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Facile Access to Multi-Aryl 1*H*-Pyrrol-2(3*H*)-ones via Copper-TEMPO Mediated Cascade Annulation of Diarylethanones with Primary Amines and Mechanistic Insights

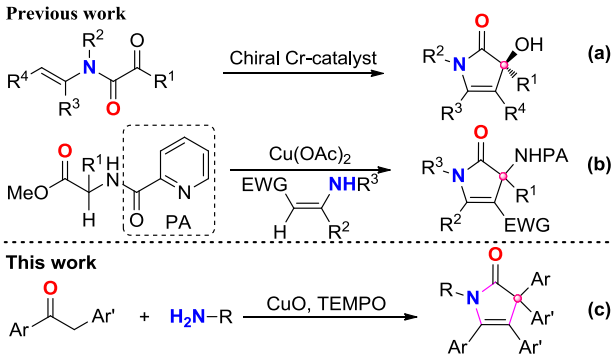
Xing Wang,[a] Chen-Yang Zhang,[a] Hai-Yang Tu,*[a] and Ai-Dong Zhang*[a]

Abstract: A straightforward approach to an array of multi-aryl 1*H*-pyrrol-2(3*H*)-ones featuring an α-diarylated all-carbon quaternary center has been developed using diarylethanones and primary amines as the raw materials. A complete mechanism involving a CuO-TEMPO mediated multi-step cascade process with an inherent delicate balance of substituent electronic effect is depicted. Moreover, this class of multi-aryl β,γ-unsaturated γ-lactams demonstrates an intriguing aggregation-induced emission effect valuable for potential application in developing luminescent materials.

Introduction

1*H*-Pyrrol-2(3*H*)-ones, a type of β,γ-unsaturated γ-lactams, represent an important class of N-heterocycles and are found as key structural motifs in many valuable biologically active molecules, or as crucial intermediates in natural products synthesis.[1] However, the approaches for synthsis of these scaffolds with polysubstitution have been scarcely reported to date,[2] which mainly take use of intramolecular cyclization or intermolecular annulation with prefunctionalized precursors. For example, Wang et al reported an elegant method for the synthesis of enantiopure functionalized 1*H*-pyrrol-2(3*H*)-ones via the intramolecular nucleophilic addition of tertiary enamide to carbonyl group (Scheme 1a);[2b] You and co-worker recently disclosed an copper-catalyzed intermolecular annulation of prefunctionalized α-amino acid esters with β-enamino esters to synthesize 3-amino-1,3-dihydro-2*H*-pyrrol-2-ones (Scheme 1b).[2c] These 1*H*-pyrrol-2(3*H*)-ones feature an α-quaternary center and a β,γ-unconjugated double bond and are hardly accessible by other methods, since the unconjugated double bond is generally more prone to shift to a conjugated one.[3] In this context, developing facile approaches to these structurally unique 1*H*-pyrrol-2(3*H*)-ones using simpler raw materials and/or routes would be highly valuable and challenging.

Diarylethanones, on the other hand, have been widely used as building blocks for synthesis of various mutil-aryl heterocycles.[4] Recently, the copper-catalyzed oxidative coupling of diarylethanones to give multi-aryl 1,4-diketones for synthesis of multi-aryl pyrroles[4b] has drawn our attention. To continue our efforts in exploiting diarylethanones for divergent synthesis,[5] we envisioned that the oxidative coupling products 1,4-diketones might be captured with amines to afford 1*H*-pyrrol-2(3*H*)-ones with a single operation (Scheme 1c) through a variant of the classic Paal-Knorr pyrrole synthesis since dehydration is unlikely to occur due to the absence of neighboring hydrogen. These 1*H*-pyrrol-2(3*H*)-ones would feature an α-diarylated all-carbon quaternary center, and the construction using easily accessible diarylethanones has not been explored so far. Herein, we report this straightforward approach and the mechanistic insights. Moreover, inspired by the unique structure, we also investigated their intriguing aggregation-induced emission (AIE) property.



Scheme 1. Methods for constructing polysubstituted 1*H*-pyrrol-2(3*H*)-ones.

