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DOI: 10.1039/x0xx00000x www.rsc.org/ Visible-light-mediated arylation of *ortho*hydroxyarylenaminones: Direct access to isoflavones.

In this work we are highlighting two new methods for the synthesis of isoflavones through consecutive domino arylation of *ortho*-hydroxyarylenaminones with *in situ* photo-generated aryl radicals. As precursors for aryl radicals we used aryl onium reagents such as diazonium and diaryliodonium salts. Of note, the photo-Meerwein arylation by aryl diazonium tetrafluoroborates demonstrated high efficiency in terms of yields and can be considered as a method of choice for the straightforward assembling of 3-aryl-substituted chromones. Quintessential, utilising the developed synthetic protocols 26 compounds were prepared in good to excellent yields.

Chromones are important privileged heterocycles, abundant not only in the nature in the form of numerous natural compounds but have also gained wide-spread applications in life science, drug discovery, food industry, and health-related domains of human life.¹ Isoflavonoids (3-arylchromones) are compounds which found numerous applications in medicines and food production.²



Scheme 1. (a-d) Literature known tactics for 3-substituted chromones based on photoredox catalysis; (e) Our concepts. Owing to the importance of these heterocycles, works presenting new conceptual synthesis of chromones in general and 3-arylchromones in particular are still keep receiving an enormous interest. There is a growing demand in cost-effective and efficient methods enabling rapid and straightforward assembling of chromone framework with different substitution patterns. Constantly growing attention and efforts are aimed at the search of new, concise and atom economic routes towards this interesting heterocyclic system. For a long time 3-arylchromones, as well as many other chromone-based drug-like heterocycles, were only available from natural sources; later, however, by the limited set of obsolete cyclisation reactions.^{1a, 3} Nowadays, bright spectrum of C-C coupling protocols⁴ including Suzuki,⁵ Neghishi,⁶ Stille,⁷ employing 3-halochromones as precursors were successfully utilised for the facile preparation of those compounds.

The direct C-H functionalisation of 2,3-unsubstituted chromones was also employed as an efficient strategy enabling the construction of diverse 3-substituted chromones, such as 3-acyloxyl, 3-alkyl, 3perfluoroalkyl, 3-vinyl, 3-alkynyl, 3-chalcogenyl chromone derevatives.⁸ Very recently we have communicated arylselenation of 2,3-unsubstituted chromones via Cu-catalysed direct C–H activation protocol using elemental Se and aryl iodides, which leveraged the corresponding 3-substituted chromones.⁹ Unfortunately, 3arylchromones, due to the innate inherent regioselectivity, cannot be prepared by the direct C-3 C-H arylation of 2,3-unsubstituted chromones using the range of arylation agents; instead, the 2arylchromones were detected as only isolable products.¹⁰ However, due to the C-2 selectivity for the mentioned arylation protocol, the efforts to establish alternative synthetic routes aiming at the straightforward and concise preparation of 3-arylchromones is nowadays one of the privileged tasks in the current field. Thus, the chromone ring construction very often entails consecutive domino reactions initiated bv the cvclisation of orthohydroxyarylenaminones triggered by numerous hard and soft electrophiles¹¹ as well as radicals.¹² Very recently, during the preparation of this manuscript, emerged a work which highlights the use of the Pd-promoted oxidative C-H bond arylation of orthohydroxyarylenaminones by arylboronic acids.¹³ The above

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mentioned tactics were successfully utilised to prepare myriads of 3-substituted chromone derivatives decorated with vast range of substituents and functional groups.

As the electrophile-triggered of orthocvclisation hydroxyarylenaminones studied very well, the corresponding radical-mediated processes involving carbon-centred radicals are scarcely presented in the modern literature, to the best of our knowledge by four examples only, those are depicted on the Schemes 1a-d.^{8d, 14} Of note, the methods for efficient radical arylation of ortho-hydroxyarylenaminones are scarce. Since the application of organic radicals in contemporary synthetic organic chemistry, in particularly with the advent of photoredox catalysis in the recent years, has gained new momentum, the studies on the application of carbon-centred radicals in the synthesis of 3arylchromones are of current synthetic interest and urgent importance.15



Scheme 2. Model reactions for reaction conditions optimization.

Aryl radicals can be generated by different light driven means from vast range of substrates. For instance, in recent years diazonium salts, diaryliodonium salts, sulfonium salts, aryl sulfonyl chlorides etc. were intensively utilised in the photoredox radical-promoted introduction of aryl substituents.¹⁵ In light of the known methods to transform *ortho*-hydroxyarylenaminones into chromones, we had a notion to study 3-arylchromone synthesis by the reactions between the *in situ* photogenerated aryl radicals and *ortho*-hydroxyarylenaminones. We surmised that this synthetic scenario (1) is of no need of substrate prefunctionalisation, (2) uses the readily available reagents, might visibly improve the preparation of 3-arylchromones.

