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Graphical Abstract

One-pot synthesis of (*E*)-3-benzylideneflavanones from 2-hydroxyacetophenones and aromatic aldehydes

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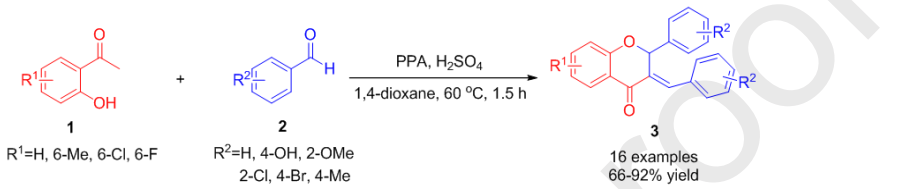

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ABSTRACT

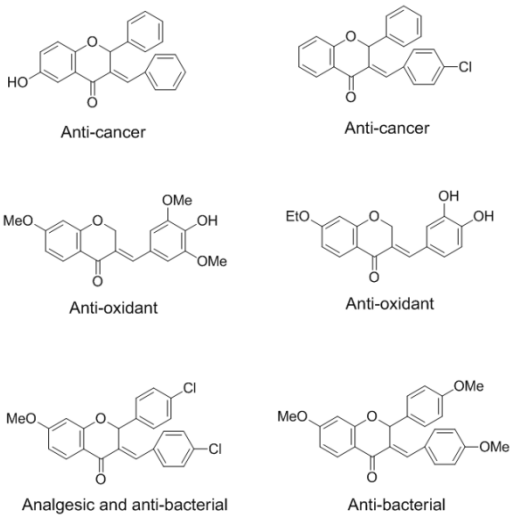
An efficient and practical PPA/H_2SO_4 promoted synthesis of (*E*)-3-benzylideneflavanones from 2-hydroxyacetophenones and aromatic aldehydes was developed. Various (*E*)-3-benzylideneflavanones were produced in good to excellent yields.

Introduction

3-Benzylideneflavanones are a significant architectural motif found in biologically active compounds and natural products.[1] For example, they are building blocks in the synthesis of spiroheterocycles,[2] and are also present in biologically active flavones.[3] These compounds exhibit various pharmacological activities such as anti-cancer,[4] anti-oxidant, anti-inflammatory, analgesic and anti-bacterial[5a-b] properties (Fig. 1). Therefore, the synthesis and applications of these scaffolds have gained widespread attention.

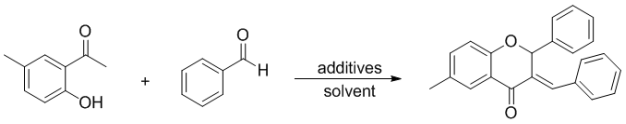
The most common synthetic method reported for the preparation of 3-benzylideneflavanones is the condensation of flavanones with aromatic aldehydes catalyzed either by an acid or base.[6] In addition, they are also formed as co-products during the condensation of 2-hydroxyacetophenones and aromatic aldehydes.[7] To the best of our knowledge, only two protocols have reported the one-pot synthesis of 3-benzylideneflavanones *via* either the NaOH[5] or $SiCl_4$[8] catalyzed condensation of 2-hydroxyacetophenones and aromatic aldehydes.

Herein, we describe a convenient and efficient one-pot procedure promoted by polyphosphoric acid (PPA) and H_2SO_4 for the preparation of (*E*)-3-benzylideneflavanones from 2-hydroxyacetophenones and aromatic aldehydes.