Results and Discussion

Initially, we evaluated feasibility of the approach by reacting diphenylethanone (**1a**) with toluidine (**2a**) in the presence of CuO catalyst, TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) and Cs_2CO_3 in DMF under an air atmosphere at 150 °C (Tables S1-S8 and discussion, Supporting Information). The desired product 3,3,4,5-tetraphenyl-1-(*p*-tolyl)-1*H*-pyrrol-2(3*H*)-one (**3a**) was indeed obtained in 38% yield (Table S1, entry 1), and its structure confirmed by single-crystal X-ray diffraction.[6] Encouraged by this result, various variables such as reaction atmosphere, catalysts, bases and solvents, etc., were systematically examined to improve the reaction efficiency. Finally, the optimal conditions were determined and **3a** was obtained in 83% yield (Scheme 2).

Under the optimized conditions, the scope and limitations of the reaction were examined, and the results are summarized in Scheme 2. Notably, a wide range of aromatic and aliphatic primary amines could be employed in this transformation and delivered 1*H*-pyrrol-2(3*H*)-ones in moderate to good yields. The steric hindrance of substituents on the aromatic amines had little influence on the yield, for example, *o*- and *m*-methylanilines gave the desired products **3c** and **3d** with slightly decreased yields. However, the electronic nature of the substituents strongly impacted the yield as exemplified by the reaction of 4-trifluoromethylaniline with diphenylethanone, in which no desired product (**3j**) was observed. Interestingly, functional groups such as Cl, Br, and vinyl on aniline ring were tolerant and the reaction gave the correspondingly 1*H*-pyrrol-2(3*H*)-ones in synthetically useful yields (**3l**, **3m**, **3q**). These functional groups would

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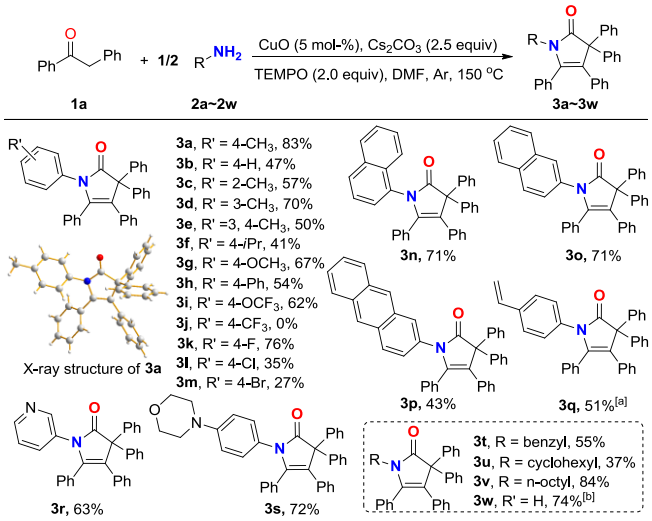
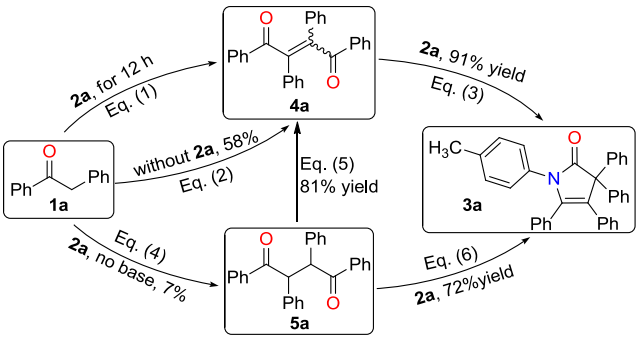
provide good handles for further functionalization, making multi-aryl 1*H*-pyrrol-2(3*H*)-ones useful in preparation of functional materials through catalyzed coupling reactions, styrene epoxidation, or vinylic polymerization. Polycyclic aromatic amines such as 1- and 2-aminonaphthalenes, and 2-aminoanthracene were able to successfully transform into the desired products **3n**, **3o**, and **3p**, respectively, in reasonable yields. Heterocycle-containing 3-aminopyridine and 4-morpholinoaniline were also suitable substrates, affording the corresponding products **3r** and **3s** in 63% and 72% yields. In addition, benzylamine and aliphatic primary amines such as cyclohexylamine and n-octyl amine furnished **3t**, **3u**, **3v** in 55%, 37% and 84% yields, respectively. Furthermore, *N*-unsubstituted 1*H*-pyrrol-2(3*H*)-one **3w** was also obtained in 74% yield when NH_4OAc was used as the ammonia source. *N*-Unsubstituted γ-lactams are important skeletons in bioactive natural products and drugs,[7] and can be further functionalized through acylation and arylation.[8] Importantly, a scale-up synthesis of **3a** was demonstrated in 65% yield (1.12g, Scheme S2).