Herein, in continuation of our work on developing new methods for the preparation of structurally diverse chromone derivatives with different substitution patterns^{12, 16}, we describe, for the first time, two unprecedented domino cyclisation scenarios, wherein the *ortho*- hydroxyarylenaminone substrates react with photogenerated from aryl onium salts aryl radicals (Scheme 2). The starting form of this study was to identify the appropriate reaction conditions for efficient preparation varieties of 3-arylchromones following the appointed synthetic scenarios. For this we set two model reactions and focused our efforts on the elaboration of the optimised reaction conditions (Schemes 2a, b). The tables illustrating the general logic used for the reaction conditions optimisation are given in the Supporting Information (Tables 1S, 2S). It has been revealed that (1) photo-Meerwein arylation of *ortho*-hydroxyarylenaminones by aryl diazonium tetrafluoroborates proceeded smoothly under the catalysis of Eosin Y I; (2) the arylation by diaryliodonium triflates underwent with high efficiency being catalysed by $Ru(bpy)_3Cl_2*6H_2O$ IV.



Scheme 3. Product scope for the synthesised of 3-arylchromones.

As outlined in the Scheme 3a, model *ortho*-hydroxyarylenaminone reacts smoothly with 4-fluorobenzenediazonium tetrafluoroborate affording the corresponding chromone product **4cp** in 86% yield (Table 1S, Entry 4). The optimised reaction conditions for this transformation consisted in use of 1.3 equiv. of salt **2p**, Eosin Y I photocatalyst (3 mol%), in DMSO, under the intensive irradiation with green light (The best efficiency was observed for 24 Wat green LED stripes), the reaction reaches its completion within 3 hours at

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room temperature under argon atmosphere. On the other hand, encouragingly, the 3-arylchromone 4cp can be also prepared in 80% yield following the route of the Scheme 3b by a reaction between ortho-hydroxyarylenaminone and diaryliodonium triflate 3p (1.5 equiv.), applying Ru(bpy)₃Cl₂*6H₂O IV (2 mol%) as catalyst, CH₃CN as solvent within 4 hours at room temperature (Table 2S, Entry 6). For this case the best outcome was obtained when we used 34 Wat Kessil KSH150B Blue LED as a source of blue light. Furthermore, other tested photocatalysts depicted in the Scheme 2, like Porphyrin II and fac-Ir(ppy)₃ III showed catalytic activity for photo-Meerwein arylation as well. For instance, the fac-Ir(ppy)₃ which under the blue light irradiation allowed the preparation of chromone 4cp in 79% yield by using diazonium salt and in 77% by using diaryliodonium salt (Table 1S, Entry 10; Table 2S Entry 2). Furthermore, a range of common Ru-based photocatalysts were tested in line with the given transformation as well. Noteworthy, species V and VI showcased also positive outcomes, however not as positive as complex IV did. (Table 2S, Entries 12, 13). In terms of light sources, the best yields were observed when the strong 24 Wat and 34 Wat irradiation LED sources of green and blue light correspondingly were used. In both cases less powerful light sources were also tested and the model reactions demonstrated high efficiency; however, reducing the power of the light resulted in longer reaction duration. (This data is not presented in the Supporting Information). On the other hand, it should be mentioned that well-defined for such reactions cupper complexes VII and VIII were rigorously studied as well. Unfortunately, these catalysts experienced a failure in application to the title arylation protocols (Table 2S, Entries 14-16).

With the inspired optimal reaction conditions for both presented synthetic scenarios in hand, as next we decided to explore a substrate scope and have evaluated the feasibility of the developed synthetic protocols for the preparation of structurally diverse 3arylchromones. We selected eight ortho-hydroxyarylenaminones 1 which were reacted with twenty-two aryl diazonium tetrafluoroborates 2 and sixteen diaryliodonium triflates 3. To our delight, various diazonium tetrafluoroborates bearing diverse functional groups including Me, Ph, OPh OMe, OEt, F, Cl, Br, CN, NO₂, CF₃, and OCF₃ substituents in ortho-, meta-, para- positions as well as reagent with 1-naphthalenyl residue readily reacted with orthohydroxyarylenaminones decorated by Me, OMe, OEt, F, Cl groups on the benzene ring. Generally, this method displayed satisfactory tolerance to both structural components affording the desired heterocycles in moderate to high yields. Importantly, these methods could be utilised for the preparation of 3-aryl-4H-benzo[h]chromen-4-ones 4hl, 4hq also in excellent yields (Scheme 3). For the second methodology involving the diaryliodonium triflates 3, we generally observed the slightly diminished overall yields. Furthermore, we illustrated gram scale reactions for both methods to prepare compounds 4av, 4ch, 4cp, 4db, 4ef, 4hq (Scheme 3). It is important to mention that besides diaryliodonium triflates the corresponding hexafluorophosphates demonstrated the ability to enter this reaction, thus six compounds (4bg, 4ci, 4cp, 4db, 4fa, 4hq) were prepared without significant deviations in the yields (Scheme 3).

