Atom-Economical Syntheses of Dihydropyrroles Using Flavin-Iodine-Catalyzed Aerobic Multi-Step and -Component Reactions

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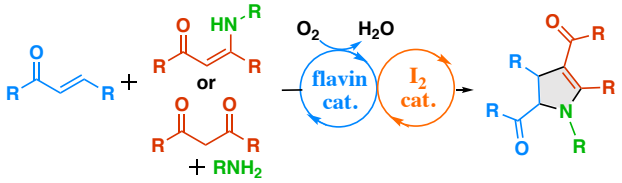


ABSTRACT: Herein, we report facile, atom-economical syntheses of multi-substituted 2,3-dihydropyrroles using flavin-iodine-catalyzed aerobic oxidative multi-step transformations of chalcones with *β*-enamine ketones or 1,3-dicarbonyl compounds and amines. Exploiting coupled flavin-iodine catalysis, the multi-step reaction, including C–C and C–N bond formation, is promoted only by the consumption of O_2 (1 atm), thus allowing aerobic oxidative synthesis that generates green H_2O as the only waste.

Dihydropyrroles are a vital class of five-membered N-containing heterocyclic moieties that occur in numerous biologically active and natural products, such as bohemamine[1] and spirotryprostatin B (Fig. 1).[2,3] Various methods of synthesizing multi-substituted 2,3-dihydropyrroles, which generally involve cycloaddition[4] and metal-mediated reactions[5], have been developed.[6] This is because of their importance not only in medicinal chemistry, but also as useful synthetic intermediates in producing diverse *N*-heterocyclic compounds using highly functionalized pyrrolidines and pyrroles.[7] The development of a novel approach to enable atom- and step-economical synthesis using readily accessible starting materials is required. In 2015, Li et al. reported the oxidative syntheses of 2,3-dihydropyrroles, which are promoted by the oxidative tandem reaction between chalcones and *β*-enamine ketones using stoichiometric amounts of I_2 and K_2CO_3 (Scheme 1A).[8] Changing the stoichiometric synthesis method to an eco-friendly catalytic process that proceeds under gentle oxidative conditions may lead to the most facile and straightforward routes to access multi-substituted 2,3-dihydropyrroles among the synthetic methods reported to date. Furthermore, we anticipated that the catalytic system is favored when using three-component reactions that afford readily accessible chalcones, 1,3-dicarbonyl compounds, and amines. The application to the multi-component reactions that provide high yields, atom/step economy, and shorter reaction times is recognized as a useful approach for developing eco-friendly processes.[9]

C–X (X = C, O, N, S…) bond formation via catalytic cross-dehydrogenative coupling (CDC) between the C–H and X–H bonds of substrates is a key, attractive strategy to enable step- and atom-economical syntheses because pre-activation of the substrates in CDC is unnecessary.[10] Although oxidative CDC requires stoichiometric amounts of oxidants, catalytic aerobic CDC, with O_2 as the terminal oxidant, is an ideal green method. The use of O_2 exhibits apparent economic and environmental

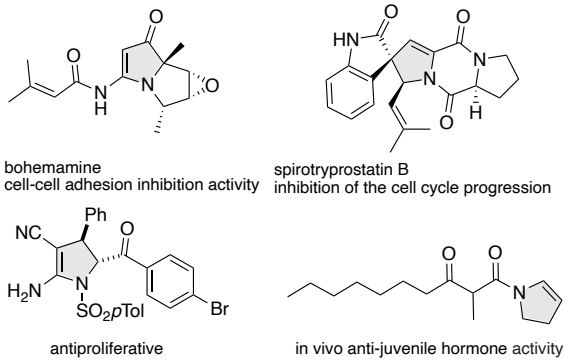
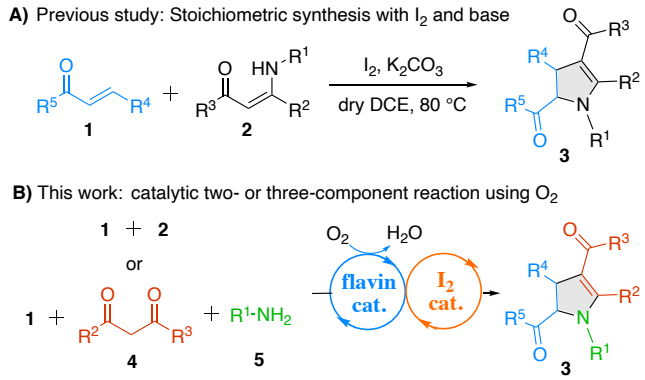


Figure 1. Biologically active dihydropyrroles.

