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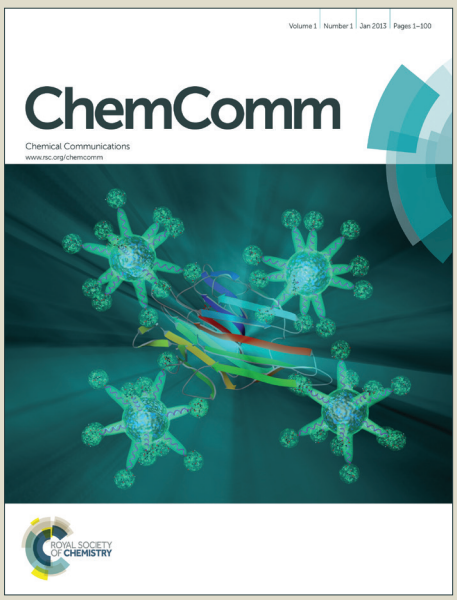

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COMMUNICATION

Copper–Mediated Intramolecular Oxidative C-H/N-H Cross–coupling of α-Alkenoyl Ketene N,S-Acetals to Pyrrolone Derivatives

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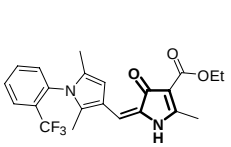
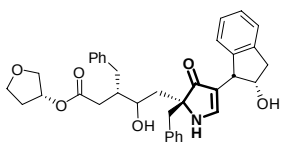
$CuCl_2$ and $CuBr_2$–mediated intramolecular oxidative C-H/N-H cross-coupling/halogenation of *β*-thioalkyl-substituted *α*-alkenoyl ketene N,S-acetals occured efficiently, affording 4-halo-5-thioalkyl-3-pyrrolones. Tunable C-S and C-halo bond transformations of the resultant pyrrolone derivatives led 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 and organoboron reagents, etc. react with an NH-bearing compound, producing the target products as well as undesired wastes and by-products.[2] Transition-metal-catalyzed cross-coupling reactions have recently been 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



TDR32750 (antimalarial)



HIV-1 protease inhibitor

been investigated as a new class of antimalarial leads, among which TDR32750 has been shown promising potent activity against plasmodium falciparum K1.[6a,6b] Pyrrolone-based HIV-1 protease inhibitors have also been pursued to form peptide-pyrrolone hybrid complex molecules.[6c]

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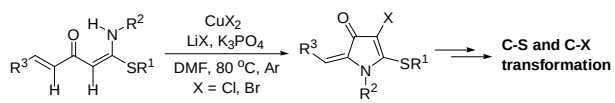
† Electronic Supplementary Information (ESI) available: Experimental details, compound characterization and NMR spectra, CCDC 999801 for **2a**. For ESI and crystallographic data in CIF or other electronic format, See DOI: 10.1039 /b000000x

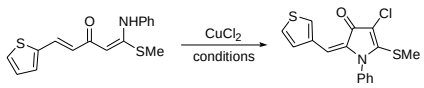
So far, only a limited number of methods have been known for the preparation of pyrrolone derivatives although various processes were documented to synthesize pyrroles.[7] In general, time-consuming multi-step procedures,[6a] multi-component reactions,[8a,8b] self-condensation of enaminones,[8c] copper-catalyzed 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 a $CuCl_2$ or $CuBr_2$-mediated intramolecular oxidative C-H/N-H cross-coupling /halogenation process 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 *α*-alkenoyl ketene N,S-acetals.

Initially, the reaction of α-alkenoyl ketene N,S-acetals **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 intramolecular 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 the 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 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

Table 1 Screening of reaction conditions



1a **2a**

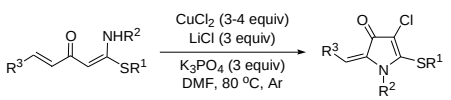
Entry	Base	Solvent	Temp. (°C)	Additive	Yield[a] (%)
1	K_3PO_4	DMF	120		77
2	K_3PO_4	DMF	100		79
3	K_3PO_4	DMF	80		81
4	K_3PO_4	DMF	60		58
5	K_3PO_4	DMSO	80		71
6	K_3PO_4	DMF/DMSO (7:1)	80		70
7	Li_2CO_3	DMF	80		50
8	Cs_2CO_3	DMF	80		80
9	K_3PO_4	DMF	80	LiCl	85
10[c]	**K_3PO_4**	**DMF**	**80**	**LiCl**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

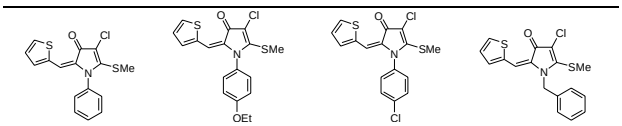
equiv further enhanced the formation of **2a** in 96% GC yield (86% isolated yield), whereas lowering the LiCl loading to 2 equiv reduced the yield to 92% (Table 1, entries 9-11). The reaction did not occur without a base or $CuCl_2$ (Table 1, entries 12 and 13), and an air or oxygen atmosphere deteriorated the reaction efficiency (Table 1, entries 12-15). It is noteworthy that $CuCl_2{\cdot}2H_2O$ could also be applied as the 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**