Figu

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



1a 2a 3a

Entry	Additive 1 (equiv.)	Additive 2 (equiv.)	Solvent	T (°C)	Time (h)	Yield **3a** (%)[b]
1[c]	PPA (15)	H_2SO_4 (4)	1,4-dioxane	90	1.0	28
2	PPA (0)	H_2SO_4 (4)	1,4-dioxane	90	1.0	/
3	PPA (15)	H_2SO_4 (0)	1,4-dioxane	90	1.0	11
4	PPA (20)	H_2SO_4 (4)	1,4-dioxane	90	1.0	39
5	PPA (25)	H_2SO_4 (4)	1,4-dioxane	90	1.0	38
6	PPA (20)	H_2SO_4 (12)	1,4-dioxane	90	1.0	58
7	PPA (20)	H_2SO_4 (16)	1,4-dioxane	90	1.0	56
8	PPA (20)	H_2SO_4 (12)	1,4-dioxane	40	1.0	40
9	PPA (20)	H_2SO_4 (12)	1,4-dioxane	60	1.0	84
10	**PPA (20)**	**H_2SO_4 (12)**	**1,4-dioxane**	**60**	**1.5**	**92**
11	PPA (20)	H_2SO_4 (12)	1,4-dioxane	60	2.0	91
12[d]	PPA (20)	HCl (12)	1,4-dioxane	60	1.5	3
13	PPA (20)	H_3PO_4 (12)	1,4-dioxane	60	1.5	9
14	PPA (20)	HNO_3 (12)	1,4-dioxane	60	1.5	2
15	PPA (20)	AcOH (12)	1,4-dioxane	60	1.5	10
16	PPA (20)	H_2SO_4 (12)	EtOH	60	1.5	/
17	PPA (20)	H_2SO_4 (12)	THF	60	1.5	/
18	PPA (20)	H_2SO_4 (12)	DMSO	60	1.5	/
19	PPA (20)	H_2SO_4 (12)	DMF	60	1.5	/

[a] Reagents and conditions: **1a** (0.1 mmol), **2a** (0.16 mmol), solvent (2 mL). [b] Isolated yield. [c] H_2SO_4 (98% concentrated sulfuric acid). [d] HCl (36.5% concentrated hydrochloric acid).

Results and Discussion

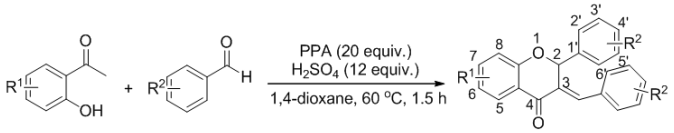
Our initial studies were carried out with readily available 2-hydroxy-5-methyacetophenone **1a** and benzaldehyde **2a** as test substrates. A mixture of **1a** (1 equiv.), **2a** (1.6 equiv.), PPA (15 equiv.) and H_2SO_4 (4 equiv.) in 1,4-dioxane was stirred at 90 °C for 1 h under an air atmosphere to give the desired product **3a** in 28% yield (Table 1, entry 1). Control experiments were performed in the absence of either PPA or H_2SO_4 (Table 1, entries 2-3). The results showed that PPA and H_2SO_4 were essential for the formation of the desired product **3a**. Increasing the amount of PPA resulted in a higher yield (Table 1, entry 4). However, further increasing the amount of PPA to 25 equiv. had no obvious effect on the reaction (Table 1, entry 5). To our delight, we found that increasing the amount of H_2SO_4 to 12 equiv. further increased the yield (Table 1, entry 6). However, a decreased yield was observed upon increasing the amount of H_2SO_4 to 16 equiv. (Table 1, entry 7). We then investigated the impact of the temperature and found that 60 °C was the best choice (Table 1, entries 8-9). Subsequently, further screening of the reaction time showed that the yield could be improved when the reaction time was increased to 1.5 h (Table 1, entry 10). However, further increasing the reaction time (2.0 h) led to a slight reduction in the yield (Table 1, entry 11). When concentrated hydrochloric acid (HCl), H_3PO_4, HNO_3 or AcOH was used instead of H_2SO_4, product **3a** was obtained in low yields (Table 1, entries 12-15). Unfortunately, the reactions performed in EtOH, THF, DMSO or DMF did not give the desired product **3a** (Table 1, entries 16-19). The optimized reaction conditions were determined as **1a** (1 equiv.), **2a** (1.6 equiv.), PPA (20 equiv.) and H_2SO_4 (12 equiv.) in 1,4-dioxane at 60 °C for 1.5 h under an air atmosphere (Table 1, entry 10).

