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Copper(II)-catalyzed Domino Reaction of the Acyclic Ketene-(*S*,*S*)-Acetals with Diazo Compounds: Convenient Synthesis of Poly-substituted Thiophenes

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Abstract. Copper(II)-catalyzed domino reaction between the acyclic ketene-(*S*,*S*)-acetals and diazo compounds has been successfully developed. This reaction proceeds through a sequential formation of electrophilic copper carbenoid, sulfur ylide and subsequent C-S bond coupling and cleavage. Notably, the domino reaction features broad the readily available acyclic ketene-(*S*,*S*)-acetals scope and provides a new strategy for the synthesis of poly-substituted thiophenes.

Keywords: Acyclic ketene-(*S*,*S*)-acetals; Diazo compounds; Poly-substituted thiophenes; Domino reaction; Copper catalyst

Poly-substituted thiophenes and analogues are valuable building blocks widely existed in pharmaceuticals and natural products,[1] and they have explicitly displayed a broad spectrum of biological activities including antibacterial,[2a] antifungal,[2b] antioxidant,[3] antithrombotic,[4] and antitumor.[5] Moreover, they also have found applications in functional material[6] and organic synthesis.[7] Among various poly-substituted thiophenes, tetrasubstituted thiophene derivatives possess potential pharmacologically activities, such as tinoridine, strontium ranelate, modulators of the adenosine A1 receptor 2A3BTs and PD81,723 (Fig. 1).[1c, 8] Given these fascinating activities and applications, the development of facile and convenient synthetic route to thiophenes is of great significance. Although a variety of protocols have been reported for synthesis poly-substituted thiophenes in recent years, these strategies often rely on the functionalization of simpler thiophenes, whereas the utility of acyclic precursors as substrate by a tandem method are scarce. Therefore, the direct and convenient synthesis of poly-substituted thiophenes from easily available acyclic starting materials in a single step is highly desirable.

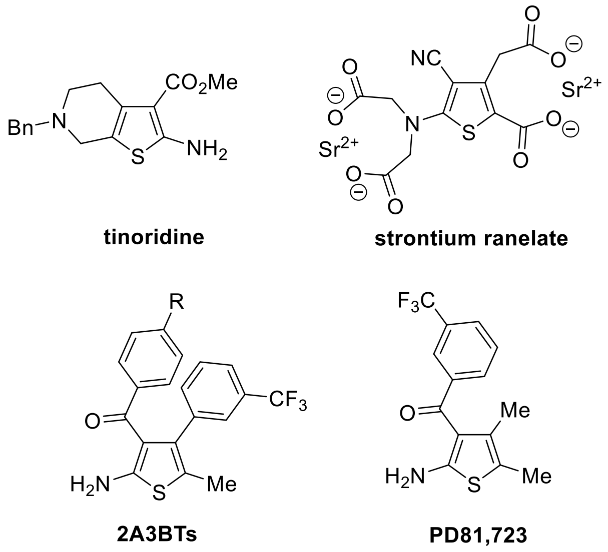


Figure 1. Representative biologically active tetrasubstituted thiophene derivatives.

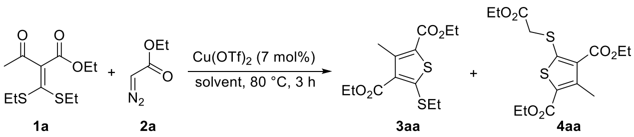
Diazo compounds are versatile synthons and have been extensively studied for numerous challenging and intriguing syntheses due to their adequate reactivity and high energy.[9] In particular, transition-metal-catalyzed reactions of diazo compounds have been highly successful.[10] Pioneered by Doyle and Hu, the applications of electrophilic trapping in *situ*-generated ylides from metal carbene have become a versatile and useful synthetic strategy for the rapid construction of complex molecules in recent decade.[11, 12] In addition, the *situ*-generation of sulfur ylides from diazo compounds and sulfide has been well documented for the construction of C-S and C-C bond[13, 14] via the Doyle-Kirmse[15] or Stevens[16] rearrangement reaction. In stark contrast, little attention has been paid to cleavage C-S bond[17] via sulfur ylide to produce thiophenes. As part of our ongoing research on ketene dithioacetal[18, 19] and diazo compounds,[20] we report herein a new strategy for the direct and convenient synthesis of poly-substituted thiophenes via a Cu(II)-catalyzed domino reaction between the acyclic ketene-(*S*,*S*)-acetals and diazo compounds.