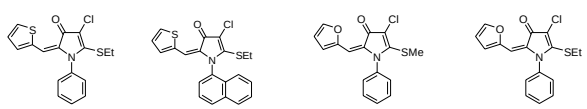
Table 2 Copper-mediated C-H/N-H cross-coupling/chlorination of α-alkenoyl ketene N,S-acetals (**1**) [a,b]



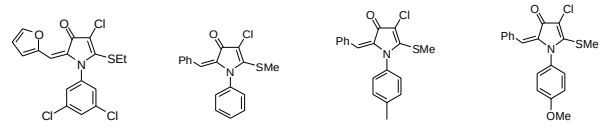
1 **2**



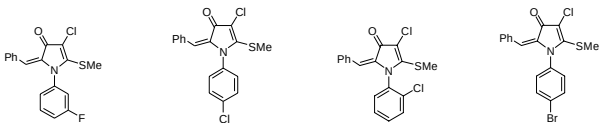
2a, 86% (75%)[b] **2b**, 92% **2c**, 87% **2d**, 59%



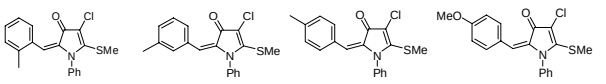
2e, 88% **2f**, 79% (61%)[b] **2g**, 77% **2h**, 80%



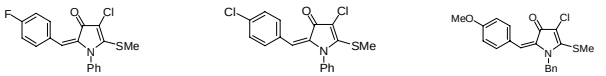
2i, 76% (53%)[b] **2j**, 70% **2k**, 87% **2l**, 93%



2m, 92% **2n**, 83% **2o**, 67% **2p**, 63%



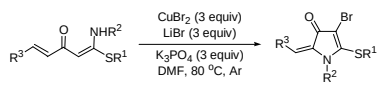
2q, 73% **2r**, 89% **2s**, 94% **2t**, 86%



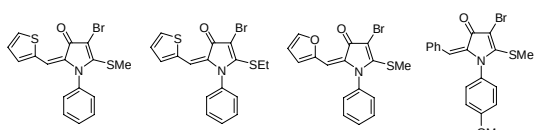
2u, 78% **2v**, 65% **2w**, 57%

[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 $CuCl_2$.

(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%



1 **3**

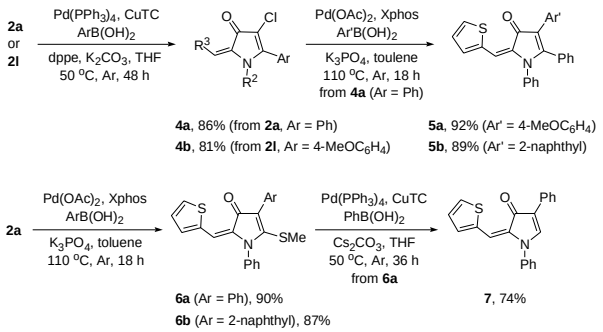


3a, 80% **3b**, 78% **3c**, 63% **3d**, 72%[a]

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).

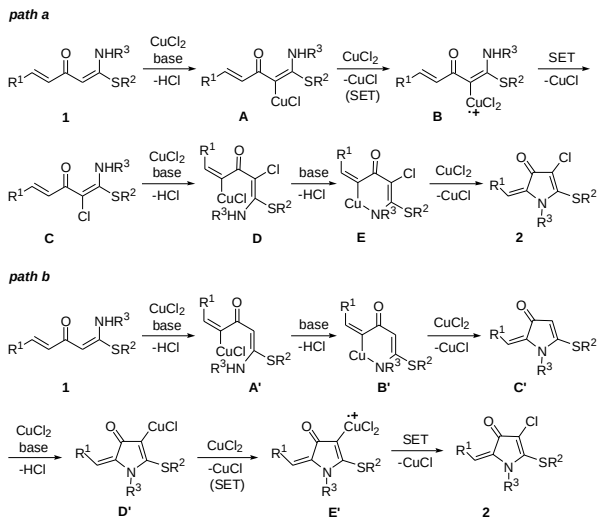
). Due to the high tolerance of substituents such as methyl, methoxy, chloro, bromo, and fluoro in the desired products, the present method provides a general and concise protocol to access substituted 4-chloro-3-pyrrolones. Using the same strategy, 4-bromo-5-thioalkyl-3-pyrrolones (**3a-3d**) were also obtained in 63-80% isolated yields in the presence of $CuBr_2$/LiBr (Scheme 2). It is noted that the molecular structure of **2a** was confirmed by the X-ray crystallographic analysis (see the Supporting Information).

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



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

Srogl 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



Scheme 4 Proposed mechanism.

