Copper-mediated intramolecular oxidative C–H/N–H cross-coupling of \( \alpha \)-alkenoyl ketene \( N,S \)-acetals to synthesize pyrrolone derivatives†

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CuCl\(_2\) and CuBr\(_2\)-mediated intramolecular oxidative C–H/N–H cross-coupling/halogenation of \( \beta \)-thiaoalkyl-substituted \( \alpha \)-alkenoyl ketene \( N,S \)-acetals occurred efficiently, affording 4-halo-5-thioalkyl-3-pyrrolones. Tunable C–S and C–halo bond transformations of the resultant pyrrolone derivatives led to highly functionalized N-heterocyclic compounds.

Synthesis of N-heterocycles via C–N bond formation has been among one of the most important tasks for organic chemists.1 Constructing a C–N bond usually requires coupling partners such as organic halides, tosylates, triflates organoboron reagents, etc. to react with an NH-bearing compound, producing the target products as well as undesired waste and by-products.2 Transition-metal-catalyzed cross-coupling reactions have recently made great progress in C–N bond formation.3,4 An intramolecular oxidative C–H/N–H cross-coupling reaction seems to be a straightforward route to access N-heterocyclic core.5 Pyrrolone derivatives are reasonably envisioned that they might be utilized to construct a pyrrolone backbone. Herein, we report CuCl\(_2\) or CuBr\(_2\)-mediated intramolecular oxidative C–H/N–H cross-coupling has seldom been paid attention for the synthesis of pyrrolones. Electron-withdrawing group-substituted ketene \( S,S \)-acetals10 and \( N,O \)-acetals11 can be used as versatile building blocks in organic synthesis, while their analogues, that is, ketene \( N,S \)-acetals, which can be readily prepared, have not attracted considerable attention.12 Intrigued by the structural feature of \( \alpha \)-alkenoyl ketene \( N,S \)-acetals, we reasonably envisioned that they might be utilized to construct a pyrrolone backbone. In this article, we report CuCl\(_2\) or CuBr\(_2\)-mediated intramolecular oxidative C–H/N–H cross-coupling/halogenation of such \( N,S \)-acetals for the synthesis of pyrrolone derivatives as well as their further functionalization through catalytic C–Cl and C–S bond cleavage (Scheme 1).

Initially, the reaction of \( \alpha \)-alkenoyl ketene \( N,S \)-acetal 1a was performed to screen the reaction conditions (Table 1). Treatment of 1a in DMF at 120 °C in the presence of CuCl\(_2\) (3 equiv.) and K\(_2\)PO\(_4\) (3 equiv.) under an argon atmosphere afforded the intra-molecular oxidative C–H/N–H cross-coupling/chlorination product, pyrrolone 2a, in 77% yield (Table 1, entry 1). The reaction within 60–120 °C reveals that 80 °C is the suitable reaction temperature (Table 1, entries 1–4). DMSO also acted as an effective reaction solvent, but a mixture of DMF/DMSO (7 : 1, v/v) led to a lower product yield (Table 1, entries 3, 5 and 6). Among the screened bases, both K\(_2\)PO\(_4\) and Cs\(_2\)CO\(_3\) efficiently promoted the transformation.

![TDR32750 (antimalarial) and HIV-1 protease inhibitor](image)

So far, only a limited number of methods have been known for the preparation of pyrrolone derivatives, although various processes have been documented for the synthesis of pyrroles.7 In general, time-consuming multi-step procedures,6b multi-component reactions,8b self-condensation of enaminoones,8c copper-catalyzed cyclization of enamino amidines,8d Pt8e and AuPt-mediated intramolecular amination of amino ynone, and NIS-promoted cyclization of diynones9 can be employed for this purpose. However, transition-metal-mediated intramolecular oxidative C–H/N–H cross-coupling reaction seems to be a straightforward route to access N-heterocyclic core.5 Pyrrolone derivatives are reasonably envisioned that they might be utilized to construct a pyrrolone backbone. Herein, we report CuCl\(_2\) or CuBr\(_2\)-mediated intramolecular oxidative C–H/N–H cross-coupling/halogenation of such \( N,S \)-acetals for the synthesis of pyrrolone derivatives as well as their further functionalization through catalytic C–Cl and C–S bond cleavage (Scheme 1).

