### Tetrahedron Letters 52 (2011) 3120-3123

Contents lists available at ScienceDirect

**Tetrahedron** Letters

journal homepage: www.elsevier.com/locate/tetlet

## An efficient one-pot synthesis of flavones

Chin Fei Chee<sup>a</sup>, Michael J. C. Buckle<sup>b,\*</sup>, Noorsaadah Abd. Rahman<sup>a</sup>

<sup>a</sup> Department of Chemistry, University of Malava, 50603 Kuala Lumpur, Malaysia <sup>b</sup> Department of Pharmacy, University of Malaya, 50603 Kuala Lumpur, Malaysia

ARTICLE INFO	A B S T R A C T			
Article history: Received 1 November 2010 Revised 18 March 2011 Accepted 4 April 2011 Available online 12 April 2011	Flavones were prepared using a one-pot procedure starting from the corresponding 2'-hydroxyacetoph- enones. The latter were treated with 3 equiv of aroyl chloride in wet K <sub>2</sub> CO <sub>3</sub> /acetone (1% w/w water) to afford a good yield of flavone and a smaller amount of 3-aroylflavone. Evidence was obtained that the reaction proceeds via a triketone intermediate. When the reactants were heated in 1,8-diazabicy- clo[5.4.0]undec-7-ene (DBU) and pyridine, the 3-aroylflavone was obtained exclusively. Use of a stoichi- ometric amount of aroyl chloride afforded only the corresponding flavone.			

Flavones are a class of natural products that are known to possess anti-oxidant activity, as well as a wide range of other pharmacological properties.<sup>1</sup> One of the classical methods for the preparation of their  $\gamma$ -pyrone structure is via the Baker–Venkataraman rearrangement.<sup>2</sup>

Recent reports on one-pot syntheses of flavones using modified Baker-Venkataraman reactions have caught our attention. In particular, Riva et al. found that heating acetophenones 1 and an equivalent amount of acyl chloride in the presence of 2 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dry pyridine produced the corresponding  $\gamma$ -pyrones **2** in reasonable yields (Scheme 1).<sup>4</sup> Ganguly et al. extended this work by using 3 equiv of both the acyl chloride and DBU to produce the corresponding 3-acylflavones, together with the phenolic esters in some instances.<sup>5</sup> On the other hand, Boumendjel and co-workers heated 2',6'-dihydroxyacetophenone 3d with 1 equiv of benzoyl chloride in the presence of potassium carbonate in dry acetone to produce 5-hydroxyflavone 4g, together with a small amount of the corresponding phenolic ester **5** (Scheme 2).<sup>6</sup> However, acetophenones with no OH group or with a masked OH group at the 6'-position did not give flavones.

Intrigued by the above observations, we decided to screen a variety of parameters for the reaction of 2'-hydroxyacetophenone (3a) and benzovl chloride, including the use of different solvents, bases, and temperatures (Table 1).

Predictably, we found that the use of excess benzoyl chloride generally led to the formation of 3-benzoylflavone (6a) as the major product (Table 1, entries 4-6 and 11), while the use of a stoichiometric amount of benzoyl chloride gave only flavone 4a (entries 3 and 10). In the absence of base (entries 1 and 2) or when triethylamine (Et<sub>3</sub>N) was used in conjunction with N,N'-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in



(30-55%)

R<sup>1</sup>COCI

DBU, pyridine

60-100 °C

dichloromethane (entry 7), only the ester, 2'-benzoyloxyacetophenone, was obtained. Employing the stronger bases potassium tertbutoxide (KOtBu/THF,<sup>7</sup> entry 8) or sodium hydride (NaH/THF, entry 9) led to the formation of the intermediate  $\beta$ -diketone, 1-(2hydroxyphenyl)-3-phenyl-1,3-propanedione.

However, a surprising change was observed when 2'-hydroxyacetophenone was heated with excess benzoyl chloride in an open K<sub>2</sub>CO<sub>3</sub>/acetone system (entry 12): the yield of flavone 4a increased to 65% compared to 12% with a nitrogen-bubbling system (entry 11).

