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Copper-mediated intramolecular oxidative C–H/N–H cross-coupling of α-alkenoyl ketene *N,S*-acetals to synthesize pyrrolone derivatives†

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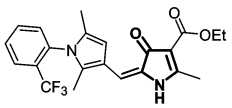
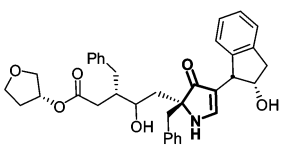
$CuCl_2$ and $CuBr_2$-mediated intramolecular oxidative C–H/N–H cross-coupling/halogenation of β-thioalkyl-substituted α-alkenoyl ketene *N,S*-acetals occurred efficiently, affording 4-halo-5-thioalkyl-3-pyrrolones. Tunable C–S and C–halo bond transformations of the resultant pyrrolone derivatives led 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-heterocycles, although intermolecular multi-component reactions can also be employed to establish a N-heterocyclic core.[5] Pyrrolone derivatives are potentially useful in the development of drugs for treating many infectious diseases.[6] For example, pyrrolone antimalarials have been investigated as a new class of antimalarial leads, among which TDR32750 has shown promising potent activity against plasmodium falciparum K1.[6a,b] Pyrrolone-based HIV-1 protease inhibitors have also been pursued to form peptide–pyrrolone hybrid complex molecules.[6c]



TDR32750 (antimalarial)



HIV-1 protease inhibitor

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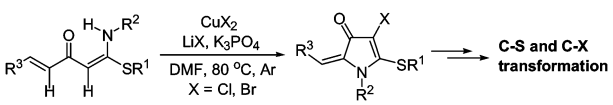
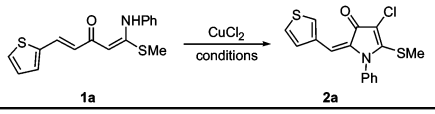
So far, only a limited number of methods have been known for the preparation of pyrrolone derivatives, although various processes have been documented for the synthesis of pyrroles.[7] In general, time-consuming multi-step procedures,[6a] multi-component reactions,[8a,b] self-condensation of enaminones,[8c] copper-catalyzed cyclization of enamino amides,[8d] Pt[8e] and Au[8f]-mediated intramolecular amination of amino ynones, and NIS-promoted cyclization of diynones[9] can be employed for this purpose. However, transition-metal-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*-acetals[10] and *N,O*-acetals[11] 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 α-alkenoyl ketene *N,S*-acetals, we 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).

Initially, the reaction of α-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_3PO_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). Testing 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_3PO_4 and Cs_2CO_3 efficiently promoted the



Scheme 1 Synthesis of pyrrolones from α-alkenoyl ketene *N,S*-acetals.

Table 1 Screening of reaction conditions



1a 2a

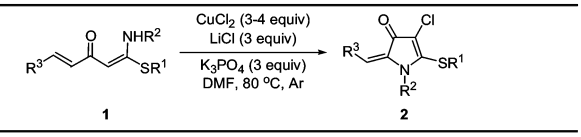
Entry	Base	Solvent	Temp. (°C)	Additive	Yield[a] (%)
1	K_3PO_4	DMF	120		77
2	K_3PO_4	DMF	100		79
3	K_3PO_4	DMF	80		81
4	K_3PO_4	DMF	60		58
5	K_3PO_4	DMSO	80		71
6	K_3PO_4	DMF/DMSO (7 : 1)	80		70
7	Li_2CO_3	DMF	80		50
8	Cs_2CO_3	DMF	80		80
9	K_3PO_4	DMF	80	LiCl	85
10[c]	**K_3PO_4**	**DMF**	**80**	**LiCl**	**96 (86)**[b]
11[c]	K_3PO_4	DMF	80	LiCl[d]	92
12[e]	K_3PO_4	DMF	80	LiCl	n.r.
13[c]		DMF	80	LiCl	n.r.
14[c,f]	K_3PO_4	DMF	80	LiCl	85
15[c,g]	K_3PO_4	DMF	80	LiCl	43

Conditions: **1a** (0.3 mmol), $CuCl_2$ (0.9 mmol), base (0.9 mmol), LiCl (0.9 mmol), solvent (3 mL), 0.1 MPa Ar, 2 h. [a] Determined by GC analysis with mesitylene as the internal standard. [b] Isolated yield given in parentheses. [c] $CuCl_2$ (1.2 mmol). [d] 0.6 mmol. [e] Without $CuCl_2$. [f] In air. [g] In 0.1 MPa O_2.

