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# Photo-induced tandem cyclization of 3-iodoflavones with electron rich five-membered heteroarenes†

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Vinyl radicals were generated from 3-iodoflavones under a mercury lamp and tandem cyclization reactions occurred with five-membered heteroarenes entailing two consecutive C–C bond formations to synthesize benzo[*e*]chromeno[2,3-*g*]indol-13(1*H*)-one derivatives. The tandem cyclization reactions worked in acetonitrile without any additives such as transition metals, ligands and oxidants, giving rise to a broad variety of novel polycyclic xanthone frameworks in good yield under mild and environmentally friendly reaction conditions.

## Introduction

Flavones are a class of natural products and can be found in numerous plants. They display various biological activities, including antioxidant, anti-tumor, anti-proliferative and anti-inflammatory activities, and have been used in the treatment of cancer, cardiovascular diseases, neurodegenerative disorders, *etc.* Flavones are also an important scaffold for medicinal chemistry and versatile building blocks for the construction of various heteroaromatics.[1–3]

Tandem cyclizations, as a powerful method for the synthesis of polycyclic compounds, have been successfully applied to the Diels–Alder reactions,[4–7] Michael addition,[8] rearrangements[9–11] and radical cyclizations.[12–14] During the last decade, extensive investigations have been made on the photo-induced tandem vinyl radical cyclization, which could build multiple C–C bonds in a single step under mild conditions.[15–17] In 2014, O. Reiser reported a radical tandem addition–cyclization of α-bromochalcones or α-bromocinnamates with heteroarenes using an iridium complex as the catalyst and irradiating with visible light (Scheme 1, top).[15] Similarly, O. Reiser reported a visible light-mediated coupling of α-bromochalcones with alkenes under the visible-light photo-redox conditions in the presence of *fac*-Ir(ppy)$_3$ at room temperature (Scheme 1, middle).[16] In 2017, another transition-metal catalyzed tandem cyclization of vinyl radicals used for the synthesis of substituted indolines was developed *via* a photoredox-mediated reductive quenching cycle (Scheme 1, bottom).[17]

Following our interest in the photo-reactions of chromone analogues[18–21] as well as nucleoside substrates,[22] we herein report a new photo-induced tandem cyclization of 3-iodoflavones with π-excessive five-membered heteroaromatics at ambient temperature without the requirement of any transition-metal-catalyst and/or oxidant additives.

## Results and discussion

Initially, a stirred solution of 3-iodoflavone **1a** (0.2 mmol) and *N*-methylpyrrole **2a** (6 mmol) in DMF (40 mL) was irradiated using a high-pressure mercury lamp (500 W) at room temperature under an argon atmosphere for 5 h. The cyclization product **3a** was isolated (13%) and characterized by NMR and HRMS (Table 1, entry 1). Inspired by this promising result, various solvents, such as THF, *t*-BuOH, Me$_2$CO and MeCN, were screened. However, only a trace amount of the cyclization product **3a** was observed in THF, while the yields of **3a** were slightly increased in other solvents (entries 2–5). In order to avoid the coupling of **1a** with benzene and toluene, such aromatic solvents were not used. As expected, the cyclization yields increased upon increasing the loading of **2a** (entries 6–8). In addition, it was noteworthy that the yield of **3a** dropped to 35% when 0.35 M of **2a** was employed (entry 9), which clearly indicated that solvent free conditions will not work very well. Finally, the irradiation time was optimized and the yield of **3a** was increased to 47% when the reaction time was extended to 7 h (entries 10–14).

