ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2014, **50**, 12479

Received 28th July 2014,
Accepted 27th August 2014

DOI: 10.1039/c4cc05837b

www.rsc.org/chemcomm

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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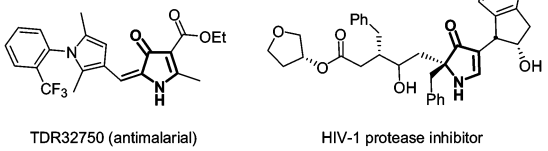
$CuCl_2$ and $CuBr_2$-mediated intramolecular oxidative C–H/N–H cross-coupling/halogenation of β-thioalkyl-substituted α-alkenoyl ketene *N,S*-acetals occurred efficiently, affording 4-halo-5-thioalkyl-3-pyrrolones. Tunable C–S and C–halo bond transformations of the resultant pyrrolone derivatives led to highly functionalized N-heterocyclic compounds.

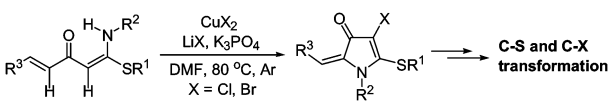
Synthesis of N-heterocycles *via* C–N bond formation has been among one of the most important tasks for organic chemists.[1] Constructing a C–N bond usually requires coupling partners such as organic halides, tosylates, triflates organoboron reagents, *etc.* to react with an NH-bearing compound, producing 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

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.

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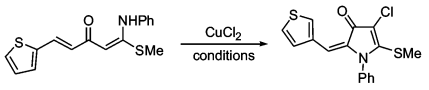
† Electronic supplementary information (ESI) available: Experimental details, compound characterization and NMR spectra. CCDC 999801 for **2a**. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc05837b

Table 1 Screening of reaction conditions



1a 2a

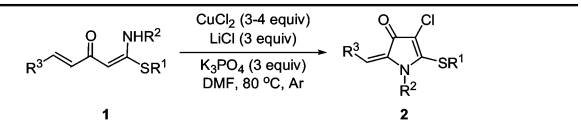
Entry	Base	Solvent	Temp. (°C)	Additive	Yield[a] (%)
1	K_3PO_4	DMF	120		77
2	K_3PO_4	DMF	100		79
3	K_3PO_4	DMF	80		81
4	K_3PO_4	DMF	60		58
5	K_3PO_4	DMSO	80		71
6	K_3PO_4	DMF/DMSO (7 : 1)	80		70
7	Li_2CO_3	DMF	80		50
8	Cs_2CO_3	DMF	80		80
9	K_3PO_4	DMF	80	LiCl	85
10[c]	**K_3PO_4**	**DMF**	**80**	**LiCl**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



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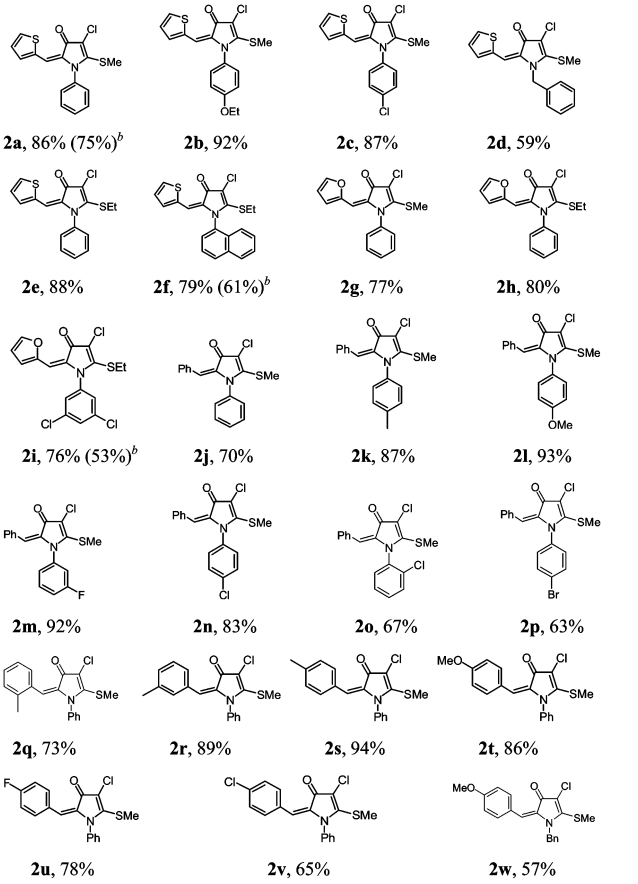
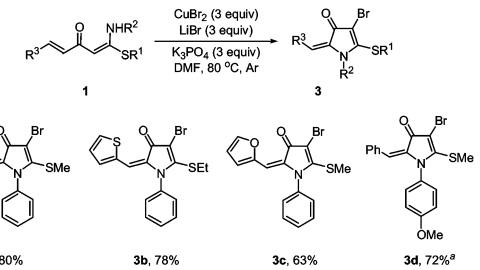


[a] Conditions: **1** (0.5 mmol), $CuCl_2$ (2.0 mmol), K_3PO_4 (1.5 mmol), LiCl (1.5 mmol), DMF (5 mL), 80 °C, 0.1 MPa Ar, 2 h. Yields refer to the isolated products. [b] Using 1.5 mmol $CuCl_2$.

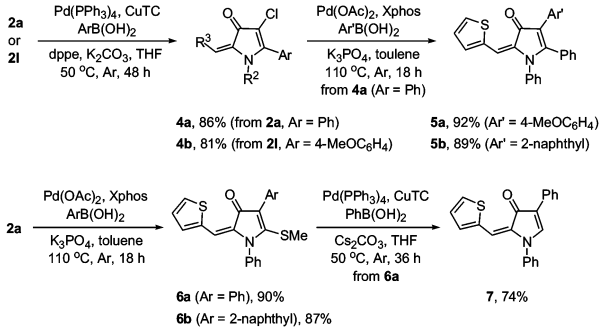
$CuBr_2$/LiBr (Scheme 2). It is noted that the molecular structure of **2a** was confirmed by the X-ray crystallographic analysis (see ESI†).

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

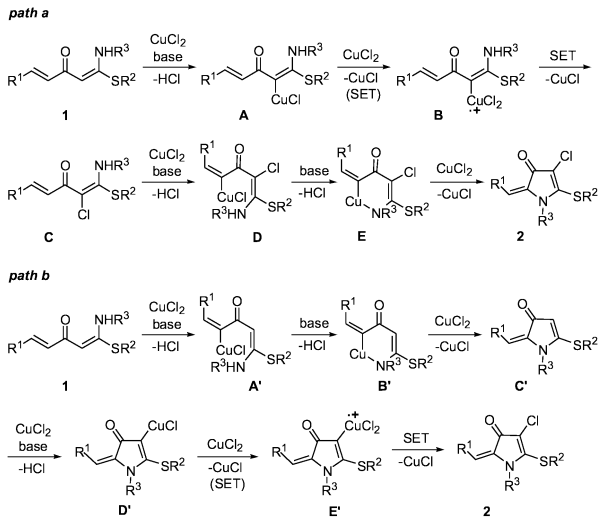


1 3

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.

This work was financially supported by the National Natural Science Foundation of China (21472185) and the National Basic Research Program of China.

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