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COMMUNICATION

Ionic liquid mediated Cu-catalyzed cascade *oxa*-Michael-oxidation: efficient synthesis of flavones under mild reaction conditions†

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Flavonoids are a class of natural products, found in a wide range of vascular plants and dietary components. Their low toxicity and extensive biological activities, including anti-cancer and anti-bacterial, have made them attractive candidates to serve as therapeutic agents for many diseases. Herein, we disclose a highly efficient synthetic method of CuI-catalyzed cascade oxa-Michael-oxidation, using chalcones as substrates, mediated by the ionic liquid [bmim][NTf2] at a low temperature. This efficient synthetic method has demonstrated high synthetic utility and can afford flavones in good to high yields (up to 98%).

Introduction

Flavonoids and isoflavonoids are a class of natural product that is found in various vascular plants and dietary components,[1] including vegetables, soy beans, nuts and fruits. Their low toxicity and extensive biological activities, including anti-tumor, anti-cancer, anti-fungal, anti-oxidant, anti-inflammatory, anti-bacterial, anti-viral, anti-mutagenic, anti-allergic, cardiovascular and DNA cleavage, make them attractive as possible therapeutic compounds for many diseases.[2–5] Flavones, oxygen heterocycles containing the 2-phenylbenzopyrone ring backbone, belong to this class of flavanoids. Chrysin[6a–b] (**A**, Fig. 1), a natural flavonoid widely distributed in plants, has been reported to have various biological activities such as anxiolytic and anti-cancer effects. In addition to the inhibitory activity of some flavonoids against COX-1 and/or COX-2,[6c] recent studies have shown that several flavone analogues such as apigenin (**B**, Fig. 1), wogonin (**C**, Fig. 1) and tectorigenin (**D**, Fig. 1) down-regulate COX-2 expression, suggesting a potential for a new class of anti-inflammatory. Besides their biomedical applications mentioned above, they are also useful precursors in the synthesis of other natural products. Rizzacasa and co-workers reported the total synthesis of (–)-episilvestrol, a metabolite that shows potent cytotoxic activity against many human tumor cell lines such as lung, prostate and breast cancer, with flavone as one of the important precursors.[6d–e]

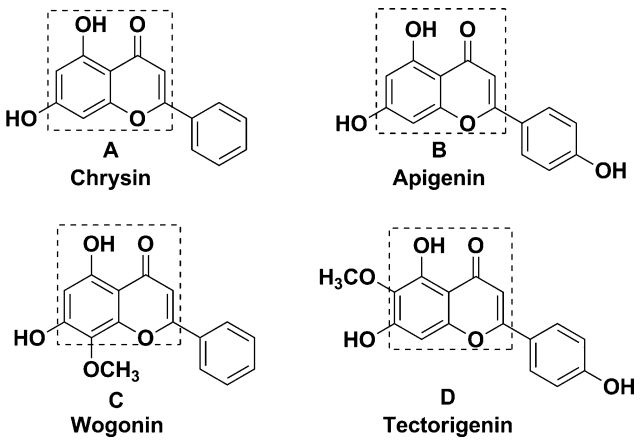

Fig. 1 Examples of naturally occurring flavones.

Although flavones were discovered in the previous century, the diverse biological activities exhibited by them led to the continual discovery and synthesis of flavones. One of the earliest methods in flavone synthesis is represented by the Auwer flavone synthesis which involves a three-step reaction using an alcoholic alkali and a dibromocoumarine.[7] However, the difficulty in preparing the latter derivative led to its limited utility in the organic synthesis of flavones. Some main synthetic methods in the synthesis of flavones[8a–f] include the use of chalcones in dimethylsulfoxide (DMSO) catalyzed by iodine (I_2) under microwave irradiation,[8g] and the cyclization of 1-(2-hydroxyphenyl-3-phenyl-1,3-propanedione) in the presence of copper(II) chloride ($CuCl_2$) under microwave irradiation.[9] Metal catalyzed reactions involving iron[10a] and other metals[10b,c] have also found application in the synthesis of flavones. Despite the existence of many methods for the synthesis of flavones and their derivatives, the development of more efficient novel methods is still an area of importance. Copper mediated reactions are commonly present in total synthesis of natural products. In fact copper was one of the earliest transition metals to be used for that purpose. Hence, this encouraged us to explore the synthesis of flavones with cheap and readily available Cu salts. Meanwhile, Cu catalyzed methods have the potential in large-scale applications because of their tolerance of various functional groups.[11] Herein, we disclose a new efficient method of copper iodide (CuI) catalyzed flavone synthesis under