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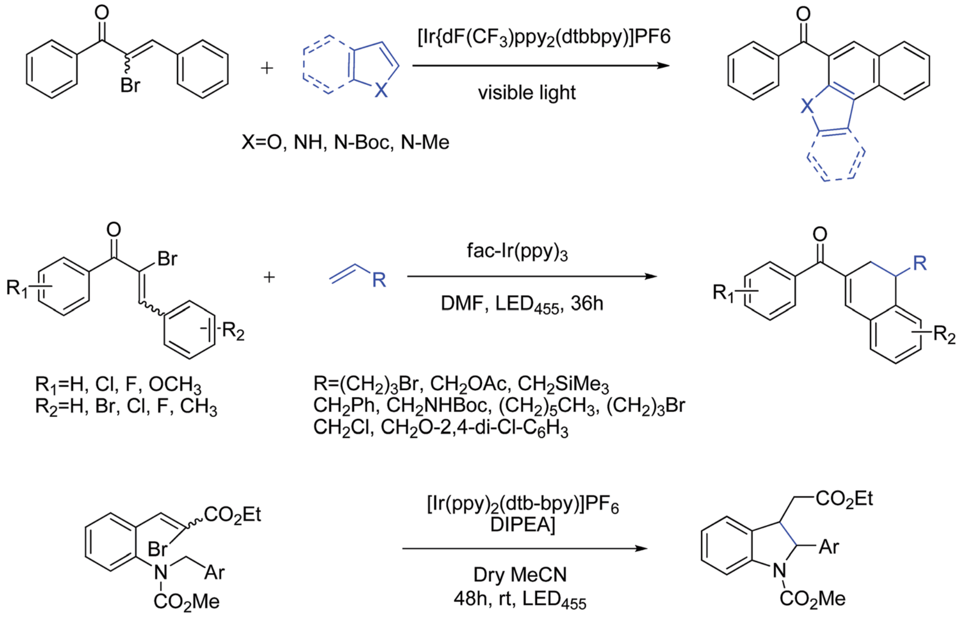
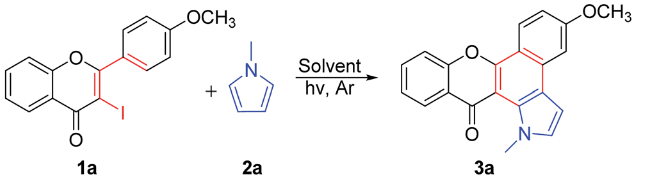


Scheme 1 The reported photo-induced tandem radical cyclization.

Table 1 Optimization of the tandem reaction of 3-iodoflavone **1a** with *N*-methylpyrrole **2a**[a]



| Entry | Solvent | Concentration of **2a** [mol $L^{-1}$] | Time [h] | Yield[b] [%] |
|---|---|---|---|---|
| 1 | DMF | 0.15 | 5 | 13 |
| 2 | THF | 0.15 | 5 | Trace |
| 3 | *t*-BuOH | 0.15 | 5 | 16 |
| 4 | $Me_2CO$ | 0.15 | 5 | 20 |
| 5 | MeCN | 0.15 | 5 | 24 |
| 6 | MeCN | 0.05 | 5 | 15 |
| 7 | MeCN | 0.2 | 5 | 31 |
| 8 | MeCN | 0.25 | 5 | 40 |
| 9 | MeCN | 0.35 | 5 | 35 |
| 10 | MeCN | 0.25 | 1 | 18 |
| 11 | MeCN | 0.25 | 3 | 30 |
| 12 | MeCN | 0.25 | 6 | 43 |
| **13** | **MeCN** | **0.25** | **7** | **47** |
| 14 | MeCN | 0.25 | 10 | 43 |

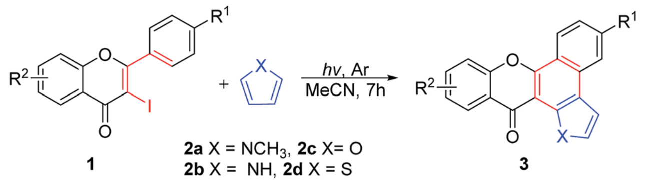
[a] A mixture of **1a** (0.2 mmol, 0.005 M) and **2a** (2–14 mmol, 0.05–0.35 M) in anhydrous MeCN (40 mL) was irradiated using a high-pressure mercury lamp (500 W) at ambient temperature under an Ar atmosphere. [b] Isolated yield.