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 the Supporting Information). A plausible single-electron-transfer (SET) mechanism involving halogenation/cyclization and/or cyclization/halogenation is proposed (Scheme 4). The copper(II) salt acts as the catalyst to activate the C-H bond, halogenating agent, and 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 route to diverse pyrrolone derivatives under mild conditions.

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Notes and references

1 (a) X. F. Xu and M. P. Doyle, *Acc. Chem. Res*., 2014, **47**, 1396; (b) J. C. Lewis, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res*., 2008, **41**, 1013; (c) A. Deiters and S. F. Martin, *Chem. Rev.*, 2004, **104**, 2199.

2 C. S. Yeung and V. M. Dong, *Chem. Rev*., 2011, **111**, 1215.

3 J. L. Roizen, M. E. Harvey and J. D. Bois, *Acc. Chem. Res*., 2012, **45**, 911.

4 For recent examples, see: (a) X. C. Ji, H. W. Huang, W. Q. Wu and H. F. Jiang, *J. Am. Chem. Soc*., 2013, **135**, 5286; (b) E. J. Yoo, S. Ma, T.-S. Mei, K. S. L. Chan and J.-Q. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 7652; (c) H. Chen, S. Sanjaya, Y.-F. Wang and S. Chiba, *Org. Lett*., 2013, **1**, 212; (d) X. Wu, Q. H. Gao, S. Liu and A. X. Wu, *Org. Lett*., 2014, **16**, 2888; (e) L. L. Zhou, S. Tang, X .T. Qi, C. T. Lin, K. Liu, C. Liu, Y. Lan and A. W. Lei, *Org. Lett.*, 2014, **16**, 3404; (f) H. L. Jiang, A. J. Lin, C. J. Zhu and Y. X. Cheng, *Chem. Commun*., 2013, **49**, 819; (g) X. Y. Li, B. J. Li, J. S. You and J. B. Lan, *Org. Biomol. Chem*., 2013, **11**, 1925.

5 D.-F. Chen, Z.-Y. Han, X.-L. Zhou and L.-Z. Gong, *Acc. Chem. Res*., 2014, 10.1021/ar500101a.

6 (a) D. Murugesan, A. Mital, M. Kaiser, D. M. Shackleford, J. Morizzi, K. Katneni, M. Campbell, A. Hudson, S. A. Charman, C.Yeates and I. H. Gilbert, *J. Med. Chem*., 2013, **56**, 2975; (b) D. Murugesan, M. Kaiser, K. L. White, S. Norval, J. Riley, P. G. Wyatt, S. A. Charman, K. D. Read, C. Yeates and I. H. Gilbert, *ChemMedChem*, 2013, **8**, 1537; (c) A. B. Smith Ⅲ, A. K. Charnley and R. Hirschmann, *Acc. Chem. Res*., 2011, **44**, 180.

7 B. Eftekhari-Sis, M. Zirak and A. Akbari, *Chem. Rev*., 2013, **113**, 2958.

8 (a) I. Erden, G. Ozer, C. Hoarau and W. Cao, *J. Heterocyclic. Chem.*, 2006, **43**, 395; (b) F. Palacios, C. Alonso, M. Legido, G. Rubiales and M. Villegas, *Tetrahedron Lett*., 2006, **47**, 7815; (c) J. Huang, Y. Liang, W. Pan, Y. Yang and D. Dong, *Org. Lett*., 2007, **9**, 5345; (d) Z.-J. Zhang, Z.-H. Ren, Y.-Y. Wang and Z.-H. Guan, *Org. Lett*., 2013, **15**, 4822; (e) N. Gouault, M. L. Roch, C. Cornée, M. David and P. Uriac, *J. Org. Chem*., 2009, **74**, 5614; (f) R. Spina, E. Colacino, B. Gabriele, G. Salerno, J. Martinez and F. Lamaty, *J. Org. Chem*., 2013, **78**, 2698.

9 Y.-F. Qiu, F. Yang, Z.-H. Qiu, M.-J. Zhong, L.-J. Wang, Y.-Y. Ye, B. Song and Y.-M. Liang, *J. Org. Chem*., 2013, **78**, 12018.

10 (a) L. D. Wang, W. He and Z. K. Yu, *Chem. Soc. Rev*., 2013, **42**, 599; (b) L. Pan, X. H. Bi and Q. Liu, *Chem. Soc. Rev*., 2013, **42**, 1251.

11 S. Basu, V. Gupta, J. Nickel and C. Schneider, *Org. Lett*., 2013, **16**, 274.

12 M. S. Singh, G. C. Nandi and S. Samai, *Green Chem*., 2012, **14**, 447.

13 W. W. Jin, W. M. Du, Q. Yang, H. F. Yu, J. P. Chen and Z. K. Yu, *Org. Lett.*, 2011, **13**, 4272.

14 M. Sai and S. Matsubara, *Org. Lett.*, 2011, **13**, 4676.