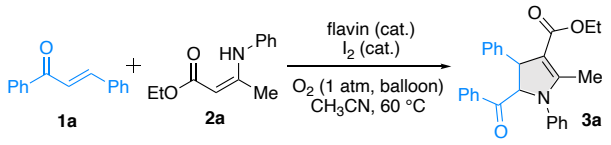
Scheme 1. Synthetic strategy in preparing pentasubstituted 2,3-dihydropyrroles **3** via the (A) previously reported stoichiometric reactions of **1** and **2**, and (B) flavin-iodine-catalyzed aerobic two-component reactions of **1** and **2** or three-component reactions of **1**, **4**, and **5**.



advantages, such as sustainable abundance, safety, cost-effectiveness, atom economy, and minimal pollution,[11] and catalytic aerobic CDC generates green H_2O as the only waste.[12] Recently, our group developed a metal-free dual catalytic system, using a biomimetic flavin organocatalyst[13,14] and an iodine catalyst, for use in aerobic oxidative transformations.[15] The flavin-iodine catalytic system was applied in aerobic CDC to form C–S[16] and C–N bonds[17], enabling the atom-economical syntheses of imidazo[1,2-a]pyridines[17b] and imidazoles.[17c] Herein, as an attractive application of the flavin-iodine catalytic system, we report the first catalytic syntheses of pentasubstituted 2,3-dihydropyrroles **3** using chalcones **1** and *β*-enamine ketones **2** (Scheme 1B). This dual catalytic system is further applied in three-component syntheses, thus providing the first three-component reactions of readily accessible **1**, 1,3-dicarbonyl compounds **4**, and amines **5**. In these systems, multiple flavin- and iodine-catalyzed processes, including aerobic CDC in ring-closing C–N bond formation, lead to atom-economical O_2-mediated synthesis.

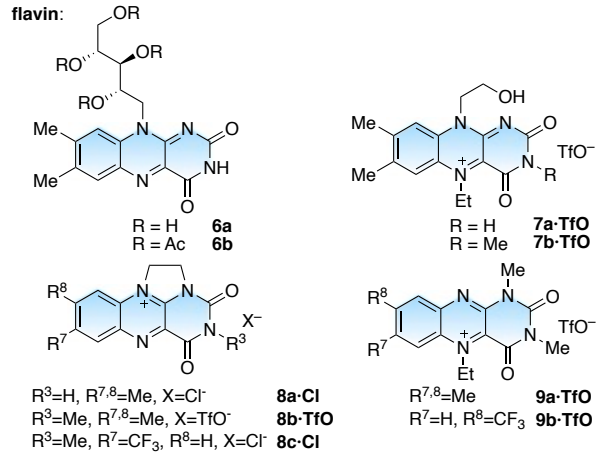
We investigated the effects of various flavins, *e.g.* neutral riboflavins **6**, 5-ethyl isoalloxaziniums **7**, 1,10-ethylene-bridged alloxaziniums **8**, and 5-ethyl alloxaziniums **9**, on the CDC reactions of **1a** and **2a** (1.2 equiv) under O_2 (1 atm, balloon) in CH_3CN at 60 °C, with I_2 as the co-catalyst (Table 1). The flavin-iodine-catalyzed system was successful, and the desired product

Table 1. Effects of flavin catalysts on the aerobic oxidative reaction between **1a** and **2a**.



entry	flavin	yield[b] (%)
1	**6a**	21
2	**6b**	22
3	**7a·TfO**	28
4	**7b·TfO**	22
5	**8a·Cl**	21
6	**8b·TfO**	31
7	**8c·Cl**	13
8	**9a·TfO**	30
9	**9b·TfO**	39
10[c]	**9b·TfO**	86

flavin:

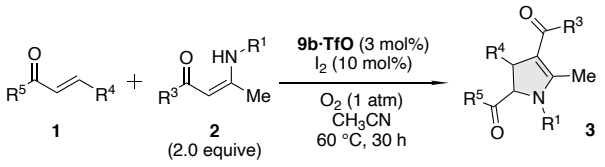


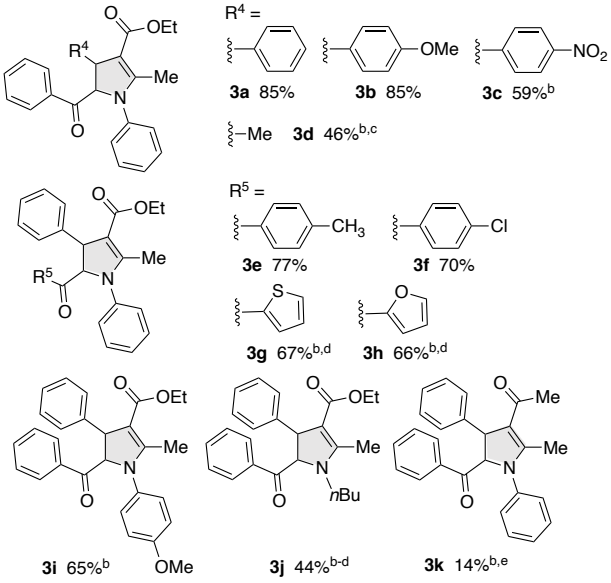
[a] Conditions: **1a** (0.13 M), **2a** (1.2 equiv), flavin (10 mol%), I_2 (10 mol%), and CH_3CN under O_2 (1 atm, balloon) at 60 °C for 18 h. [b] Yield determined via ^1H nuclear magnetic resonance (NMR) spectroscopy, with 1,3,5-trimethoxybenzene as the internal standard. [c] **1a** (0.50 M), **2a** (2 equiv), and **9b·TfO** (3 mol%) for 30 h.

3a was produced via the aerobic oxidative tandem reactions (entries 1–9). Among the flavin catalysts evaluated, the use of electron-deficient 8-trifluoromethyl-substituted alloxazinium salt **9b·TfO**[18] (TfO = triflate) resulted in the optimal yield (entry 9). Further optimization of the reaction conditions revealed that **3a** was obtained in an 86 % yield when 3 mol% **9b·TfO** and 2 equiv of **2a** were used in CH_3CN (entry 10). Under the present condition, the further dehydrogenative oxidation of 2,3-dihydropyrroles to pyrroles hardly occurred. Although investigation of the solvent effect revealed that 1,2-dichloroethane (DCE) accelerated this reaction in comparison to that in CH_3CN (Table S1), we used non-halogenated CH_3CN as the solvent in the two-component reaction.[19]

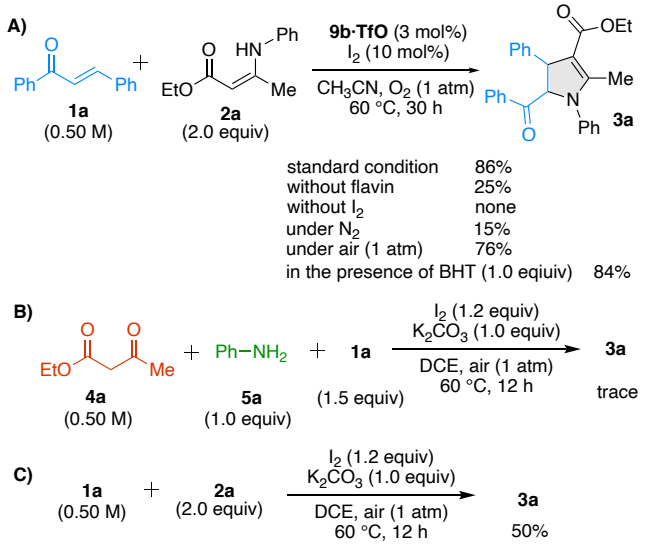
After optimizing the reaction conditions, we studied the substrate scope and limitations of the two-component reactions between **1** and **2** (Scheme 2). **1** bearing electron-donating or -withdrawing substituents, such as methoxy, nitro, methyl, and chloro groups, efficiently reacted with **2** to generate the desired products **3a**–**3f** in moderate to good yields. Even when R^4 of **1** was a methyl group, the reaction proceeded and yielded the product **3d** in 46% yield. Dihydropyrrole formation also proceeded using thiophenyl and furyl propenones, producing the desired products **3g** and **3h** in 67 and 66% yields, respectively. The use of **2** bearing an *N*-methoxyphenyl or a butyl group at the N-position furnished the corresponding 2,3-dihydropyrrole **3i** or **3j** in a 65% or 44% yield, respectively. Conversely, when

Scheme 2. Substrate scope of dihydropyrrole synthesis via the flavin-iodine-catalyzed oxidative reaction of **1** and **2**. [a] Conditions: **1** (0.50 M), **2** (1.0 M), **9b·TfO** (3 mol%), I_2 (10 mol%), and CH_3CN under O_2 (1 atm, balloon) at 60 °C for 30 h. [b] I_2 (20 mol%) was used. [c] In 1,2-DCE. [d] **1** (1.0 M) and **2** (0.50 M). [e] At 80 °C for 18 h.