The proposed mechanism for the formation of flavone 4a and 3-benzoylflavone (6a) is shown in Scheme 3. When 2'-hydroxyacetophenone (**3a**) was treated with benzoyl chloride and  $K_2CO_3$ ,





2011 Elsevier Ltd. All rights reserved

 $R^1$  = aliphatic or aromatic

= CH<sub>3</sub> or H

= ester or olefin

<sup>\*</sup> Corresponding author. Tel.: +60 3 79676658; fax: +60 3 79674964. E-mail address: buckle@um.edu.my (M.J.C. Buckle).

<sup>0040-4039/\$ -</sup> see front matter © 2011 Elsevier Ltd. All rights reserved. doi:10.1016/j.tetlet.2011.04.022

Screening of the reaction conditions<sup>a</sup>

		OH PhCC condition 3a	DCI Dons O 4a	+ $0$ $0$ $0$ $0$ $6a$	
Entry	Base (equiv)	Solvent	Temp (°C)	Benzoyl chloride (equiv)	Product; yield <sup>b</sup> (%)
1	_	Pyridine	110	1	d
2	_	Pyridine	110	3	d
3	DBU (3)	Pyridine	110	1	<b>4a</b> (25)
4	DBU (3)	Pyridine	110	3	<b>6a</b> (55)
5	KOH (3)	Pyridine	110	3	<b>6a</b> (50)
6	$K_2CO_3$ (10)	Pyridine	110	3	<b>6a</b> (40)
7	$Et_3N(5)^c$	CH <sub>2</sub> Cl <sub>2</sub>	rt	3	d
8	KOtBu (3)	THF	-78 to rt	3	e
9	NaH (3)	THF	-78 to rt	3	e
10	$K_2 CO_3 (10)^{f}$	Acetone	60	1	<b>4a</b> (5)
11	$K_2CO_3$ (10)	Acetone	60	3	<b>4a</b> (12), <b>6a</b> (47)
12	$K_2CO_3 (10)^{f}$	Acetone	60	3	<b>4a</b> (65), <b>6a</b> (20)

<sup>a</sup> All reactions were allowed to run for 24 h using acetophenone (1 mmol) under an N<sub>2</sub> atmosphere (except where stated below).

<sup>b</sup> Isolated yield calculated from 2'-hydroxyacetophenone.

<sup>c</sup> In the presence of DCC (2 equiv) and DMAP (2 equiv).

<sup>d</sup> Only formation of the ester 2'-benzoyloxyacetophenone was observed.

<sup>e</sup> Only formation of the -diketone 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanedione was observed.

<sup>f</sup> The reaction was carried out in open atmosphere.



Scheme 3.

addition of the first equivalent of benzoyl chloride produces 2'-benzoyloxyacetophenone (**8**).<sup>8</sup> In the presence of a base, the enolate of the acetyl group is formed and attacks the carbonyl of the ester to give the hemiacetal **9**, which may either dehydrate to produce flavone **4a** or undergo ring-opening to give the  $\beta$ -diketone **10a**, the Baker–Venkataraman rearrangement product. In an excess of benzoyl chloride, the phenolic group of  $\beta$ -diketone **10a** undergoes esterification with another equivalent of benzoyl chloride to form benzoyloxydiketone **11**.<sup>8,9</sup> Rearrangement of the benzoyloxydiketone **11** gives triketone intermediate **12** which finally cyclodehydrates to produce 3-benzoylflavone (**6a**) via hemiacetal **13**.

While it is known that  $\beta$ -diketones such as **10a** are readily cyclised by heating in strongly acidic medium such as (HOAc/cat. H<sub>2</sub>SO<sub>4</sub>) or BF<sub>3</sub>·Et<sub>2</sub>O, cyclisation under basic conditions is uncommon, although it has been known to occur in methanolic KOH.<sup>2</sup> However, we observed the formation of flavones during the onepot Baker–Venkataraman reaction in the K<sub>2</sub>CO<sub>3</sub>/acetone system even without acidification of the crude product in the work-up. The presence of a flavone in the reaction mixture was further verified by GC–MS, whereby portions were sampled and the molecular weight of each compound was determined. The results revealed that compounds **8**, **10a**, **11**, **6a** and **4a** all existed during the course of the reaction, but it was unclear whether the formation of flavone **4a** occurred via the cyclisation of 2'-benzoyloxyacetophenone **8** or  $\beta$ -diketone **10a**, or from cleavage of the benzoyl group from 3-benzoylflavone (**6a**).