![Scheme 1 Synthesis of pyrrolones from \( \alpha \)-alkenoyl ketene \( N,S \)-acetals.](image)
An additive effect was observed, and LiCl (3 equiv.) improved the reaction to produce 2a in 85% yield. Increasing the CuCl₂ loading to 4 equiv. further enhanced the formation of 2a in 96% GC yield (86% isolated yield), whereas lowering the LiCl loading to 2 equiv. reduced the yield to 92% (Table 1, entries 9–11). The reaction did not occur without CuCl₂ or a base (Table 1, entries 12 and 13), and an air or oxygen atmosphere deteriorated the reaction efficiency (Table 1, entries 14 and 15). It is noteworthy that CuCl₂·2H₂O could also be applied as a mediator to give 2a in 65% yield.

Under the optimized reaction conditions, the protocol generality was explored (Table 2). 4-Chloro-5-thiomethyl-3-pyrrolones 2b (92%) and 2c (87%) were obtained from the reactions of the corresponding N,S-acetals of type 1, while the N-benzyl substrate reacted less efficiently to afford 2d (59%) and the N-allyl analogue did not react. The thioethyl substrate underwent the same type of reaction to form 2e (88%). Increasing the steric hindrance of the N-aryl moiety reduced the product yield of 2f (79%). The furyl-alkenoyl substrates also reacted to produce 2g–2i (76–80%). Treatment of α-cinnamoyl ketene N,S-acetals in a similar fashion gave pyrrolones 2j–2w in 57–94% yields. The substituent on the NAr moiety of 1 such as p-Me, p-OMe, m-F, and p-Cl groups did not obviously affect formation of the desired products 2k–2n (83–93%). However, 2-Cl and 4-Br on the NAr moiety inhibited the reaction by exhibiting a steric or electronic effect on the formation of 2o (67%) and 2p (63%), respectively. 4-OMe and 4-Cl on the aryl group of a cinnamoyl moiety showed a negative electronic effect on the yield of 2v (65%) and 2w (57%). Due to the high tolerance of substituents such as methyl, methoxy, chloro, bromo, and fluoro in the desired products, the present method provides a general and concise protocol to access substituted 4-chloro-3-pyrrolones.

Using the same strategy, 4-bromo-5-thioalkyl-3-pyrrolones (3a–3d) were also obtained in 63–80% isolated yields in the presence of CuBr₂/LiBr (Scheme 2). It is noted that the molecular structure of 2a was confirmed by the X-ray crystallographic analysis (see ESI†).

Transition-metal-catalyzed transformations of 2 were conducted through catalytic C–S and C–Cl activation. Under Liebeskind–Srogl CuBr₂/LiBr (Scheme 2), CuBr₂/LiBr (Scheme 2). It is noted that the molecular structure of 2a was confirmed by the X-ray crystallographic analysis (see ESI†).
A plausible single-electron-transfer (SET) mechanism involving halogenation/cyclization and/or cyclization/halogenation is proposed (Scheme 4). The copper(II) salt acts as a catalyst to activate the C–H bond, a halogenating agent, and an oxidant in the overall catalytic cycle.

In summary, a combination of $\text{CuX}_2$/LIX ($X = \text{Cl}$ or $\text{Br}$) mediated the intramolecular oxidative $\text{C–H}/\text{N–H}$ cross-coupling/halogenation of $\alpha$-alkenoyl ketene $\text{N,S}$-acetals, efficiently affording 4-halo-5-thioalkyl-3-pyrrolones. Highly functionalized pyrrole derivatives were obtained via the catalytic C–S and C–Cl bond cleavage in the resultant pyrrolones. This method provides a new concise synthetic route to diverse pyrrole derivatives under mild conditions.

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Notes and references

Correction: Copper-mediated intramolecular oxidative C–H/N–H cross-coupling of \( \alpha \)-alkenoyl ketene \( N,S \)-acetals to synthesize pyrrolone derivatives

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The Royal Society of Chemistry apologises for these errors and any consequent inconvenience to authors and readers.