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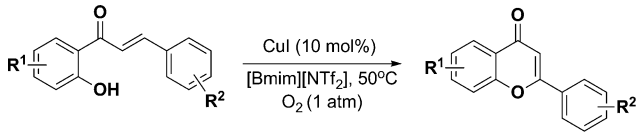
mild conditions that involves a cascade sequence, intramolecular Michael-oxidation (Scheme 1). This method has high synthetic utility as it is simple and the starting substrates, chalcones, can be easily synthesized by aldol condensation.[12] In addition, desired products are obtained in considerably high yields from a variety of substrates. More importantly, this reaction is completed at a low temperature.



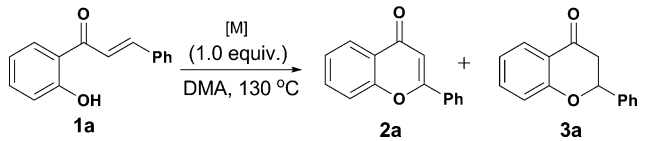
Scheme 1 CuI catalyzed synthesis of flavones.

Results and discussion

Our research was first initiated by investigating the feasibility of the conversion of a simple chalcone (**1a**) into the corresponding flavone (**2a**) by using 1 equivalent of CuI. The reaction was carried out in 2 mL of DMA at 130 °C for 6 h. The desired product (**2a**) was isolated in 71% yield (Table 1, entry 1). This encouraging result prompted us to carry out an initial screen of Cu(I) (Table 1, entries 1 to 5) and Cu(II) (Table 1, entries 6 to 9) metal salts for the reaction.

The experimental results suggested that both Cu(I) and Cu(II) could promote the reaction, but their abilities were undoubtedly affected by the counter anions. In general, copper halides gave the most promising results (Table 1, entries 1 to 3 and 6). CuI, CuBr, CuCl, and $CuCl_2$ gave **2a** in 71%, 20%, 34% and 34% yield respectively. Further, various iron(II) halides (Table 1, entries 10 and 11), iron(III) halides (Table 1, entries 12 to 14) and silver iodide (AgI) (Table 1, entry 15) were then examined. $FeBr_2$ and $FeBr_3$ afforded product **2a** in synthetically useful yields, while

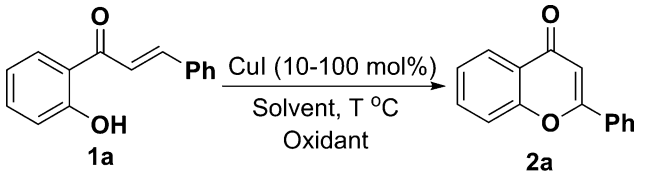
Table 1 Investigation of metal salts[a]



Entry	[M]	*t* (h)	**2a** (%)[b]	**2a′** (%)[b]
1	*CuI*	*6*	*71*	—[c]
2	CuBr	6	20	—[c]
3	CuCl	6	34	—[c]
4	CuOAc	24	—[c]	—[c]
5	CuCN	24	—[c]	60
6	$CuCl_2$	6	34	—[c]
7	$Cu(OAc)_2$	6	16	—[c]
8	$Cu(OTf)_2$	6	22	—[c]
9	$Cu(acac)_2$	6	23	—[c]
10	$FeBr_2$	6	45	—[c]
11	$FeCl_2$	6	12	—[c]
12	$FeBr_3$	6	57	—[c]
13	$FeCl_3$	24	—[c]	72
14	FeF_3	24	—[c]	58
15	AgI	24	—[c]	55

[a] The reactions were performed in 0.2 mmol scale in 2 mL of DMA in the presence of metal salt (1.0 equiv.) at 130 °C. [b] Isolated yield after column chromatography. [c] Not determined.