## Cyclization of 3-iodoflavones with various five membered heteroarenes

In order to screen the scope of the substrates and compatibility of functional groups, various 3-iodoflavones **1** and π-excessive five-membered heteroarenes **2** were screened, and the cyclization yields are listed in Table 2. Thus, irradiation of **1a** and *N*-methylpyrrole **2a** in MeCN using a high-pressure mercury lamp (500 W) at room temperature for 7 h gave **3a** in 47% yield (entry 1). Analogously, treatment of **1b**, bearing an additional methyl group at the $R^2$ position, gave the cyclization product **3b** in a lower yield (entry 2). However, treatment of **1c**, bearing an additional fluoro group at the $R^2$ position, gave the cyclization product **3c** in a higher yield (entry 3). Various combinations of hydrogen, electron-withdrawing and electron-donating groups were explored for the 3-iodoflavone **1** substrates (entries 4–16). As shown in the table, the yields of **3** were significantly affected by the functional groups attached. The presence of electron-donating groups on both $R^1$ and $R^2$ gave the cyclization products **3** in much lower yields (entries 2, 4, 6 and 7) when compared to the substrate bearing only one electron-donating group at either $R^1$ or $R^2$ (entries 1, 5 and 10–11). For example, the yield of **3d** was decreased to 38% when $-OCH_3$ was present at both $R^1$ and $R^2$ (entry 4). On the other hand, the yield of **3** could be easily increased to over 68% with the introduction of an electron-withdrawing group to either $R^1$ or $R^2$ (entries 3, 8 and 13–15).

Various π-excessive five-membered heteroarenes **2** were also explored to examine their compatibility and reactivity (entries 17–19). Thus, irradiation of **1i** with pyrrole **2b** in MeCN at room temperature for 10 h gave the cyclization product **3q** (entry 17). Due to the ring closure for the formation of an aromatic system (*vide infra*), the stability issue[22] was not observed with the current protocol. The cyclization of 3-iodoflavone **1a** also proceeded smoothly with furan **2c** and thiophene **2d** to give the corresponding products in fair yields (entries 18–19). It is noteworthy that no cyclization products were observed for benzene or other six-membered aromatics under the optimal conditions. Generally, the cyclization efficiency follows the electrophilic reactivity *N*-methylpyrrole > pyrrole > furan >

Table 2 Cyclization of different 3-iodoflavones 1 and heteroarenes 2[a]



| Entry | $R^1$ | $R^2$ | 1 | 2 | 3 | Yields[b] [%] |
|---|---|---|---|---|---|---|
| 1 | $OCH_3$ | H | **1a** | **2a** | **3a** | 47 |
| 2 | $OCH_3$ | 6-$CH_3$ | **1b** | **2a** | **3b** | 40 |
| 3 | $OCH_3$ | 6-F | **1c** | **2a** | **3c** | 49 |
| 4 | $OCH_3$ | 7-$OCH_3$ | **1d** | **2a** | **3d** | 38 |
| 5 | $CH_3$ | H | **1e** | **2a** | **3e** | 50 |
| 6 | $CH_3$ | 6-$CH_3$ | **1f** | **2a** | **3f** | 46 |
| 7 | $CH_3$ | $OCH_3$ | **1g** | **2a** | **3g** | 42 |
| 8 | $CH_3$ | 6-F | **1h** | **2a** | **3h** | 56 |
| 9 | H | H | **1i** | **2a** | **3i** | 61 |
| 10 | H | 6-$CH_3$ | **1j** | **2a** | **3j** | 51 |
| 11 | H | 7-$OCH_3$ | **1k** | **2a** | **3k** | 45 |
| 12 | H | 6-F | **1l** | **2a** | **3l** | 66 |
| 13 | F | H | **1m** | **2a** | **3m** | 68 |
| 14 | F | 6-$CH_3$ | **1n** | **2a** | **3n** | 54 |
| 15 | F | 7-$OCH_3$ | **1o** | **2a** | **3o** | 49 |
| 16 | $COOC_2H_5$ | H | **1p** | **2a** | **3p** | 64 |
| 17 | H | H | **1i** | **2b** | **3q** | 40[c] |
| 18 | $OCH_3$ | H | **1a** | **2c** | **3r** | 25 |
| 19 | $OCH_3$ | H | **1a** | **2d** | **3s** | 18 |

[a] A mixture of **1** (0.2 mmol, 0.005 M) and **2** (10 mmol, 0.25 M) in anhydrous MeCN (40 mL) was irradiated using a high-pressure mercury lamp (500 W) at ambient temperature for 7 h under an Ar atmosphere. [b] Isolated yield. [c] Irradiation for 10 h.

thiophene, which can easily explain why no cyclization product was observed for the six-membered aromatics.

