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DOI: 10.1039/C9CC01801H

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Visible-Light-Driven Copper-Catalyzed Aerobic Oxidative Cascade Cyclization of *N*-Tosylhydrazones and Terminal Alkynes: Regioselective Synthesis of 3-Arylcoumarins

Received 00th January 20xx,
Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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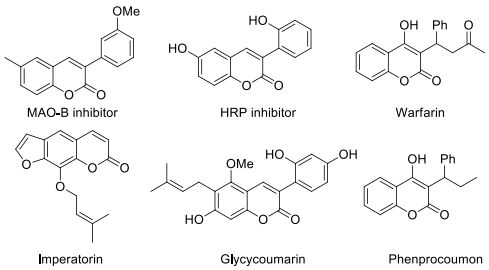
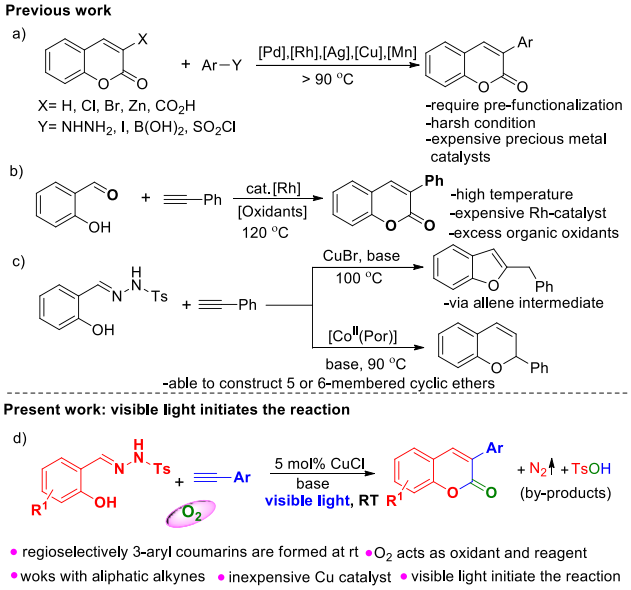
We present the first example of sustainable, intuitive, highly regioselective, visible-light-driven copper catalyzed aerobic oxidative cascade cyclization of *N*-tosylhydrazones with terminal alkynes for the preparation of 3-arylcoumarins at room temperature. This operationally simple methodology has been successfully applied to a wide range of *N*-tosylhydrazones, alkynes (49 examples), and proceeds well to afford biologically active compounds, such as monoamine oxidase B (MAO-B) inhibitor, horseradish peroxidase (HRP) inhibitor in satisfactory yields under mild conditions. Furthermore, mechanistic studies suggest that the reaction proceeds via copper(II)-superoxo or -peroxo complex mediated oxidative annulation of terminal alkynes, as evidenced by $^{18}O_2$ isotopic-labelling experiments.

Direct utilization of readily accessible starting materials on the development of a new and highly efficient synthetic approach for the construction of heterocyclic molecules has become a challenging goal in modern synthetic organic chemistry. Among heterocycles, coumarins are important and ubiquitous structural motifs found in natural products, pharmaceuticals, photochemotherapy, photosensitizers, flavours, and organic luminescent materials.[1] In particular, 3-arylcoumarin skeletons are used as pharmaceutical drugs, such as; anticancer, anti-HIV, antimalarial, antibacterial, antioxidant, anti-inflammatory, anti-depressant, anti-tumour drugs **(Scheme 1)** [2] and could be used in a diverse array of powerful bond-forming reactions for the construction of complex natural products and macromolecules.[3] Due to their great potentials of biological activities,[2,3] considerable powerful approaches have been developed for the synthesis of the coumarin moiety, including the classical name reactions such as; (a) Pechmann condensation;[4] (b) Perkin reaction;[5] (c) Wittig reaction;[6] (d) Knoevengal condensation.[7] Apart from these classical reactions, recently transition metal complexes have emerged as promising catalysts in various methods for the preparation of 3-arylcoumarins (Scheme 2a).[8,9] Despite significant developments has been made,



Scheme 1. Biologically active compounds with 3-arylcoumarin motif.

common drawbacks include: a) requirement of preparation of pre-functionalized starting materials with low stability, b) overall multi-steps process, thus being less eco-friendly, c) harsh reactionconditions, d) requires an precious metal catalyst, and e) a stoichiometric amount of strong oxidants/ ligands.



Scheme 2. Transition-metal-catalyzed cascade cyclization reactions.