Table 2 Investigation of other parameters[a]



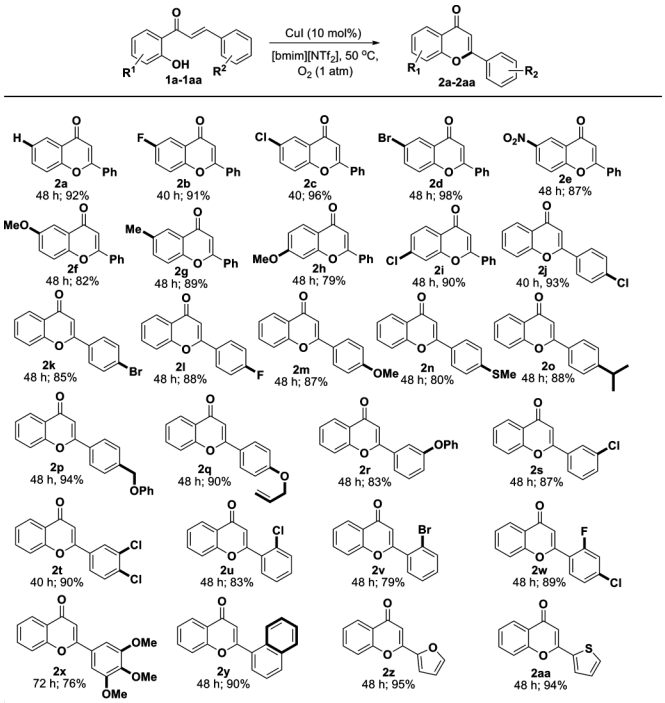
Entry	Solvent	CuI (mol%)	Oxidant	*T*/°C	*t* (h)	**2a** (%)[e]
1	DMA	100%	Air	130	3	71
2	DMF	100%	Air	130	3	69
3	DMSO	100%	Air	130	3	45
4[b]	CH_3CN	100%	Air	90	48	—[d]
5	Acetone	100%	Air	60	48	—[d]
6	DCM	100%	Air	50	48	—[d]
7[c]	MeOH	100%	Air	70	48	—[d]
8	$PhCF_3$	100%	Air	110	48	—[d]
9	Toluene	100%	Air	120	48	—[d]
10	[bmim][Cl]	100%	Air	130	3	67
11	[bmim][Br]	100%	Air	130	3	62
12	[bmim][BF_4]	100%	Air	130	3	73
13	[bmim][PF_6]	100%	Air	130	3	68
14	[bmim][OTf]	100%	Air	130	3	78
15	[bmim][NTf_2]	100%	Air	130	0.5	94
16	[bmim][NTf_2]	100%	Air	80	3	90
17	[bmim][NTf_2]	100%	Air	50	12	97
18	[bmim][NTf_2]	100%	Air	23	48	21
19	*[bmim][NTf_2]*	*20%*	*Air*	*50*	*48*	*65*
20	[bmim][NTf_2]	20%	O_2 (1 atm)	50	24	96
21	***[bmim][NTf_2]***	***10%***	***O_2 (1 atm)***	***50***	***48***	***92***

[a] The reactions were performed in 0.2 mmol scale in 2 mL of solvent in the presence of CuI (1.0 equiv.) and air. [b] **3a** was isolated at 58% yield. [c] **3a** was isolated at 77% yield. [d] Not determined. [e] Isolated yield after column chromatography.

the other iron halides provided poor yields or no yields at all (Table 1, entries 10 and 12, 45% and 57% respectively). Silver iodide (AgI) also did not form **2a** (Table 1, entry 15). However, flavanone **2a′** was formed favourably instead. On the basis of preliminary results, CuI was found to be the most efficient promoter among the various copper salts.

