesis of coumarins lacking substituents at positions 3 and 4

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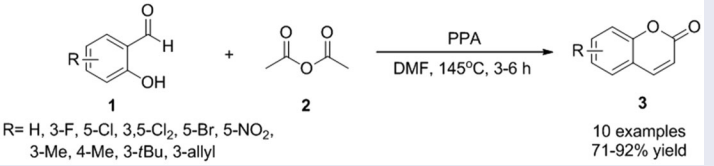
ABSTRACT

Coumarins have recently emerged as a hot topic of research due to their diverse pharmacological properties. This work described a method for the synthesis of 3,4-diunsubstituted coumarins promoted by polyphosphoric acid (PPA) from salicylaldehydes and acetic anhydride. Various coumarins were produced in good to excellent yields.

GRAPHICAL ABSTRACT



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Condensation; coumarin; polyphosphoric acid; salicylaldehyde

Introduction

Coumarin (benzopyran-2-one, or chromen-2-one) ring system, present in numerous natural and synthetic products, displays varied bioactivities such as anti-oxidant,[1] anti-inflammatory,[2] anti-HIV,[3] anti-microbial,[4] anti-cancer,[5] anti-tuberculosis,[6] anti-convulsant,[7] and anti-coagulant[8] (Fig. 1). Therefore, the synthesis and applications of the coumarin skeleton have gained widespread attention.

The general synthetic routes reported for coumarin derivatives involving Pechmann reaction,[9] Knoevenagel condensation,[10] Perkin condensation,[11] and Wittig reactions[12] are all well documented in the literature.[13] The classical Perkin condensation is perhaps the most simple method used to produce coumarins.[14] However, most methods suffer from drawbacks including limited substrate scope and sometimes the necessity of multi-step reactions. Modifications have been done to the classical Perkin

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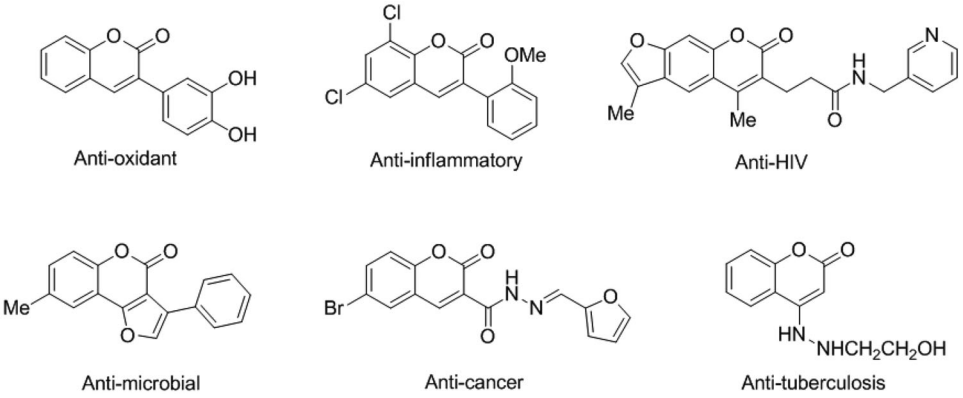


Figure 1. Selected bioactive coumarins.

condensation to prepare 3-substitutedcoumarins by using Mukaiyama esterification protocol to broad substrate and functional group tolerance.[15]

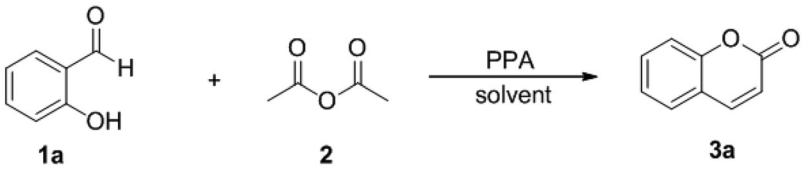
Herein, we describe a convenient procedure promoted by PPA for the preparation of coumarins from salicylaldehydes and acetic anhydride.