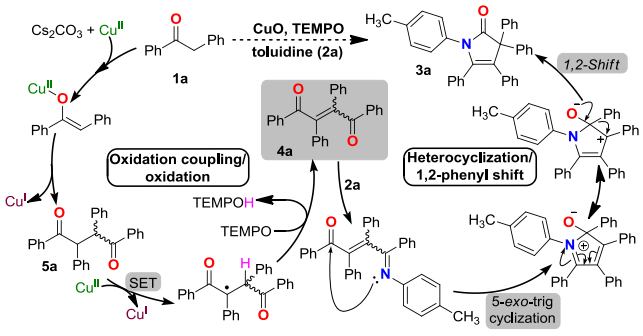
Scheme 2. Substrate scope. Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), CuO (5 mol-%), TEMPO (2.0 equiv) and Cs_2CO_3 (2.5 equiv) in DMF (8 mL) at 150 °C under an argon atmosphere for 12~24 h. Yields are based on isolated products. [a] 3.0 Equiv of TEMPO was used. [b] NH_4OAc was used.

It is interesting that there is no direct correlation in structure between the reactants and the products, and this attracted us to gain insight into the underlying mechanism using control reactions as shown in Scheme 3 [Eqs.(1~6)]. It was first noted that two major new spots appeared on the TLC plate after the reaction of **1a** with **2a** for 12 h, and gradually disappeared over time to produce the desired product **3a**. The two spots were isolated and characterized to be compound **4a** in *E/Z* isomers by single crystal X-ray diffraction [Eq.(1)].[6] Without adding **2a**, the reaction stopped at the stage of formation of **4a**, which was obtained in 58% yield [Eq.(2)] and able to react with 1.7 equiv of **2a** to give **3a** in 91% yield [Eq.(3)], indicating that **4a** is a key intermediate. On the other hand, without adding Cs_2CO_3, **1a** underwent oxidative homocoupling to give 1,2,3,4-tetraphenyl-1,4-butanedione (**5a**) in 7% yield [Eq.(4)], implying that **5a** may be another key intermediate. The low yield of **5a** means the radical oxidative homocoupling unlikely to occur because of the existence of TEMPO. Next, if **5a** was subjected to the reaction without adding **2a**, **4a** was isolated in 81% yield [Eq.(5)], suggesting **5a** is one precursor of **4a**. Finally, **5a** was able to convert to **3a** in 72% yield by reacting with **2a** [Eq.(6)]. Therefore, **4a** and **5a** are two possible key intermediates.



Scheme 3. Control reactions under the standard conditions and the inner relationship network in mechanistic insights.

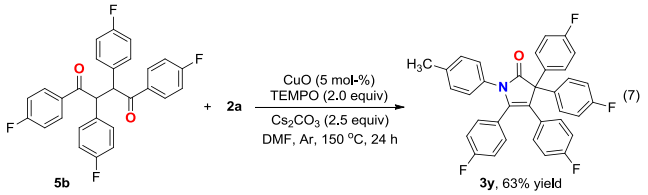
Based on these control reactions, a complete mechanism can be outlined in Scheme 4 using the model reaction of **1a** with **2a** as example. First, **1a** undergoes enolization to give a copper enolate intermediate, which partakes in oxidative enolate homocoupling[9] to yield **5a**. Following the conversion of **5a** to a radical intermediate via a single electron transfer (SET) process,[10] the key intermediate **4a** is generated with TEMPO mediated oxidative dehydrogenation.[11] Next, **4a** is attacked nucleophilically by **2a** to afford an imine intermediate, which takes part in 5-*exo*-trig cyclization to give a cyclic iminium intermediate. Finally, the iminium intermediate undergoes the Wagner-Meerwein 1,2-shift[12] of phenyl group leading to formation of **3a**. Interestingly, as shown in Scheme 4, the whole mechanism can be arranged in two symmetric hemicyclic parts and the key intermediate **4a** locates at the intersectional point. Before the point, Cu(II) participates in the enolate homocoupling and the one-electron oxidation, following with the TEMPO mediated oxidative dehydrogenation and the internal regeneration of Cu(II).[13] It is worthy of mention that 2.0 equiv of



Scheme 4. Proposed mechanism for the cascade annulation.