Next, we surveyed several solvents for the reaction. The results were summarised in Table 2. Aprotic solvents like DMA (Table 2, entry 1) and dimethylformamide (DMF) (Table 2, entry 2) afforded similar higher yields, while DMSO (Table 2, entry 3) gave lower yields. Other aprotic solvents like acetonitrile (Table 2, entry 4) and acetone (Table 2, entry 5) did not give our product **2a**. DMA, DMF and DMSO have high boiling points, which allowed the reaction to run at a high temperature of 130 °C and promote the formation of **2a**. Other low boiling point solvents like acetone (Table 2, entry 5) and dichloromethane (DCM) (Table 2, entry 6) did not give **2a** in quantitative amounts. Trifluorotoluene (Table 2, entry 8), despite having a higher polarity and boiling point than DCM, did not promote the reaction. A likely reason is its inability to coordinate to the Cu metal centre with three electron-withdrawing fluorine atoms. Protic solvent methanol favoured the formation of **2a′** over **2a** (Table 2, entry 7), while non-polar solvent toluene (Table 2, entry 9) did not promote the reaction. With all the information obtained, we found that a highly polar solvent supported a better efficiency. However, the reaction temperature is still high in current reaction conditions. To further improve the reaction rate, we wish to seek other superior reaction media. Recently, ionic liquids based

Table 3 Substrate scope



on [bmim]$^+$ are widespread in the literature,[13] being readily prepared and purified and representing a range of observed physical properties.[14] In many of these cases, increases in the reaction rate were noted on moving from a molecular solvent to an ionic liquid.

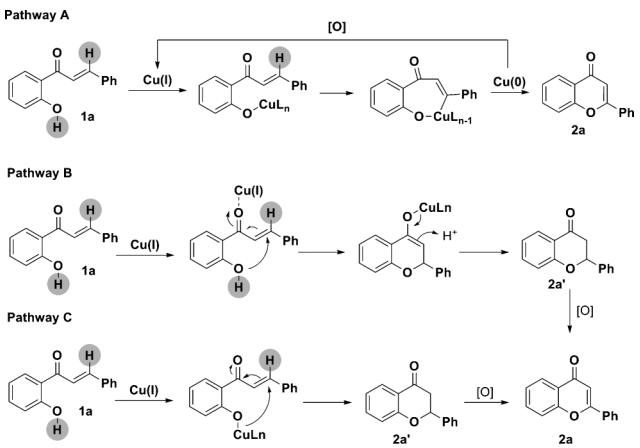
In the next step, we carried out this reaction by ionic liquid screening and the results are shown in Table 2 (entries 10–22). In general, [bmim] based ionic liquids supported moderate to good yields in the presence of CuI (1.0 equiv.) at 130 °C (Table 2, entries 10–14, 3h, 62–78% yield). Gratifyingly, [bmim][NTf_2] promoted this reaction very quickly and afforded a high yield in a short time (Table 2, entry 15, 0.5 h, 94% yield). Following this finding, we wished to see how the temperature affected the reaction rate. In Table 3, entries 16 and 17, both 80 °C and 50 °C gave almost similar high yields even through there required a longer time (90% and 97% yield, 3 h and 12 h, respectively). Unfortunately, a lower temperature would reduce the reaction rate considerably (Table 2, entry 18, 23 °C, 48 h, 21% yield). As a result, the final choice of temperature was 50 °C to reduce the energy consumption and avoid the potential decomposition of substrates at high temperatures.

Our next goal was to use catalytic amounts of CuI to catalyze this reaction. However, 20 mol% CuI only afforded a 65% yield after 48 h at 50 °C (Table 2). We wondered whether the oxidant air affected this reaction rate. To this end, we used molecular oxygen (1 atm) to replace air. As the results shown in Table 2, molecular oxygen accelerated the reaction and afforded a high yield (20 mol% CuI, 50 °C, 24 h, 96% yield). Even when 10 mol% CuI was applied to this system, a 92% yield still could be obtained in a suitable time (50 °C, 48 h).