At the outset of our studies, we investigated to the multi-substituted thiophene synthesis from the ethyl 2-(bis(ethylthio)methylene)-3-oxobutanoate **1a** with ethyl 2-diazoacetate **2a** via a tandem process. Using CuBr (7 mol%) as a catalyst, desired multi-substituted thiophenes **3aa** and **4aa** were obtained in 48% and 18% yields in DCE under air, respectively (Table 1, entry 1). Screening of copper catalysts revealed that $Cu(OTf)_2$ was optimal one (entries 2-5). When switching the copper catalyst to $FeCl_3$, $[RhCp^*Cl_2]_2$, $[Rh(COD)Cl]_2$, $Rh(PPh_3)_3Cl$, $Rh_2(OAc)_4$, or $[Ru(p\text{-cymene})Cl_2]_2$ catalyst, the reaction could not be activated however (Table 1, entries 6-11). Solvent effects have also been observed, and the reaction proceeded well in DCE, while DMF, THF and CH_3CN are not suitable for this reaction (Table 1, entries 12-14).

With the optimized reaction conditions in hand, the scope and generality with respect to dithioacetal derivatives were examined in table 2. Thus, a series of α-EWG ketene dithioacetals **1** were conveniently synthesized and reacted with ethyl 2-diazoacetate by copper-catalyzed C-S bond coupling and cleavage. When the R^1 group in **1** were CO_2Me, CO_2Et, and 4-$OMeC_6H_4$ (**1a-1c**), the multi-substituted thiophenes **3aa-3ca** and **4aa-4ca** were observed simultaneously in good yields. Notably, substituents R^1 were changed for cyano, amide, and benzoyl (**1d-1f**), the tandem reaction proceeded smoothly and the exclusive multi-substituted thiophenes **3da-3fa** were isolated in moderate to good yields. In comparison, the non-substituted at the α-position (R^1 = H), the R^3 group in **1** bearing varied from alkyl to alkenyl groups, and afforded the desired products **3ga-3na** in moderate to good yields. To scope of the diazo compounds was next explored. Ketene-(*S*,*S*)-acetals **1h** can proceed smoothly with various diazo compounds (such as **2b**, **2c**, **2d**, **or 2e**), resulting in the formation of the corresponding multi-substituted thiophenes in moderate yields (**3hb-3he**). In comparison, no reaction was observed for substrates **2f-2i**, as a result of the steric effects. To demonstrate the synthetic applicability of the catalytic system, synthesis of product **3ha** on a gram-scale was carried out and a 36% isolated yield was obtained.

Surprisingly, under the optimized reaction conditions, when substituents R^1 were replaced by

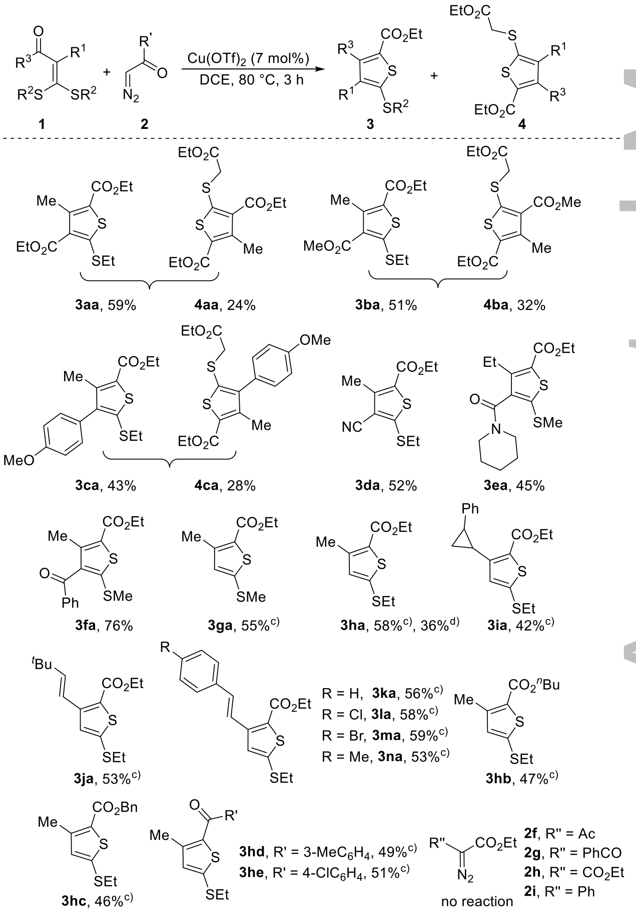
Table 1. Sceening of reaction condition[a), b)]