TEMPO is needed in this hemicycle as expected and demonstrated in the conditions optimization. After the intersectional point, the most worthwhile to note is the Wagner-Meerwein 1,2-shift of phenyl group to form an on-ring α-diarylated all-carbon quaternary center, which is otherwise inaccessible.[14]

After the successful one-pot one-step synthesis of multi-aryl 1*H*-pyrrol-2(3*H*)-ones and the mechanism insights, we intended to explore further the substrate scope of diphenylethanones. It has proven to be a great challenge that whatever substituents, electron-rich or electron-poor, are present on the phenyl ring, the diphenylethanones could not be converted to the desired 1*H*-pyrrol-2(3*H*)-ones. Closely inspecting the reaction products found that diphenylethanones bearing an electron-rich substituent (e.g., 4-OCH_3, **1b**) gave the non-cyclized (*E*/*Z*)-1,2,3,4-tetra(4-methoxyphenyl)-2-butene-1,4-dione (**4b**). By contrast, diphenylethanones bearing an electron-poor substituent (e.g., 4-F, **1c**) yielded no desired product either but a complicated mixture. Furthermore, if **4b** was used to react with **2a**, no desired product but 98% of **4b** was recovered [Scheme S1, Eqs.(1-3)]. Interestingly, 1,2,3,4-tetra(4-fluorophenyl)butane-1,4-dione (**5b**),[4e] an analogue of intermediate **5a**, could react with **2a** and delivered the desired product **3y** in 63% yield [Eq. (7)]. This two-pot two-step procedure looks like the classic Paal-Knorr pyrrole synthesis[15] in reaction substrate although 1*H*-pyrrol-2(3*H*)-ones instead of pyrroles were obtained in our case.



The above exploration manifests a delicate balance of the substituent electronic effect of diphenylethaones in the transformation, and any deviation would result in terminating the cascade process. This balance may originate from twofold: 1) an electron-rich substituent disfavors the imine formation of diphenylethanone with **2a**, thus the reaction proceeds well along the first hemicycle of the mechanism to form **4b**; but the next imine formation of **4b** with **2a** is impeded at the beginning of the second hemicycle; 2) an electron-poor substituent favors the imine formation of diphenylethanone with **2a**, which inactivates the enolate oxidative homocoupling at the beginning of the first hemicycle, leading to neither expected intermediates nor desired product. Thus the transformation of diphenylethanones with electron-poor substituent must occur via a two-pot two-step procedure where **2a** is added in the second pot.

One of the most attractive features of these 1*H*-pyrrol-2(3*H*)-ones is the highly arylated structure resembling the multi-aryl five-membered heterocyles, such as hexaphenylsilole[16] and pentaphenylpyrrole[17], that have the intriguing aggregation-induced emission (AIE) effect as firstly introduced by Tang's group.[18] We examined the fluorescence behavior of selected representative compounds including **3a**, **3b**, **3k**, **3o**, **3v** and **3y** in solutions with different THF/water ratio, and found that all these compounds showed the typical AIE effect with the fluorescence intensity order of **3y**<**3k**<**3b**<**3v**<**3a**<**3o** (Figure 1a and Supporting Information Figures S7-S13). Taking **3o** as an example, it displayed a fluorescence emission onset at the water fraction of 70%, following a sharp increase till the maximum intensity reached at the water fraction of 90% (Figure 1b). There are several mechanisms proposed for the AIE effect and the most typical one is the restriction of intramolecular rotation (RIR) upon formation of nanoaggregates in poor mixed solvent.[19] As shown in Figures 1c-d, **3a** presents a clearly propeller-like conformation preventing π-π stacking from the peripheral phenyl groups; but there exist multiple intra- and intermolecular C-H···π interactions, as revealed by X-ray analysis. The massive C-H···π interactions help restrict the rotation of phenyl groups and lead to blocking the nonradiative relaxation pathways and opening the radiative processes.[19b]