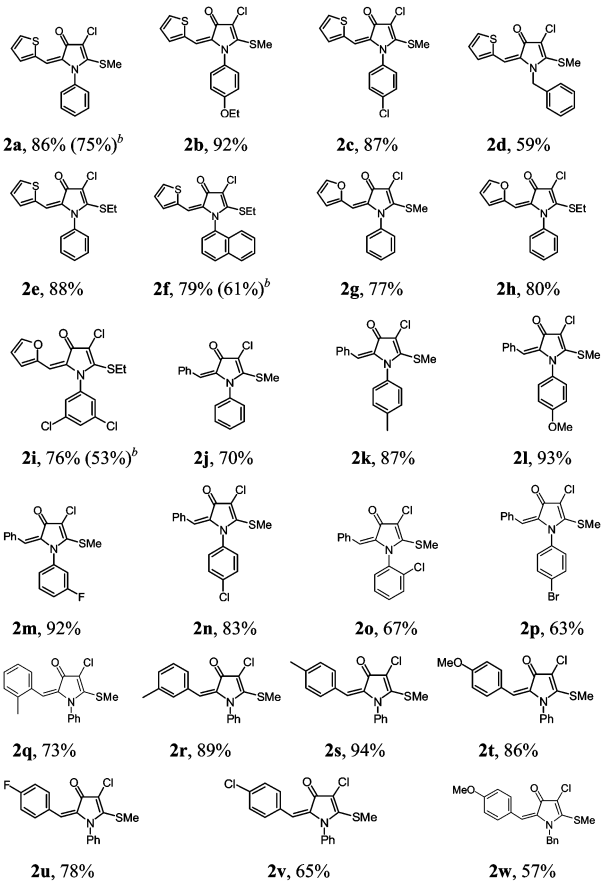
reaction (Table 1, entries 3, 7 and 8). An additive effect was observed,[4a] and LiCl (3 equiv.) improved the reaction to produce **2a** in 85% yield. Increasing the $CuCl_2$ loading to 4 equiv. further enhanced the formation of **2a** in 96% GC yield (86% isolated yield), whereas lowering the LiCl loading to 2 equiv. reduced the yield to 92% (Table 1, entries 9–11). The reaction did not occur without $CuCl_2$ 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 $CuCl_2{\cdot}2H_2O$ 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

Table 2 Copper-mediated C–H/N–H cross-coupling/chlorination of α-alkenoyl ketene *N*,*S*-acetals (**1**)[a,b]



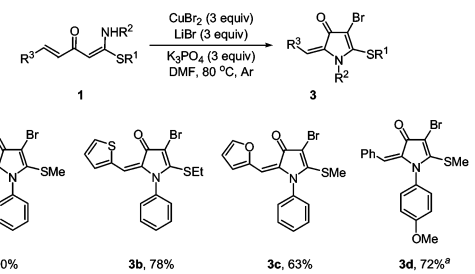
1 2



[a] Conditions: **1** (0.5 mmol), $CuCl_2$ (2.0 mmol), K_3PO_4 (1.5 mmol), LiCl (1.5 mmol), DMF (5 mL), 80 °C, 0.1 MPa Ar, 2 h. Yields refer to the isolated products. [b] Using 1.5 mmol $CuCl_2$.