Entry	Solvent	Catalyst	Yield of **3aa** (%)	Yield of **4aa** (%)
1	DCE	CuBr	48	18
2	DCE	CuI	40	15
3	DCE	$CuBr_2$	46	16
4	DCE	$CuCl_2$	45	17
5	DCE	$Cu(OTf)_2$	59	24
6	DCE	$FeCl_3$	0	0
7	DCE	$[RhCp^*Cl_2]_2$	trace	0
8	DCE	$[Rh(COD)Cl]_2$	8	trace
9	DCE	$Rh(PPh_3)_3Cl$	trace	0
10	DCE	$Rh_2(OAc)_4$	17	trace
11	DCE	$[Ru(p\text{-cymene})Cl_2]_2$	trace	0
12	DMF	$Cu(OTf)_2$	0	0
13	THF	$Cu(OTf)_2$	trace	trace
14	CH_3CN	$Cu(OTf)_2$	38	10

a) Reaction conditions: **1a** (0.2 mmol) and catalyst (7 mol%) were dissolved in solvent (1 mL), followed by a solution of **2a** (0.6 mmol) and solvent (1 mL) were added over 1 h via syringe pump, after the reaction mixture was heated to at 80 °C for 3 h under air. b) Isolated yield.

Table 2. Synthesis of poly-substituted thiophenes[a), b)]

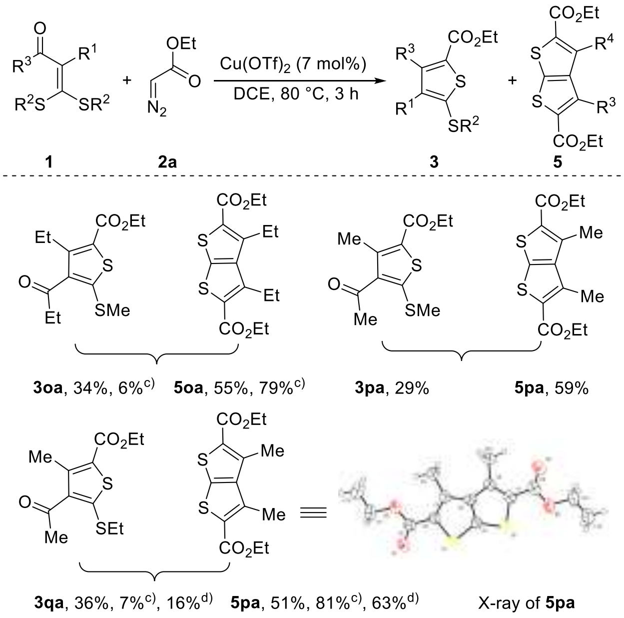


a) Reaction conditions: **1** (0.2 mmol) and $Cu(OTf)_2$ (7 mol%) were dissolved in DCE (1 mL), followed by a solution of **2** (0.6 mmol) and DCE (1 mL) were added over

1 h via syringe pump, after the reaction mixture was heated to at 80 °C for 3 h under air. [b)] Isolated yield. [c)] Reaction was performed at 40 °C. [d)] Reaction was performed with 5.5 mmol of **1h**, followed by a solution of **2a** (16.5 mmol) and DCE (15 mL) were added over 1.5 h via syringe pump.