A control experiment was, therefore, performed by heating  $\beta$ diketone **10a** in an open K<sub>2</sub>CO<sub>3</sub>/acetone system in the absence of benzoyl chloride and the reaction was again monitored by GC– MS. The result revealed that  $\beta$ -diketone **10a** slowly cyclised to form flavone **4a** (10% yield after treatment for 24 h).<sup>10</sup> When the control experiment was performed on ester **8** instead, GC–MS showed the formation of  $\beta$ -diketone **10a** and flavone **4a**. Thus, cyclisation of  $\beta$ diketones under basic conditions is possible, but only occurs slowly. Hence the formation of flavone **4a** in low yield in reactions using 1 equiv of benzoyl chloride can be explained (Table 1, entries 3 and 10).

However, this explanation is not sufficient to account for the higher yields of flavone that were obtained using 3 equiv of benzoyl chloride in the open  $K_2CO_3$ /acetone system. Another control experiment was, therefore, performed by heating 3-benzoylflavone







Scheme 5.





# Table 2 Yields and melting points of the flavones 4 and 3-aroylflavones $\mathbf{6}^{a}$

Entry	Flavone <sup>b</sup> (yield %)	mp (°C)		3-Aroylflavone <sup>b</sup> (yield %)	mp	(°C)
		Found	Reported		Found	Reported
1	<b>4a</b> (60%)	99	99 <sup>12a</sup>	<b>6a</b> (20%)	132	121–122 <sup>5a</sup>
2	<b>4b</b> (55%)	243	241-242 <sup>5a</sup>	<b>6b</b> (19%)	265	270–271 <sup>5a</sup>
3	<b>4c</b> (63%)	263	260-263 <sup>12b</sup>	6c (12%)	Amorphous	-
4	<b>4d</b> (60%)	280	268-270 <sup>12b</sup>	<b>6d</b> (16%)	Amorphous	-
5	<b>4e</b> (51%)	232	235.5-236.5 <sup>12c</sup>	<b>6e</b> (23%)	162	-
6	<b>4f</b> (58%)	160	158-159 <sup>12d</sup>	<b>6f</b> (11%)	174	177-178 <sup>12d</sup>
7	<b>4g</b> (53%)	285	284–285 <sup>5a</sup>	<b>6g</b> (19%)	190	193–194 <sup>5a</sup>

<sup>a</sup> All products were identified by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy.

<sup>b</sup> Isolated yield calculated from the corresponding acetophenone.

(**6a**) in an open K<sub>2</sub>CO<sub>3</sub>/acetone system to afford a 35% yield of flavone **4a**.<sup>11</sup> It, therefore, appears that the open K<sub>2</sub>CO<sub>3</sub>/acetone system absorbs moisture from the air and thus enables cleavage of the 3-benzoyl moiety (compare entries 11 and 12 in Table 1).

We also found that heating the  $d_5 \beta$ -diketone **10b** and an equivalent amount of benzoyl chloride in pyridine or K<sub>2</sub>CO<sub>3</sub>/acetone gave a mixture of  $d_5$  3-benzoylflavones **6h** and **6i** which were deacylated un-