To gain insights into the mechanism and prove that the illustrated routes indeed involve photochemically-generated aryl radicals, the set of control experiments were conducted. Namely, first, we run the reactions under our optimised reaction conditions in dark, as well as

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without photocatalysts, this led to the failure of the reactions (Table 1S, Entries 5, 6; Table 2S, Entries 9, 10). Second the addition of radical quencher such as the 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO 1.5 and 1.7 equiv. respectively) inhibited both reactions through the suppressing the formation of product **4cp**, most likely by trapping most of Ar radicals (Table 1S, Entry 7; Table 2S, Entry 11). These experiments can be accepted as an indication that photochemically-generated radical intermediates are indeed involved in both transformations.



Scheme 4. Proposed mechanism for the synthesis of 3arylchromones by photocatalytic arylation of *ortho*hydroxyarylenaminones by aryl onium salts.

Finally, according to the above illustrated results and literature on visible-light photoredox-catalysed reactions available to date,¹⁵ a plausible reaction mechanism for these visible-light promoted domino cyclisation was proposed and is outlined in the Scheme 4. Initially, under the irradiation by appropriate light source Eosin Y and Ru(II) complex are transferred to their excited states. Under visiblelight conditions the generation of aryl radical (Ar•) from aryldiazonium tetrafluoroborates and diaryliodonium triflates occurs as the first step in the current mechanism sequences catalysed by exited *Eosin Y and *Ru(II) species respectively (Schemes 4a, 4b). Giving more details: The corresponding excited *Eosin Y species undergoes the oxidative quenching by the ArN₂⁺ cation which proceeds according to the major literature data¹⁵ via a single electron transfer (SET) to afford the Ar. The excited triplet state of the *Ru(II) contains an electron located in the higher singly occupied molecular orbital (SOMO), this electron participates in the SET event, thus making the excited *Ru(II) species as an one-electron reductant. Noteworthy, the generation of Ar• by visible-light from Ar₂I⁺ follows the route typical for transition-metal photocatalysts.^{15c,e, 17} Namely, the exited *Ru(II) donates an electron onto Ar₂I⁺. This causes its decomposition to ArI and the Ar•. Subsequently, the formed Ar• undergoes prompt attack on the enaminone to afford the radical intermediate 5 which afterwards is oxidised to carbocation 6 followed by the pyrone ring formation. Finally, after the elimination of dimethylamine from the 2-(dimethylamino)chroman-4-one 7 the chromone framework 4 forms. Similar type of mechanism was very

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recently proposed for the visible-light driven synthesis of 3thiocyanato and 3-polyfluoroalkyl chromones (Scheme 1a-d).¹⁴ In conclusion, we have developed two instrumentally simple, concise and facile routes to structurally diverse 3-arylchromones using photo arylation reactions of ortho-hydroxyarylenaminones by two different reagents, namely the aryldiazonium tetrafluoroborates and the diaryliodonium triflates, utilising as photocatalysts Eosin Y and Ru(bpy)₃Cl₂*6H₂O respectively. In the practical context, these two methods provide the desired products with good to excellent yields, with absolute C-3 selectivity and demonstrated excellent level of functional group tolerance. Comparing these methodologies, it is important to admit that the photo-Meerwein arylation reaction is more efficient esteemed by many parameters: it shows higher yields, utilises less expensive organo photocatalyst; and last but not the least, the aryldiazonium salts are more readily available than the corresponding diaryliodonium salts. Preliminary mechanistic studies indicated that the protocols described above involve free-radical pathways. Future work that should focus on the extension of these concepts to other sources of aryl radicals is currently in progress in our laboratories.

Conflicts of interest

There are no conflicts to declare.

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Graphical Abstract:



The first visible-light-promoted direct synthesis of isoflavones following the arylation of ortho-hydroxyarylenaminones by aryl onium salts was developed.