In 2014, Li et al. reported an efficient method for regioselective synthesis of 3-arylcoumarins through rhodium-catalysed oxidative

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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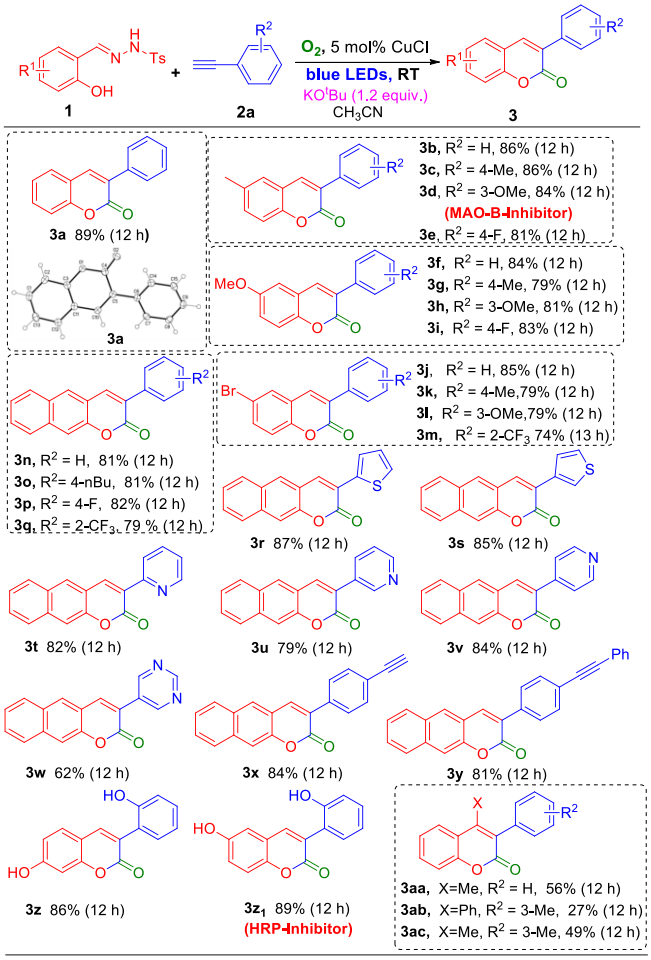
DOI: 10.1039/C9CC01801H

coupling of salicylaldehydes and terminal alkynes at high temperature **(Scheme 2b)**.[10] This approach, however, suffers from limited substrates scope, as well as employing stoichiometric pyridine-*N*-oxides as an oxidant, thus leading to generation of undesired waste, and is less eco-friendly. Thus, further development and discovery of new types of cheap metal- catalyzed cascade cyclization reactions using molecular oxygen as an oxidant, especially under low-energy visible-light irradiation, would be of great importance, which remains unexplored neither by thermal nor by the photochemically initiated process.

Recently, visible light initiated, copper catalysed reactions have enabled the invention of a wide variety of non-traditional bond constructions in modern synthetic organic chemistry,[11,12] such as; C-C cross-couplings, and various C-N, C-S, and C-O cross-coupling reactions. In this communication, we report the first example of visible-light-driven oxidative annulation of *N*-tosylhydrazones with terminal alkynes for the preparation of regioselective 3-arylcoumarins through a SET process with molecular O_2 as a green oxidant, simple and inexpensive catalyst (5 mol% CuCl, KO^{t}Bu (1.2 eq.) as a catalyst under mild conditions without any external organic oxidants/ligands at room temperature **(Scheme 2d)**. Moreover, the use of molecular O_2 as an oxidant for oxidative functionalization of organic molecules has attracted considerable attention owing to its low-cost, abundant, and environmentally benign nature.[13] In this regards, copper-catalyzed activation of molecular O_2 for the construction of oxygen-containing heterocycles (i.e. coumarins) via *in-situ* forming copper(II)-superoxo or -peroxo complex has been of long-standing interest to synthetic organic chemistry. Furthermore, due to the stability and versatile reactivity, *N*-tosylhydrazones have recently been employed as a powerful coupling partner with terminal alkynes for the synthesis of allenes or heterocyclic molecules catalysed by transition-metal-catalysts (Cu or Pd or Co-complexes) **(Scheme 2c)**.[14] Importantly, as compared to previous work of copper-catalyzed coupling of *N*-tosylhydrazones and terminal alkynes (at harsh thermal condition),[14a] the current photoredox process is an unprecedented and powerful method for regioselective synthesis of 3-arylcoumarin via copper-catalyzed oxidative cascade cyclization (6-endo-dig ring closure) of *N*-tosylhydrazones and terminal alkynes with O_2 under low energy visible-light irradiation **(Scheme 2d)**, which was not achievable by existing literature thermal processes.