Scheme 3. Control experiments.



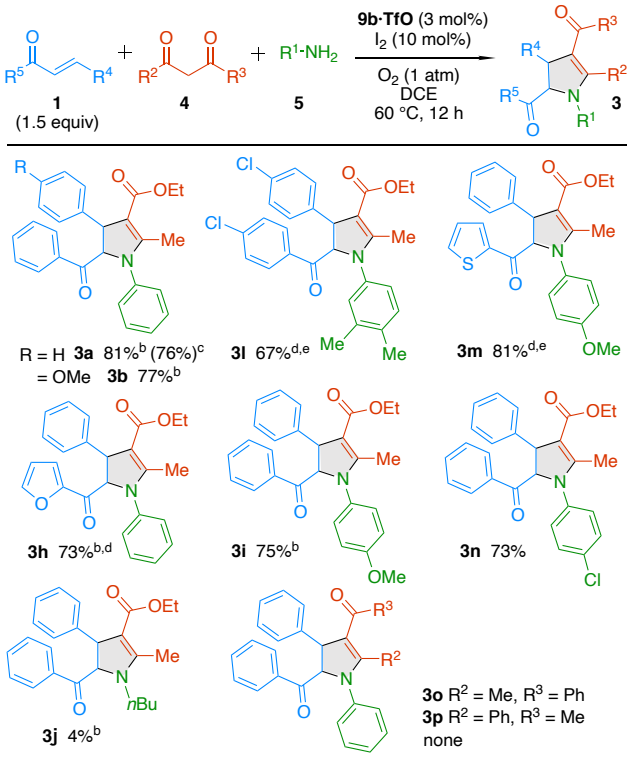
the ester functionality was changed to an acyl unit, the yield of **3k** decreased to 14%.

Following the assessment of the scope and limitations of the two-component reaction, we conducted control experiments to elucidate the reaction mechanism of the flavin-iodine catalytic system. The reaction of **1a** with **2a** did not proceed efficiently in the absence of flavin, I_2, or O_2 (Scheme 3A). Notably, **3a** was catalytically synthesized when atmospheric air was used instead of O_2. The addition of the radical scavenger 2,6-di-*tert*-butyl-4-hydroxytoluene (BHT, 1.0 equiv) did not influence the yield of **3a**, suggesting that no radical process occurred in this reaction.

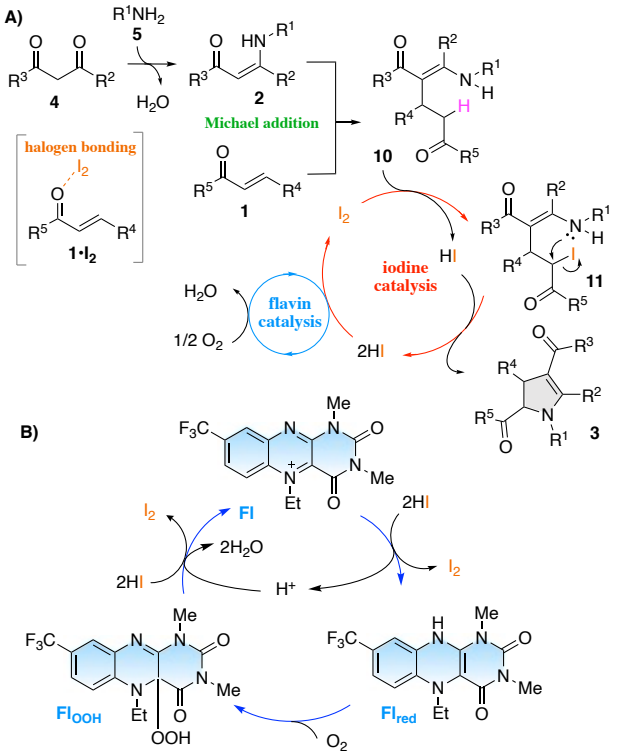
The flavin-iodine-catalyzed system provided an efficient two-component synthesis of **3**, but **2** should be prepared via the dehydrogenative condensation of **4** and **5** prior to use. As the pre-functionalization of **2** should be reduced using this catalytic system, we attempted three-component syntheses of **3** via multi-step reactions using the readily accessible starting materials **1**, **4**, and **5**. The three-component reaction of **1a**, **4a**, and **5a** successfully produced **3a** in an 81% yield within 12 h when DCE was used as the solvent (Scheme 4). The reaction was successfully scaled up to gram-scale, resulting in **3a** with 76% yield. Gratifyingly, the substrate scope of the three-component reaction was almost equivalent to that of the two-component reaction with **2** as the starting material. Via reactions between **1**, **4**, and **5**, diverse pentasubstituted 2,3-dihydropyrroles could be readily prepared. Compounds **1**, **4**, and **5** were amenable to these dihydropyrrole syntheses, generating products **3b**, **3l**, **3m**, **3h**, **3i**, and **3n** in 67–81% yields. However, the three-component reaction using butyl amine or 1-phenyl-1,3-butanedione hardly gave the desired products **3j**, **3o**, or **3p**.