## Electrophilic aromatic substitution (EAS)

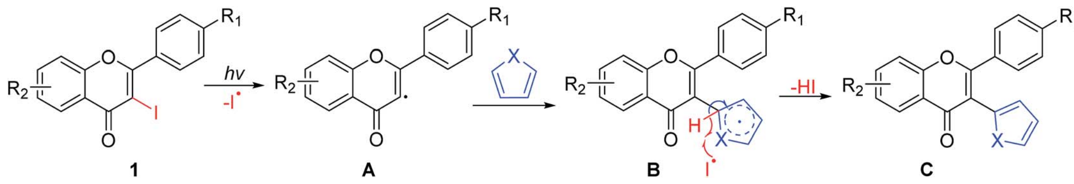
On the basis of the experimental results and literature,[19,20,24,25] a two-step mechanism for the cyclization of 3-iodoflavones **1** with π-excessive five-membered heteroarenes **2** has been proposed. Initially, the photo-induced hemolytic cleavage of the C–I bond of **1** under UV light irradiation gave the radical intermediate **A**. Coupling of **A** with heteroarenes **2** afforded the reactive intermediate **B**, followed by the abstraction of hydrogen with an iodine radical to give the coupling product **C** with the release of HI (Scheme 2).[19,20]

The cyclization step (second step, Scheme 3) started with the UV irradiation of **C** *via* the formation of the ring closed intermediate **D**,[21,23] followed by a thermal suprafacial [1,5]-H shift to form intermediate **E**. Furthermore, keto–enol tautomerization of **E** led to the formation of the enol intermediate **F**, which generated a more stable *syn*-isomer **G** *via* another keto–enol tautomerization.[21–24] Finally, the cyclization product **3** was formed *via* the *syn*-elimination of a hydrogen molecule from intermediate **G** along with the restoration of the aromaticity of the conjugated system.

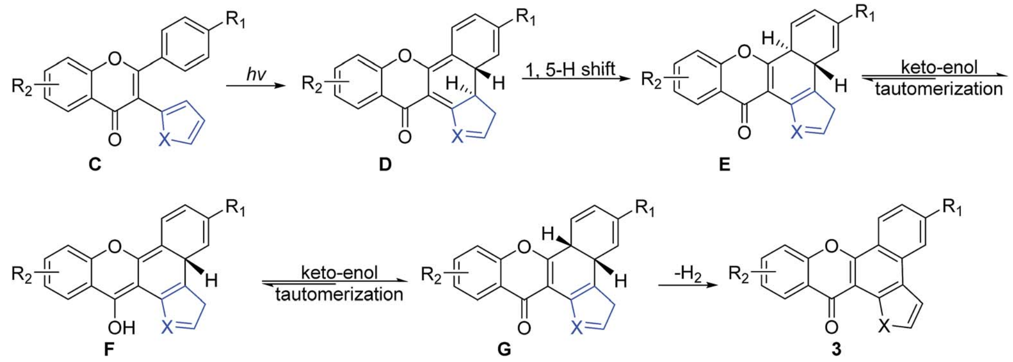
In order to study the importance of keto–enol tautomerization and figure out the rate limiting step, coupling product **1aa** was isolated and subjected to the cyclization conditions separately (Scheme 4). Thus, irradiation of **1a** and **2a** under a high-pressure mercury lamp at ambient temperature for 1 h yielded the coupling product **1aa** with 25% along with a trace amount of the cyclization product **3a**. A solution of **1aa** (5 mM) in MeCN was irradiated under a high-pressure mercury lamp at ambient temperature in parallel with a solution of **1a** (5 mM) and **2a** (0.25 M) in MeCN. After 7 h, substrate **1aa** gave the cyclization product **3a** in 95% yield, while only 47% of **3a** was obtained for 3-iodoflavone **1a**. Thus, we could easily conclude that coupling of 3-iodoflavone with heteroarenes was the rate-limiting step.