propionyl and acetyl, the multi-substituted thiophenes **3oa-3qa** were isolated as the minor products. The fused-ring thienothiophenes **5oa-5pa** could be obtained in 55-59% yields as the major products. Notably, increasing the amount of **2a** to 5 equiv. delivered **5oa-5op** in high yields (Table 3). The molecular structure of **5pa** was unambiguously confirmed by X-ray crystallography (CCDC 1949636).[21] To evaluate the practical synthesis of the catalytic system, a large-scale (4.5 mmol) reaction was performed, and a satisfactory isolated yield could be obtained for **5pa** (from **1q**).

Table 3. Synthesis of poly-substituted thiophenes and fused-ring thienothiophene[a), b)]

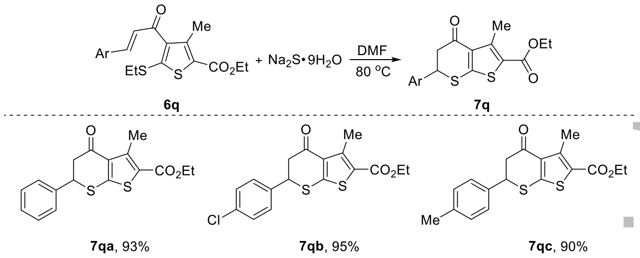


[a)] Reaction conditions: **1** (0.2 mmol) and $Cu(OTf)_2$ (7 mol%) were dissolved in DCE (1 mL), followed by a solution of **2a** (0.6 mmol) and DCE (1 mL) were added over 1 h via syringe pump, after the reaction mixture was heated to at 80 °C for 3 h under air. [b)] Isolated yield. [c)] Reaction was performed using **2a** (1 mmol). [d)] Reaction was performed with 4.5 mmol of **1q**, followed by a solution of **2a** (22.5 mmol) and DCE (15 mL) were added over 1.5 h via syringe pump.

To demonstrate the synthetic utility of the multi-substituted thiophenes, the substrate **6q** was conveniently prepared in high yield by the reaction of product **3qa** with aldehydes. Formation of **6q** was proposed to occur the [5C+1S] annulation with $Na_2S\cdot 9H_2O$,[22] and furnished thieno[2,3-*b*]thiopyran-4-ones **7q** in excellent yield (Table 4).

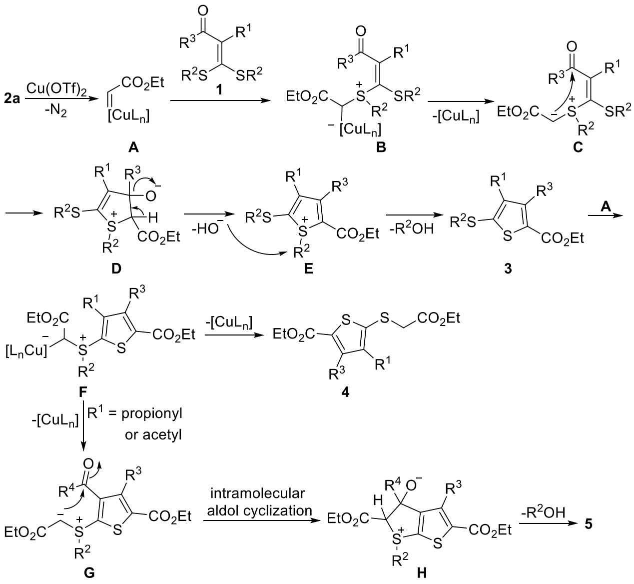
Based on the above results and previously reported studies,[10, 17, 20] a plausible mechanism is proposed for this reaction (Scheme 1). First, decomposition of nucleophilic diazo compounds in the presence of $Cu(OTf)_2$ affords electrophilic copper carbenoid **A** with the elimination of N_2.[23] The intermediate **A** is then attacked by the acyclic ketene-(*S*,*S*)-acetal **1** to deliver a sulfonium ylide **B**, which produces intermediate **C** via elimination of $[CuL_n]$.[10e]

Table 4. Synthesis of poly-substituted thiophenes[a), b)]



[a)] Reaction conditions: **6q** (0.2 mmol) and $Na_2S\cdot 9H_2O$ (0.22 mmol) in DMF (1 mL) at 80 °C for 2 h. [b)] Isolated yield.