With the optimized reaction condition in hand (**Table S1, entry 4** in SI), we next moved on to examine the substrate scope of this cascade oxidative annulation reaction. As shown in Table 1, a great variety of electron rich and deficient salicyl *N*-tosylhydrazones (**1b, 1f & 1j)** were subjected to react with phenylacetylenes and derivatives of aryl alkynes (R^2 = H, 4-Me, 3-OMe, & 4-F) (**2b-2m**), leading to the formation of the corresponding 3-arylcoumarins (**3b-3m**) smoothly in good yields of 74-86% yields with good regioselectivity. Remarkably, the naphthalene based *N*-tosylhydrazones (**1n**) also proceeded well in this cascade oxidative annulation and produced **3n** in 81% yield. To improve this context, we further evaluated distinct phenylacetylene derivatives (4-nBu, 4-F, 2-CF_3), which furnished the desired 3-arylcoumarins derivatives in better yields (79~81%, **3o-3q**). It is noteworthy that various substituents on hetero arylalkynes, such as 2- and 3-thienylalkynes, 2-, -3,and 4-ethynyl pyridine and 5-ethynylpyrimidine were also well tolerated, providing the corresponding 3-arylcoumarin products in 62-87% yield (**3r-3w**). Note that the hetero atom-substituted coumarins and naphthalene-fused 3-arylcoumarin derivatives are useful in the field of pharmaceuticals drugs, material science, and photo luminescence.[15] Moreover, 1,4-diynes and substituted internal alkynes are also well tolerated to generate the corresponding 3-aryl coumarins in good yields (**3x-3y**).

Table 1. The scope of *N*-tosylhydrazones (**1**).[a]



[a] Standard condition. Isolated yield after purification by column chromatography on silica gel.

Impressively, hydroxyl salicyl hydrazones can also react well with hydroxyl aryl alkyne to produce the corresponding desired products (**3z-3z$_1$**) in 86-89% yields under very mild conditions without the need of pre-protection at the hydroxy functional group.[14b] Products containing phenol functional group on the coumarin ring are very useful for a broad range of further synthetic transformations, or to act as radical scavengers in the field of pharmaceuticals.[16] Finally, we further explore the diversity of substituted 2-hydroxyacetophenone-*N*-tosyl-hydrazone and 2-hydroxybenzophenone-*N*-tosylhydrazone to couple with arylalkynes. It was found that these coupling reactions proceeded very successfully to afford the corresponding substituted 3-arylcoumarin products in moderate yields (27-56%, **3aa-3ac**).

To further explore the substrates scope, a variety of terminal alkynes were examined. As shown in Table 2, the current reaction is not limited to electron rich and electron deficient alkynes, but it also works well with other electron-rich and deficent bearing substituents on the phenyl ring at all ortho, meta, and para positions, and substituted internal alkynes, leading to the formation of corresponding functionalized 3-arylcoumarins(77-86%, **4b-4o**) (Table 2). Notably, aliphatic terminal alkynes, such as cyclohexyl, cyclohexenyl, and liner terminal alkynes (hexyl, heptyl, and 1,9-

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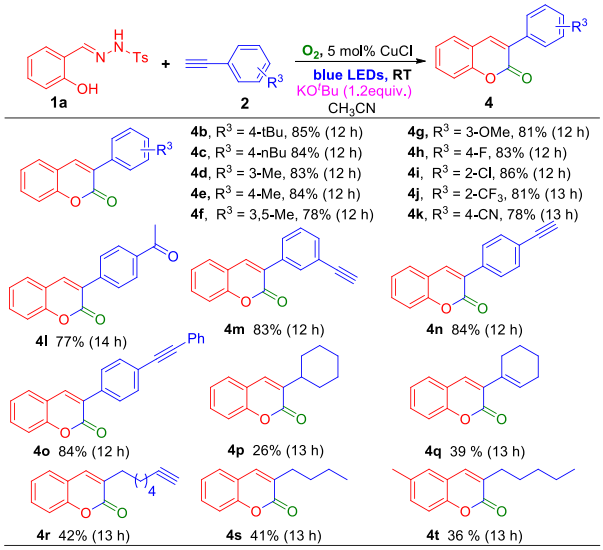
DOI: 10.1039/C9CC01801H

dialkyne) were also compatible in the current reaction, and afford the corresponding desired products, albeit in low yields (26-42%, **4p-4t**).