To obtain further insight into reaction mechanism pathway and validate the rationality of the proposed mechanism, a substrate without the presence of $C_4{=}O$ was synthesized and subjected to the cyclization conditions. Initially, **1aa** was reduced to **1ab** using $LiAlH_4$–$AlCl_3$ according to the procedure reported in literature[26,27] (Scheme 5). Then, the 4,4-dihydro substrate **1ab** was subjected to the optimal conditions. As expected, no cyclization product **1ac** was detected, which could be explained by the lack of keto–enol tautomerization.

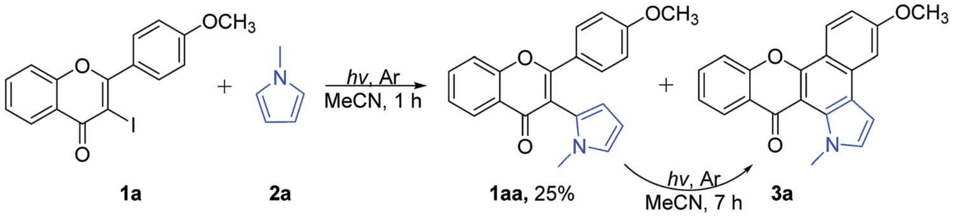
In order to expand the photo-induced tandem cyclization of 3-iodoflavones with π-excessive five-membered heteroarenes methodology to other systems bearing a similar functional moiety, we subjected the (*Z*)-α-bromo-β-phenylvinylketone analogues **4** to our cyclization protocol (Scheme 6). Thus, irradiation of α-bromochalcones **4a** and the pyrrole analogues **2** under the optimal conditions for 10 h yielded **5a** and **5b** in 57% and 42% yield, respectively. Similarly, irradiation of **4b** with pyrrole analogues **2** gave **5c** and **5d** in 47% and 38% yield, respectively. Due to the stabilization of the additional phenyl ring through the larger conjugation system, α-bromochalcone **4a** gave the cyclization product in an improved yield compared to the methyl substrate **4b**. Even though a similar cyclization has been reported,[15] it is important to mention that the current protocol avoids the



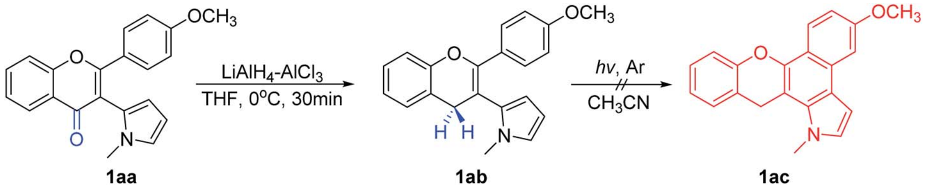
Scheme 2 Proposed mechanism for the preparation of coupling product C.



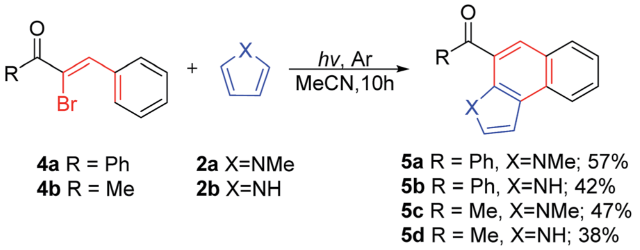
Scheme 3 Proposed mechanism for the preparation of the photocyclization product.



Scheme 4 The stepwise reaction of the tandem cyclization reaction.



Scheme 5 Reductive carbonyl experiments.



Scheme 6 Cyclization of α-bromo-β-phenylvinylketone analogues **4** with pyrrole **2**.

use of transition-metal complexes and high boiling solvent, which could be problematic during the purification stage.

## Conclusion

In conclusion, we have demonstrated a new tandem cyclization protocol for the synthesis of fused heterocyclic aromatic systems *via* the coupling of both 3-iodoflavone and α-bromochalcone derivatives with various π-excessive five-membered heteroarenes. The described methodology provides rapid access to polycyclic xanthones with excellent regioselectivity under mild and environment friendly conditions without the requirement of any catalyst or additives.