Based on the experimental results and reported literature[8], we propose the mechanism of this flavin-iodine-catalyzed three-component reaction (Scheme 5). *β*-Enamine ketone **2** is initially formed via dehydrative condensation between **4** and **5** (Scheme 5A). I_2 acts as a good halogen bond catalyst in Michael addition at the carbonyl oxygen of **1**.[20] In this system, **1** is activated via the formation of **1•I₂** that undergoes Michael addition with **2**, affording intermediate **10**. The C–H bond of **10** is activated via electrophilic substitution with I_2 to yield the iodo adduct **11**, which undergoes intramolecular nucleophilic substitution. This might be one of the examples where in-situ umpolung of carbonyl compounds is generated by the flavin-catalyzed system.[21] Thus, the I_2-mediated intramolecular CDC of **10** produces the desired 2,3-dihydropyrrole **3**, along with HI. The flavin catalyst **Fl** may regenerate I_2 via aerobic oxidation of the *in situ*-generated HI (Scheme 5B). In the flavin catalytic cycle, HI oxidation is efficiently promoted by the reaction not only with **Fl** but also the flavin hydroperoxide $\mathbf{Fl_{OOH}}$, which is formed by the reaction of O_2 and $\mathbf{Fl_{red}}$ that is formed from **Fl**.[15] Therefore, flavin-iodine catalysis enables the atom-economical syntheses of **3** via two- or three-component reactions that consume only O_2 and generate green H_2O as the only waste. Flavin catalysis contributes to the regeneration of I_2 from I^-, but it notably consumes the H^+ generated by the intramolecular CDC of **10**. Due to flavin catalysis, this reaction system does not require the addition of a stoichiometric amount of base to trap H^+. Remarkably, the three-component reaction of **1a**, **4a**, and **5a** hardly occurred under the reaction conditions using stoichiometric amounts of I_2 and K_2CO_3 (Scheme 3B), whereas the stoichiometric reaction between **1a** and **2a** afforded **3a** in a 50 % yield under these conditions (Scheme 3C). This clearly revealed the advantage of this flavin-iodine catalytic system, with the successful facile three-component syntheses of **3** using readily available **1**, **4**, and **5**.

Scheme 4. Facile three-component syntheses of **3** via the flavin-iodine-catalyzed oxidative reactions of **1**, **4**, and **5**. [a] Conditions: **1** (0.75 M), **4** (0.50 M), **5** (0.50 M), **9b·TfO** (3 mol%), I_2 (10 mol%), and DCE under O_2 (1 atm, balloon) at 60 °C for 12 h. [b] Determined via ^{1}H NMR spectroscopy, using 1,3,5-trimethoxybenzene as the internal standard. [c] Gram-scale reaction using 1.0 g of **1a**. [d] **1** (1.0 M). [e] For 18 h.



Scheme 5. Plausible mechanisms of the (A) aerobic oxidative three-component reactions of **1**, **4**, and **5** catalyzed by flavin and iodine and (B) flavin catalysis.



We demonstrated the first atom-economical catalytic syntheses of pentasubstituted **3** using **1** and **2**. Furthermore, we performed facile three-component syntheses of **3** using readily available **1**, **4**, and **5** for the first time. In the multi-step synthesis, coupled flavin-iodine catalysis efficiently promoted the aerobic intramolecular CDC of intermediate **10** to form the new C–N bond of **3**. Therefore, it enables atom-economical multi-step transformations under metal-free conditions, consuming only O_2 and generating only H_2O as a by-product. Our findings demonstrated that the coupled redox organocatalysis system enhances the electron transfer from the substrates to O_2, which is an interesting and powerful tool for the design of eco-friendly synthesis protocols using aerobic oxidative multi-step processes.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data for known and new compounds (PDF)

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Notes

There are no conflicts to declare.

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