Subsequent an intramolecular aldol cyclization affords the five-membered intermediate **D**, which undergoes elimination of HO^- to give intermediate **E**. Finally, the product **3** is formed via C-S bond cleavage in the presence of HO^-.[13] In the case of α-EWG ketene dithioacetals **1a-1c**, the product 3 attacked the intermediate **A** to furnish a sulfonium ylide **F**, which undergoes elimination of $[CuL_n]$ and C-S bond cleavage, leading to the formation of multi-substituted thiophenes **4**. In addition, the substitution R^1 are propionyl and acetyl, intermediate **F** further undergoes an intramolecular aldol cyclization to afford the fused five-membered alcohol intermediate H. Finally, the product **5** is formed via elimination of R^2OH. Since the propionyl and acetyl group have the stronger electron-withdrawing property than esters or amides, intramolecular aldol cyclization reaction is more likely to proceed.



Scheme 1. Postulated Mechanism.

In conclusion, we have developed a novel copper(II)-catalyzed domino reaction between the acyclic ketene-(*S*,*S*)-acetals and diazo compounds. This reaction provides simple and convenient, modular approaches to a range of poly-substituted thiophenes through a copper-catalyzed tandem process involving the generation of sulfur ylides and the C-S bond formation and cleavage sequence. Moreover, this transformation is not only tolerated to a diverse range of the acyclic ketene-(*S*,*S*)-acetals, but also the poly-substituted thiophenes could be transformed into the thieno[2,3-*b*]thiopyran-4-ones via [5C+1S] annulation.

Experimental Section

General Information.

All reagents were commercial and were used without further purification. Chromatography was carried on flash silica gel (300-400 mesh). Melting points were uncorrected. Unless noted, the ^{1}H NMR spectra were recorded at 400 or 500 MHz in CDCl$_3$ and the ^{13}C NMR spectra were recorded at 100 or 125 MHz in CDCl$_3$ with TMS as internal standard. All coupling constants (J values) were reported in Hertz (Hz). High-resolution mass spectra (HRMS) were obtained using a Bruker micro TOF II focus spectrometer (ESI).

General Procedure for the Preparation of 3 (3aa as Example)

To a solution of **1a** (0.2 mmol) and Cu(OTf)$_2$ (7 mol%) were dissolved in DCE (1 mL), followed by a solution of **2a** (0.6 mmol) and DCE (1 mL) were added over 1 h via syringe pump. The reaction mixture was stirred at 80 °C for 3 h under air. After completion of the reaction (monitored by TLC), the solvent was removed under reduced pressure, the residue was purified by chromatography (silica gel, petroleum ether/ diethyl ether = 60/1, V/V) to give **3aa** as a white solid.

General Procedure for the Preparation of 7q (7qa as Example)

To a solution of **6qa** (0.2 mmol) and Na$_2$S·9H$_2$O (0.22 mmol) in DMF (1 mL) at 80 °C for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured into water (50 mL) and extracted with CH$_2$Cl$_2$ (10 mL × 3). The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure to yield the corresponding crude product, which was purified by chromatography (silica gel, petroleum ether/ diethyl ether = 30/1, V/V) to give **7qa** as a white solid.

Acknowledgements

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[21] CCDC-1949636 (**5p**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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UPDATE

Copper(II)-catalyzed Domino Reaction of the Acyclic Ketene-(*S*, *S*)-Acetals with Diazo Compounds: Convenient Synthesis of Poly-substituted Thiophenes

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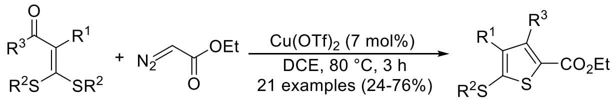

-broad substrate scope
-readily available substrates
-one-pot synthesis of poly-substituted thiophenes