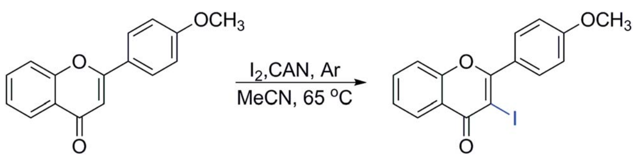
## Experimental section

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. MeCN was distilled from $CaH_2$ just prior to use. Thin-layer chromatography (TLC) was performed using silica gel 60 GF254 plates. The silica gel (size 200–300 mesh) used for the column chromatography was purchased from Qingdao Haiyang Chemistry Plant (China). $^1$H NMR and $^{13}$C NMR spectra were recorded on 400 ($^1$H) and 100 ($^{13}$C) MHz spectrometers. The spectra were referenced internally to $CDCl_3$ or DMSO-$d_6$. High-resolution mass spectrometry (HRMS) was recorded using the electron-spray ionization (ESI) technique. The melting points were measured using X-5 micro-melting point apparatus and were uncorrected. IR spectra were recorded on a Nicolet 170SX FT-IR spectrophotometer using KBr pellets. All the irradiation experiments were performed on a BL-GHX-V photochemical reactor equipped with a 500 W high-pressure Hg lamp.

### General procedure for the preparation of 3-iodoflavones 1[28]

A solution of 2-(4-methoxyphenyl)-4*H*-chromen-4-one (1.0 mmol), $I_2$ (1.2 mmol) and CAN (1.1 mmol) in anhydrous MeCN (100 mL) was stirred at 65 °C (oil/water bath) under an Ar atmosphere until the disappearance of the substrate. After being cooled to ambient temperature, the reaction mixture was poured into a cold solution of $Na_2S_2O_3$ (50 mL, 0.1 M) and extracted with $CH_2Cl_2$ (20 mL, ×3). The organic layers were combined, washed ($H_2O$), dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (hexane : EtOAc = 9 : 1) to afford the desired product **1a** (70%) as a white solid.

Analogously, compounds **1b–1p** were prepared using the same method as described for **1a**.

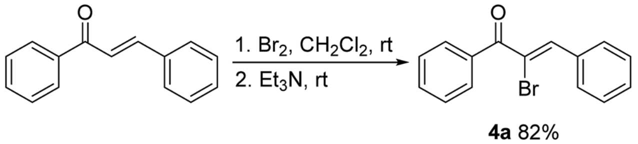


**1a** 70%

### General procedure for the synthesis of α-bromochalcones 4[16]

Bromine ($Br_2$, 4.0 mmol) was added to a stirred solution of chalcone (2.0 mmol) in $CH_2Cl_2$ (40.0 mL) over 10 min at ambient temperature. Triethylamine (10.0 mmol) was slowly added to the resulting mixture when chalcone was completely converted to dibromide (judged by TLC). After stirring for another 12 h, the reaction mixture was extracted with $CH_2Cl_2$ (20 mL, ×3). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$ and the volatiles were removed under reduced pressure. The oily residue was purified using column chromatography to give α-bromochalcone **4a** (82%) as a white solid.

Analogously, **4b** was obtained in 92% yield using the same method described for **4a**.



**4a** 82%

### General procedure for the cyclization of 3-iodoflavones or α-bromochalcones with heteroarenes

A solution of 3-iodo-2-(4-methoxyphenyl)-4*H*-chromen-4-one **1** (0.2 mmol) and *N*-methylpyrrole **2a** (10 mmol) in anhydrous MeCN (40 mL) in a 50 mL quartz tube was degassed (bubbling Ar for 30 min) and irradiated for 7 h using a high-pressure mercury lamp (500 W) at ambient temperature. The volatiles were removed under reduced pressure and the residue was purified using column chromatography (hexane : EtOAc = 20 : 1) to give the corresponding product **3a** (47%) as a white solid.

Analogously, **3b–3s**, **5a–5d** were prepared using the same method described for **3a**.

## Conflicts of interest

There are no conflicts to declare.

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