As shown in Table 2, the reaction represents a general method to construct different substituted 3-benzylideneflavanones. Notably, the electronic properties of the substituents have an effect on the reaction. Electron-donating groups (Me, OMe and OH) on the 2-hydroxyacetophenones and/or the aromatic aldehydes provided the highest yields (Table 2, entries 1-2, 6-8). 2-Hydroxyacetophenone also reacted with benzaldehyde to give the desired product **3e** in good yield (Table 2, entry 5). However, electron-withdrawing groups, such as F, Cl and Br, led to slightly lower yields (Table 2, entries 3-4, 9-16). Aromatic aldehydes with electron-donating or electron-withdrawing groups at the *ortho*-position gave the corresponding products in similar yields compared with aromatic aldehydes substituted at the *para*-position (Table 2, **3c** vs. **3d**, **3f** vs. **3g** vs. **3h**, **3i** vs. **3j**, **3l** vs. **3m** and **3n** vs. **3o)**. Substrates with electron-withdrawing groups gave lower yields (Table 2, entries 12-13 and 16).

The stereochemistry of the 3-benzylideneflavanone derivatives was unambiguously determined from their ^{1}H NMR spectra. The product **3** exist in the *E* form, based on their NMR spectra and in accordance with literature reports.[9] The arylidene proton signal of **3** resonates at a lower field (around 8.00) and was more shielded than the *Z*-isomer. In addition, the NOEs of selected products **3** are shown in the ESI.

Table 2. Evaluation of substrate scope.[a]

Entry	R^1	R^2	Product	
			3	Yield **3** (%)[b]
1	6-Me	H	**3a**	92
2	6-Me	4'-OH	**3b**	87
3	6-Me	2'-Cl	**3c**	80
4	6-Me	4'-Br	**3d**	79



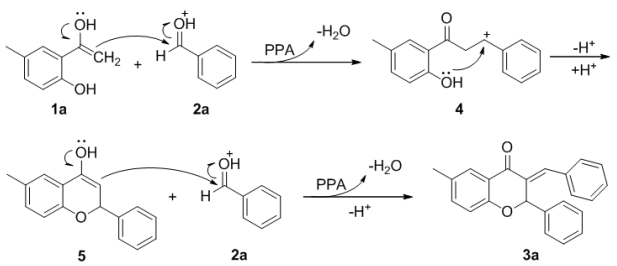
1 2 3

5	H	H	**3e**	85
6	H	4'-OH	**3f**	84
7	H	2'-OMe	**3g**	83
8	H	4'-Me	**3h**	86
9	H	2'-Cl	**3i**	75

10	H	4'-Br	**3j**	78
11	6-Cl	4'-OH	**3k**	77
12	6-Cl	2'-Cl	**3l**	70
13	6-Cl	4'-Br	**3m**	72
14	6-F	4'-OH	**3n**	75
15	6-F	4'-Me	**3o**	79
16	6-F	4'-Br	**3p**	66

[a] Reagents and conditions: **1** (0.1 mmol), **2** (0.16 mmol), 1,4-dioxane (2 mL).

[b] Isolated yield.



Scheme 1. Plausible mechanism for the one-pot synthesis of (*E*)-3-benzylideneflavanones.

A plausible mechanism for the one-pot synthesis of (*E*)-3-benzylideneflavanones is depicted in Scheme 1. PPA promotes the condensation of 2-hydroxyacetophenone **1a** with benzaldehyde **2a** to form intermediate **4**, which after subsequent cyclisation gives intermediate **5**. Finally, the PPA promoted condensation of intermediate **5** with benzaldehyde **2a** leads to the desired product **3a**.

Conclusion

In summary, we have developed an efficient one-pot method for the preparation of (*E*)-3-benzylideneflavanones using 2-hydroxyacetophenones and aromatic aldehydes as the starting materials.

Acknowledgments

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:

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- benzylideneflavanones.
- Moderate to good yields of the products.
- Experimentally simple procedures working under air.
- Simple starting materials.