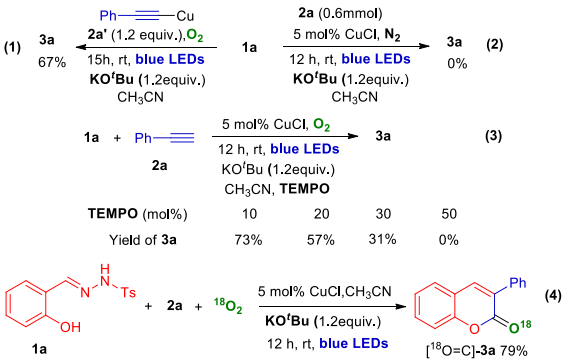
Table 2. The scope of terminal alkynes (**2**).[a]



[a] Standard condition. Isolated yield after purification by column chromatography on silica gel.

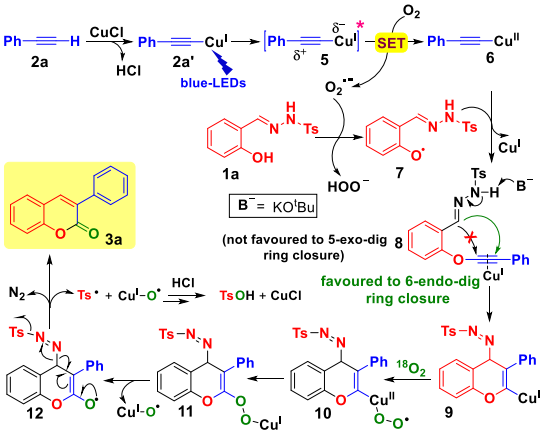
Notably, aliphatic terminal alkynes are unsuccessful coupling partners in the previous thermal processes, [10,14d] on the contrast, the current photoredox method proved to be amenable with aliphatic terminal alkynes. Finally, the product of **3a**, **4f,** and **4k** was confirmed by single-crystal X-ray diffraction.[17] It is worth noting that in all cases, a trace amount of homocoupling 1,3-diyne product was observed under aerobic conditions.[12] Finally, to demonstrate the applicability of the current protocol, bioactive molecules, such as MAO-B inhibitor (**3d**) and HRP-inhibitor (**3z$_1$**) were prepared in a gram scale under the standard reaction condition. Compared with traditional literature thermal routes,[3] the current photoredox method circumvents the need of any protecting reagents for acid sensitive functional groups (such as OH, COOH, etc.) and high temperature, providing a greener and more economical route for the synthesis of hydroxyl functionality-bearing coumarin derivatives under very mild conditions in two steps (75-79% total yields) (See details in SI). In addition, we have also evaluated the green metrics for the compounds **3d** and **3z$_1$** (see details in the SI).

To gain mechanistic insights, a series of control experiments were carried out (**Scheme 3**). First, in the absence of phenyl acetylene and CuCl, pre-synthesized Cu(I)-phenylacetylide(**2a'**) was used to react with salicylhydrazones (**1a**), which leads to the generation of the desired 3-arylcoumarins (**3a**) in 67% yield after 15h blue LED irradiation (eq 1). This result suggests that *in situ* generated Cu(I)-phenylacetylide might be the key light-absorbing photocatalyst responsible for the cascade oxidative cyclization reaction.[12] Furthermore, when the reaction was performed under an N_2 atmosphere (see eq. 2), the corresponding 3-arylcoumarin was not formed, indicating the necessity of molecular O_2 for the formation of coumarins. Moreover, under the standard reaction condition, the presence of a radical scavenger, TEMPO (10~50 mol%), totally quenches the formation of 3-arylcoumarin (**3a**) (see eq 3), suggesting that a radical intermediate might be involved in the reaction. Finally, isotopic-labelling experiments using $^{18}O_2$ (98%) instead of $^{16}O_2$ (see eq 4), were performed. The ^{18}O atoms were found to incorporate into the product (at the carbonyl oxygen position, 82% enrichment) (see mass spectra in SI), unambiguously indicating that the oxygen atom in the 3-arylcoumarin products mainly originates from molecular O_2.



Scheme 3. Mechanistic control experiments.