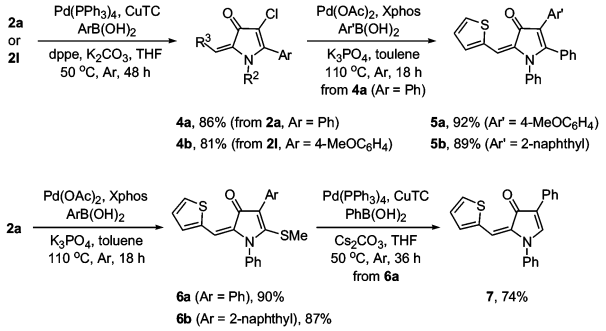
$CuBr_2$/LiBr (Scheme 2). It is noted that the molecular structure of **2a** was confirmed by the X-ray crystallographic analysis (see ESI†).

Transition-metal-catalyzed transformations of **2** were conducted through catalytic C–S and C–Cl activation. Under Liebeskind–Srogl

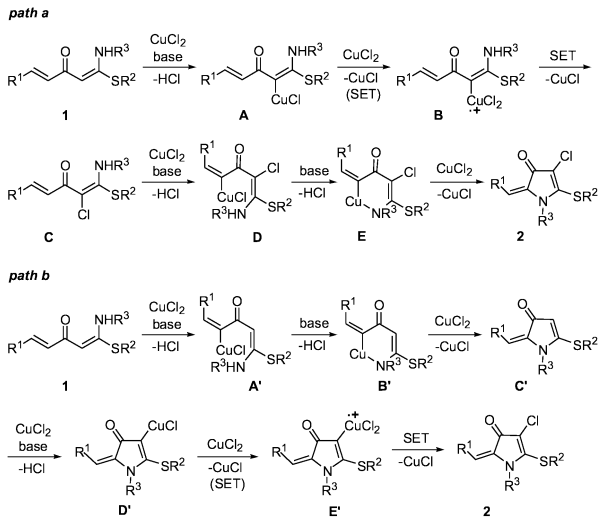


1 3

Scheme 2 Copper-mediated oxidation C–H/N–H cross-coupling/bromination of α-alkenoyl ketene *N*,*S*-acetals (**1**). Conditions: **1** (0.5 mmol), $CuBr_2$ (1.5 mmol), K_3PO_4 (1.5 mmol), LiBr (1.5 mmol), DMF (5 mL), 80 °C, 0.1 MPa Ar, 2 h. Yields refer to the isolated products. [a]Using $CuBr_2$ (2.0 mmol).



Scheme 3 Functionalization of 4-chloro-5-thioalkyl-3-pyrrolones.



Scheme 4 Proposed mechanism.

cross-coupling conditions for α-oxo ketene *S*,*S*-acetals,[13] 5-thioalkyl-4-chloro-3-pyrrolones **2a** and **2l** were reacted with an arylboronic acid to form 5-aryl-4-chloro-3-pyrrolones **4a** (86%) and **4b** (81%) by palladium-catalyzed C–S bond cleavage, and subsequent Suzuki–Miyaura cross-coupling reactions[14] of the C–Cl bond in **4** gave 4,5-diaryl-3-pyrrolones **5a** (92%) and **5b** (89%), respectively (Scheme 3). Interestingly, switching the cross-coupling conditions also switched the cleavage order of the C–S and C–Cl bonds in **2a**. Thus, the Suzuki–Miyaura cross-coupling products **6a** (90%) and **6b** (87%) were efficiently produced (Scheme 3). However, only the reductive desulfative product, that is, 4-phenyl-5*H*-3-pyrrolone (**7**), was formed in 74% yield from the reaction of **6a** under the C–S cross-coupling conditions. In this way, highly functionalized pyrrolone derivatives were prepared.

Addition of 3 equiv. of the well-known radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) or BHT (2,6-di-*tert*-butyl-4-methyl phenol) to the reaction mixture completely inhibited the reaction of **1a**, suggesting a radical reaction pathway (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 CuX_2/LiX (X = Cl or Br) mediated the intramolecular oxidative C–H/N–H cross-coupling/halogenation of α-alkenoyl ketene *N*,*S*-acetals, efficiently affording 4-halo-5-thioalkyl-3-pyrrolones. Highly functionalized pyrrolone 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 pyrrolone derivatives under mild conditions.

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