der one-pot conditions to produce  $d_5$  flavone **4h** and flavone **4a** (Scheme 4). We obtained a 1:1 mixture of products **6j** and **6k** by heating either  $\beta$ -diketone **10a** with cinnamoyl chloride in pyridine or 1-(2hydroxyphenyl)-3-styryl-1,3-propanedione (**10c**) with benzoyl chloride in pyridine (Scheme 5). These findings provide evidence that the reaction does indeed proceed via a triketone intermediate which can undergo ring closure by two possible pathways. Upon further investigation of the reaction conditions, we found that addition of an excess of benzoyl chloride in wet  $K_2CO_3/acetone$  (containing 1% w/w water) gave essentially the same ratio of products as that found with the open  $K_2CO_3/acetone$  system. Various combinations of 2',4'-dihydroxy-, 2',5'-dihydroxy-, 2',6'-dihydroxy-, and 2',4',6'-trihydroxyacetophenones and aroyl chlorides **7a–c** gave flavones **4a–g** (51–63%) and 3-aroylflavones **6a–g** (11–23%) (Scheme 6). These results suggested that the presence of an additional OH group at the 6'-position of the 2'-hydroxyacetophenone was not a requirement for the formation of flavones, in contrast to the findings of Boumendjel.<sup>6</sup> Table 2 shows the different flavones and 3-aroylflavones prepared by this method and the yields obtained.

In summary, we have investigated the reaction between 2'hydroxyacetophenone and aroyl chlorides under different conditions. We found that when 2'-hydroxyacetophenone was heated with a stoichiometric amount of aroyl chloride, either in a DBU/ pyridine system or in an open  $K_2CO_3/acetone$  system, only the flavone was obtained, but in modest yield. However, when heated with excess aroyl chloride in a DBU/pyridine system, the 3-aroylflavone was the only product, while treatment in an open  $K_2CO_3/$ acetone system afforded the flavone as the major product along with a smaller amount of 3-aroylflavone. Control experiments under the latter conditions gave evidence that the reaction proceeds via a triketone intermediate. An extension of the method using wet  $K_2CO_3/acetone (1\% w/w water)$  has been successfully applied to the synthesis of flavones bearing a variety of substituents.

#### Acknowledgements

This work was supported by grants from the Ministry of Science, Technology and Innovation (Science Fund) and the Ministry of Higher Education (Fundamental Research Grant Scheme). We would also like to thank Professor Naresh Kumar for giving C.F.C. the opportunity to carry out some of this work at UNSW, Sydney.

#### Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.04.022.

### **References and notes**

- Middleton, E., Jr.; Kandaswani, C.; Theoharides, T. C. Pharmacol. Rev. 2000, 52, 673.
- 2. Baker, W. J. Chem. Soc. 1933, 1381.
- 3. Mahal, H. S.; Venkataraman, K. Curr. Sci. 1933, 2, 214.
- Riva, C.; DeToma, C.; Donadd, L.; Boi, C.; Pennini, R.; Motta, G.; Leonardi, A. Synthesis 1997, 195.
- (a) Ganguly, A. K.; Kaur, S.; Mahata, P. K.; Biswas, D.; Pramanik, B. N.; Chan, T. M. *Tetrahedron Lett.* **2005**, *46*, 4119; (b) Ganguly, A. K.; Mahata, P. K.; Biswas, D. *Tetrahedron Lett.* **2006**, *47*, 1347.
- 6. Bois, F.; Beney, C.; Mariotte, A. M.; Boumendjel, A. Synlett 1999, 1480.
- Ares, J. J.; Outt, P. E.; Kakodkar, S. V.; Buss, R. C.; Geiger, J. C. J. Org. Chem. 1993, 58, 7903.
- Although β-ketoesters are expected to be mainly in the enolate form under the reaction conditions, they are represented here in the keto form for clarity.
- This is in contrast to Baker's hypothesis that the acylation of a β-diketone might be expected to occur on the methylene carbon atom to give the triketone intermediate directly.
- A higher conversion rate could be achieved by heating compound 10a in a DBU/pyridine system (90% conversion after 8 h treatment).
- Heating the pure compound 6a in NaHCO<sub>3</sub> satd/MeOH for 2 h gave flavone 4a in 85% yield.
- (a) Jain, P. K.; Makrandi, J. K.; Grover, S. K. Synthesis **1982**, 221; (b) Costantino, L.; Rastelli, G.; Albasini, A. Eur. J. Med. Chem. **1996**, 31, 693; (c) Looker, J. H.; Hanneman, W. W. J. Org. Chem. **1962**, 27, 381; (d) Looker, J. H.; Hanneman, W. W. J. Org. Chem. **1962**, 27, 3261.