Based on the above mechanistic results, a reaction mechanism is depicted and shown in (**Scheme 4**). Photoirradiation of *in-situ* generated Cu(I)-phenylacetylide (**2a'**) generates a long-lived triplet excited state of Cu(I)-phenylacetylide **5** (T= 15.95 μs).[12] The excited state of Cu(I)-phenylacetylide **5** (E_{redox}= -2.048 V_{SCE} in CH_3CN)[12a,b] then undergoes a SET process to donate an electron to O_2 and generates the intermediates Cu(II)-phenylacetylide **6** as well as superoxide radical anion, as evidenced by EPR measurements (see S.I.).[12a,b] The bond dissociation energy of the phenoxyl O-H bond is ~90 kcal mol^{-1},[18] which is smaller than the O-H bond formation energy (105~110 kcal/mol)[18] of H_2O_2. Hydrogen atom abstraction from the phenoxyl O-H group of **1a** by superoxide anion radical is thus exothermic and thermadynamically allowed, which leads to the generation of phenoxyl radical **7**. In the next stage, the phenoxyl radical **7** attacks the Cu^{II}-phenylacetylide **6** to regenerate the copper(I) catalyst and furnishes the copper(I)-coordinated alkyne complex **8.** It is known that free CuCl could coordinate to the disubstituted alkyne moiety through a π-alkyne complex, thereby enhancing its electrophilicity.[19,12c] The resulting electron-deficient Cu^{I}-coordinated complex **8** then undergoes base (KO^{t}Bu)-promoted 6-endo-dig ring closure, which selectively occurred over 5-endo-dig ring closure pathway,[20] leading to the formation of the complex **9**. Indeed, Cu(I) containing complex **9** readily reacts with molecular O_2 to form copper(II) peroxo complex **10.**[21,12c] Isomerization of the resulting copper(II) peroxo complex **10** to copper(I) species **11** occurs with concurrent formation of a carbon-oxygen bond.[22,12c] Finally, complex **11** would generate oxy-radical **12 (***via* homolytic



Scheme 4. A proposed reaction mechanism.

cleavage)[13,23] and a subsequent radical elimination of N_2, TsOH to

provide the desired product **3a** and regenerate the CuCl catalyst.

In summary, we have demonstrated the first example of visible-light-driven copper-catalyzed oxidative annulation of salicyl hydrazones with wide range of commercially available terminal alkynes, including aliphatic terminal alkynes, as starting substrates without any need of external oxidants (organic oxidants) at room temperature with complete regioselectivity. The reaction occurs most probably via a unique base-promoted 6-endo-dig ring closure process, photoredox initiated C=N double bond cleavage and N_2 evolution. Also, we have observed that the desired products are totally different from those obtained by thermal heating methods. It is mainly due to the different reaction mechanisms, i.e., photoinduced electronic excitation-single electron transfer vs. thermal heating induced nuclear vibrational excitation-bond stretching/breaking/re-formation. As an additional benefit, this efficient method gives the best synthetic route to prepare bioactive molecules, such as MAO-B inhibitor and HRP-inhibitor at very mild conditions without the need of hydroxy group pre-protection. The current method can be readily scaled up to a preparative gram (1–2 g) scale. From a synthetic point of view, the current photoredox method involving utilization of O_2 as oxidant, inexpensive copper as a catalyst and low energy visible light for photo-excitation, represents an extremely simple and an eco-friendly process for the regioseletive synthesis of 3-arylcoumarins under very mild conditions.

This work was supported by the Ministry of Science and Technology, Taiwan.

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DOI: 10.1039/C9CC01801H

Visible-Light-Driven Copper-Catalyzed Aerobic Oxidative Cascade Cyclization of *N*-Tosylhydrazones and Terminal Alkynes: Regioselective Synthesis of 3-Arylcoumarins

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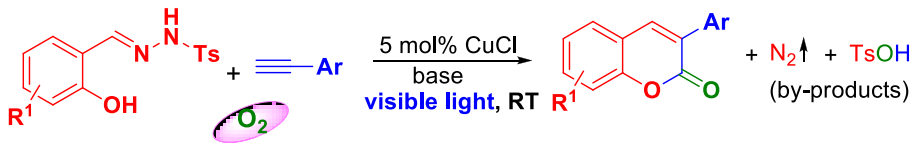
An intuitive visible-light-driven copper-catalyzed process can accomplish regioselective functionalized 3-arylcoumarins via oxidative annulation of simple *N*-tosylhydrazones with terminal alkynes under O_2 (1 atm.) at room temperature. This transformation represents a green and atom economical approach to preparation of substituted 3-arylcoumarins with single regio-isomer from readily available feedstocks.



• regioselectively 3-aryl coumarins are formed at rt • O_2 acts as oxidant and reagent
• woks with aliphatic alkynes • inexpensive Cu catalyst • visible light initiate the reaction