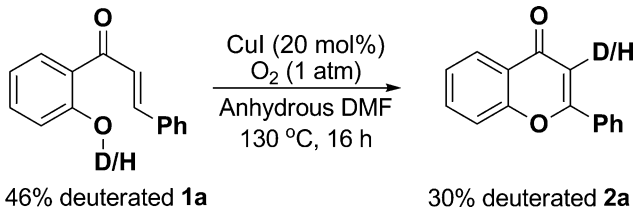
The scope and generality of the process was then investigated under the above optimized conditions. A variety of chalcones can be converted into the corresponding flavones as shown in Table 3. Various functional groups can be tolerated both in the *o*-hydroxy-acetophenone and phenyl fragment, including a large range of halogen substituents. The ability to incorporate the halogen substituents makes this reaction attractive for increasing the molecular complexity by other transition-metal catalyzed coupling reactions. It was found that both electron-withdrawing groups and electron-donating groups at the *para* position of the 2-hydroxy-acetophenone moiety gave higher yields of 82% to 98% (Table 3, **2b–g**). Meanwhile, *meta*- substituted substrates also gave good to high yields (Table 3, **2h** and **2i**; 79% and 90%, respectively).

On the other hand, the positions of the substituent R^2 were generally well tolerated. A variety of R^2 substituents were tolerated on the *para*- position of phenyl ring and gave good to high yields of 80–93% (Table 3, **2j–2q**). In addition, halogen Cl, when positioned at the *ortho*, *meta* and/or *para* position all gave high yields (83–93% yields; **2j**, **2s**, **2t**, and **2u**). Encouraged by these results, we extended our reaction to other interesting heterocycles and excellent yields were obtained (Table 3, **2z** and **2aa**; 95% and 94%; respectively). The scope of substrates possible in this reaction is definitely not limited to those shown in Table 3. Various substituents can be incorporated into both two ring systems, giving rise to a greater variety of products in this reaction. An intermolecular reaction between a simple chalcone and phenol was also attempted under the standard reaction conditions but no desired product was formed.

Three postulated reaction pathways are summarized in Scheme 2. Pathway **A** is the oxidative cross-coupling reaction mechanism. In this process, the molecular oxygen will oxidize Cu(0) to Cu(I) to regenerate the catalyst. To probe the action of this mechanism, an isotope experiment was designed to approve this reaction mechanism. A deuterated chalcone **1a** with 46% deuteration was obtained.[14] The deuterated **1a** was allowed to react in the anhydrous solvent DMF, as shown in Scheme 3. Finally, flavone **2a** with 30% deuteration was isolated after 16 h (NMR results, see ESI†). This suggests that our proposed pathway **A**, oxidative cross-coupling, is not a suitable process under this reaction condition. Furthermore, another two plausible mechanism were proposed in Scheme 2 (pathways **B** and **C**). If molecule **1a** chose pathway **B**, firstly, Cu coordinates to the



Scheme 2 Postulated catalytic pathway for Cu catalyzed reaction.



Scheme 3 Isotope experiment.

carbonyl oxygen of chalcone **1a** to increase the electrophilicity of the conjugated system, which facilitates the later nucleophilic addition to β-carbon. Deprotonation of the hydroxyl proton, followed by intramolecular addition to the C=C leads to the formation of an enolate. The enolate then abstracts a proton to form the intermediate **2a′**. During this process, the active Cu catalytic specie was believed to be regenerated. Lastly, **2a′** is oxidized to **2a** in the presence of CuI and molecular oxygen. It is also possible for CuI to deprotonate the hydroxyl proton of **1a** directly first (pathway **C**), followed by intramolecular conjugate addition to form **2a**. In this process, the CuI catalyzed conjugate addition from **1a** to **2a′** was predicted as the slowest step of the cascade sequence. Once **2a′** was formed, it undergoes oxidation, promoted by CuI and molecular oxygen,[15] to form stable flavone **2a**. To further approve our hypothesis, we started an oxidation reaction from the intermediate **2a′**. As shown in Scheme 4, intermediate **2a′** could be oxidized to final product **2a** under above optimized reaction condition in 18 h and with 93% yield.

Scheme 4 Oxidation of **2a′**.

Conclusions

In conclusion, we have developed an efficient method for the synthesis of substituted flavones derivatives through a Cu(I)-catalyzed cascade intramolecular *oxa*-Michael-oxidation sequence. There is a notable rate enhancement upon going from regular organic solvent to ionic liquid [bmim][NTf_2]. This increase in activity might be partially due to the nature of the solvent used. In addition, a variety of useful functional groups were well tolerated in reaction process. Further applications of this activation mode, with respect to other organic transformations, will be reported shortly together with detailed mechanistic aspects.

Acknowledgements

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