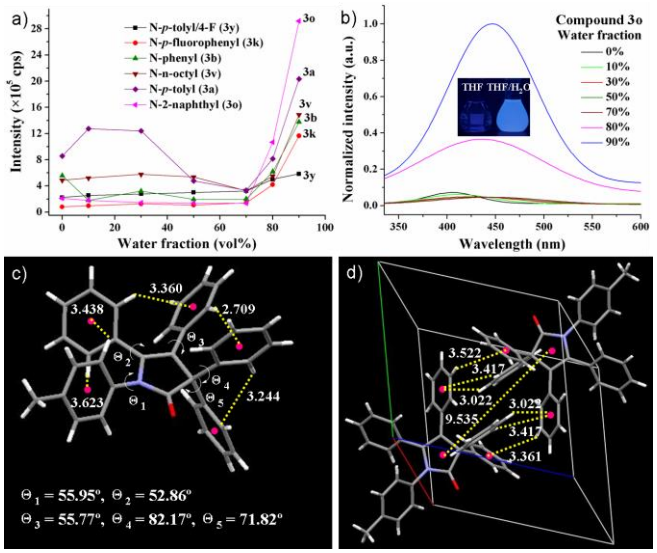


Figure 1. a) Relative fluorescence peak intensities in THF/water for selected compounds. b) Fluorescence spectra of **3o** in THF/water (inset: digital image of **3o** fluorescence excited at 365 nm in THF and the mixed solvent of 90% H_2O). Concentration: 8×10^{-5} mol/L; excitation: 310 nm. c) Conformation of **3a** in crystal with intramolecular C−H···π interactions and the dihedral angles indicated. d) Unit cell of **3a** crystal and intermolecular C−H···π interactions.

Conclusions

In summary, we have developed an unprecedented one-pot one-step strategy to achieve the rapid construction of multi-aryl 1*H*-pyrrol-2(3*H*)-ones featuring an α-diarylated all-carbon quaternary center from easily accessible diarylethanones and primary amines. A plausible mechanism was proposed that involves a copper-TEMPO mediated cascade process comprising oxidative enolate homocoupling, oxidative dehydrogenation, heterocyclization, and Wagner-Meerwein 1,2-shift of phenyl group. The delicate balance of the substituent electronic effect from diphenylethanones makes the cascade a great challenge; and in this situation, an alternative two-pot two-step procedure was provided. Moreover, these compounds as new AIEgens showed interesting aggregation-induced emission. The present developed atom- and step-economic approach to

multi-aryl 1*H*-pyrrol-2(3*H*)-ones and the handles such as bromo and vinyl groups on *N*-phenyl ring may find potential application in the development of luminescent materials.

Acknowledgements

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Keywords: annulation • aggregation-induced emission • dehydrogenation • homocoupling • γ-lactam

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Layout 2:

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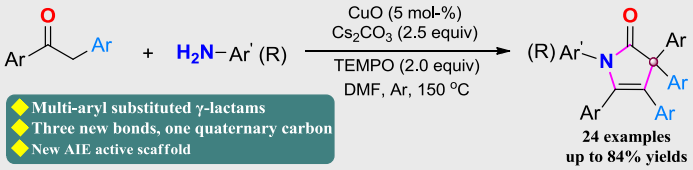

Long way in short path: An unprecedented copper-TEMPO mediated cascade process comprising oxidative enolate homocoupling, oxidative dehydrogenation, heterocyclization, and Wagner-Meerwein 1,2-phenyl shift has been revealed in the rapid access to mutil-aryl 1*H*-pyrrol-2(3*H*)-ones, a class of structurally unique and highly phenylated β,γ-unsaturated γ-lactams that have intriguing AIE effect.

Cascade Annulation

Xing Wang, Chen-Yang Zhang, Hai-Yang Tu, and Ai-Dong Zhang**

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Facile Access to Multi-Aryl 1*H*-Pyrrol-2(3*H*)-ones via Copper-TEMPO Mediated Cascade Annulation of Diarylethanones with Primary Amines and Mechanistic Insights

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