Results and discussion

Our initial studies were carried out with readily available salicylaldehyde **1a** and acetic anhydride **2** as test substrates. A mixture of **1a** (1 equiv.), **2** (4 equiv.), PPA (2 equiv.) in DMF was stirred at 120 °C for 2 h under a nitrogen atmosphere to give the desired product **3a** in 30% yield (Table 1, entry 2). Increasing the amount of PPA had no obvious effect on the reaction (Table 1, entry 1). However, decreasing the amount of PPA to 1 equiv. resulted in lower yield (Table 1, entry 3). We then investigated the temperature impact on the efficiency of the reaction and found that 145 °C was the best choice (Table 1, entries 4–7). Subsequently, a decreased yield was observed upon reducing the reaction time to 1 h (Table 1, entry 8). To our delight, further screening of the reaction time showed that the yield could be improved when the reaction time increased to 3 h (Table 1, entry 9). However, prolonging the reaction time (4 h) had very a slight reduction in yield (Table 1, entry 10). Unfortunately, the reaction performed in EtOH, THF, 1,4-dioxane or DMSO did not give the desired product **3a** (Table 1, entries 11–14). The optimized reaction conditions were determined as **1a** (1 equiv.), **2** (4 equiv.), PPA (2 equiv.) in DMF at 145 °C for 3 h under a nitrogen atmosphere (Table 1, entry 9). With the optimized reaction conditions in hand, a gram scale reaction was carried out and provided the product **3a** in 72% yield (Table 1, entry 15).

Under the optimized conditions, the scope of the substrates was investigated by varying salicylaldehyde **1** (Table 2). As shown in Table 2, desired products **3b**–**3j** were successfully obtained in good to excellent yields (Table 2, entries 2–10). The electronic properties of the substituents had an obvious effect on the reaction. Electron-withdrawing groups (F, Cl, Br and NO_2) on salicylaldehyde **1** led to lower yields (Table 2, entries 6–10). Additionally, fluoro-, dichloro- or nitro-substituted salicylaldehyde had limited influence on the reactivity (Table 2, entries 6, 9 and 10). The classical Perkin

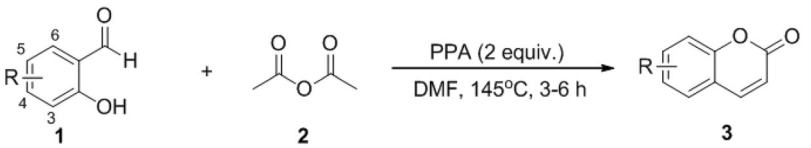
Table 1. Optimization of the reaction conditions[a].



Entry	PPA (equiv.)	Solvent	*T* (°C)	Time (h)	Yield **3a** (%)[b]
1	3	DMF	120	2	31
2	2	DMF	120	2	30
3	1	DMF	120	2	14
4	2	DMF	110	2	9
5	2	DMF	140	2	60
6	2	DMF	145	2	77
7	2	DMF	150	2	76
8	2	DMF	145	1	41
9	2	DMF	145	3	91
10	2	DMF	145	4	90
11	2	EtOH	75	3	/
12	2	THF	65	3	/
13	2	1,4-dioxane	100	3	/
14	2	DMSO	145	3	/
15[c]	2	DMF	145	3	72

[a]Reagents and conditions: **1a** (0.3 mmol), **2** (1.2 mmol), solvent (0.3 mL).
[b]Isolated yield.
[c]Reagents and conditions: **1a** (8.4 mmol), **2** (33.6 mmol), solvent (6.0 mL).

Table 2. Evaluation of substrate scope[a].



Entry	*R*	Time (h)	Product **3**	Yield **3** (%)[b]
1	H	3	**3a**	91
2	3-Me	3	**3b**	88
3	4-Me	3	**3c**	92
4	3-*t*Bu	3	**3d**	87
5	3-allyl	3	**3e**	85
6	4-F	4	**3f**	80
7	5-Cl	3	**3g**	82
8	5-Br	3	**3h**	77
9	3,5-Cl_2	4	**3i**	80
10	5-NO_2	6	**3j**	71

[a]Reagents and conditions: **1** (0.3 mmol), **2** (1.2 mmol), DMF (0.3 mL).
[b]Isolated yield.

condensation involves the use of simple starting materials in the presence of basic condensing agents including NaOAc, KOAc, CsOAc and Cs_2CO_3.[16] The same coumarins **3a**, **3b**, **3f**, and **3h** were formed in 79%,[16d] 85%,[17] 88%,[18] and 56%[19] yields under the classical conditions (heated at 145–180 °C for 6–48 h) from salicylaldehydes and acetic anhydride.

Conclusion

In summary, we have developed a simple and practicable reaction for the synthesis of 3,4-diunsubstituted coumarins promoted by PPA from accessible salicylaldehydes and acetic anhydride.

Experimental section

General procedure for the preparation of coumarins 3 (3a–3j)

To the solution of polyphosphoric acid (PPA, 0.6 mmol) in DMF (0.3 mL) were added salicylaldehydes **1** (0.3 mmol) and acetic anhydride **2** (1.2 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at 145 °C 3–6 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution, dried over Na_2SO_4 and evaporated. The resulting crude compound was purified by silica gel column chromatography, affording the pure coumarins **3**.

Detailed procedures and spectral characterization data for all compounds reported herein can be accessed on the publisher's website.

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