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Palladium-Catalyzed C−S Bond Cleavage with Allenoates: Synthesis of Tetrasubstituted 2-Alkenylfuran Derivatives

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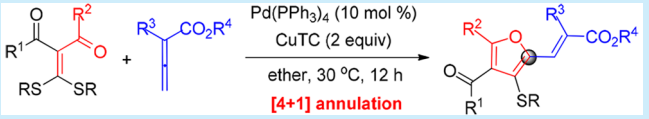
Supporting Information

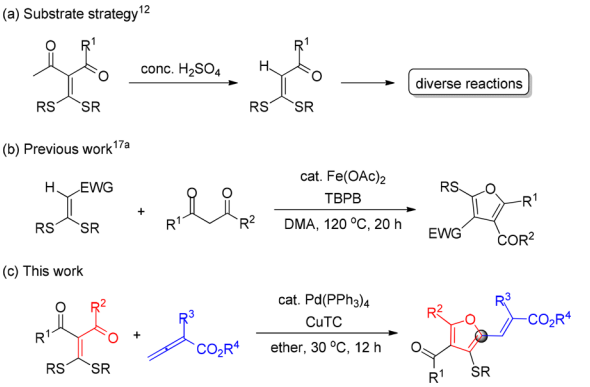
ABSTRACT: Palladium-catalyzed C−S cleavage of tetrasubstituted internal alkene α-oxo ketene dithioacetals was realized with allenoates as the coupling partners, efficiently affording tetrasubstituted 2-alkenylfuran derivatives with excellent regioselectivity under mild conditions. Allenoates acted as C1 synthons in the desulfurative [4 + 1] annulation.



The furan motif is a key structural unit in many bioactive molecules, natural products, and pharmaceuticals,[1] and furan compounds can be used as the important building blocks in organic synthesis.[2] To access multisubstituted furan derivatives, two strategies can be applied: (a) functionalization of an existing furan ring and (b) direct construction of a substituted furan ring by ring closure of suitable precursor compounds. Although direct C−H functionalization of furans seems to be an attractive method to prepare multisubstituted furans,[3] this method remains a great challenge in the reaction scope, efficiency, and chemoselectivity. As for the ring closure method, much progress has recently been made by means of the cyclization reactions of allenes. In this regard, cycloisomerization of allenyl ketones has been applied for the construction of multisubstituted furans by Marshall,[4a] Hashmi,[4b] Ma,[4c−f] Gevorgyan,[4g,h] and others.[4i−m] Palladium-catalyzed cycloisomerization of homoallenyl amides was developed to furnish 2-aminofurans.[5] Intramolecular cyclization of the allene precursors, that is, propargylic alcohols[6] and γ-acyloxybutynoates,[7] was also used to synthesize multisubstituted furans. Owing to their intrinsic reactivity,[8] allenes usually act as C2 and C3 synthons in the synthesis of heterocyclic compounds through cycloaddition reactions.[9] However, such cycloaddition reactions have rarely been applied for furan synthesis from allenes.[10] So far, only a few examples have been documented for allenes serving as the C1 synthons in the synthesis of vinyl-substituted heterocycles,[11] and transition-metal-catalyzed cycloaddition by means of allenes as the C1 synthons has not yet been achieved for the construction of furan derivatives.

α-Oxo ketene dithioacetals have recently demonstrated their diversity in organic synthesis.[12] However, they have usually been used as substrates in the trisubstituted form which is obtained by hydrolysis of the corresponding tetrasubstituted diketone ketene dithioacetals under strong acidic conditions (Scheme 1a). Direct C−H alkylation,[13] alkenylation,[14] arylation,[15] and other C−H functionalization reactions[16] of trisubstituted α-oxo ketene dithioacetals have been achieved, and transition-metal-catalyzed construction of heterocyclic compounds was also reported.[17] In comparison to trisubstituted α-oxo ketene dithioacetals, their tetrasubstituted analogues have been paid much less attention, and only a few reports have been documented for the desulfurative synthesis of tetrasubstituted alkenes,[18] carbocycles,[19] and *N*-[20] and *O*-containing heterocycles.[21] We recently reported iron-catalyzed oxidative C−H/C−H cross-coupling of trisubstituted α-oxo ketene dithioacetals with carbonyl methylenes, affording tetrasubstituted furans (Scheme 1b).[17a] Thus, we reasonably envisioned that tetrasubstituted 2-alkenylfurans might be accessed through the cyclization of tetrasubstituted α-oxo ketene dithioacetals with allenes as the C1 synthons. Herein, we disclose palladium-catalyzed [4 + 1] annulation of

Scheme 1. Strategy for Furan Synthesis



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tetrasubstituted α-oxo ketene dithioacetals with allenoates for the synthesis of tetrasubstituted 2-alkenylfurans (Scheme 1c).

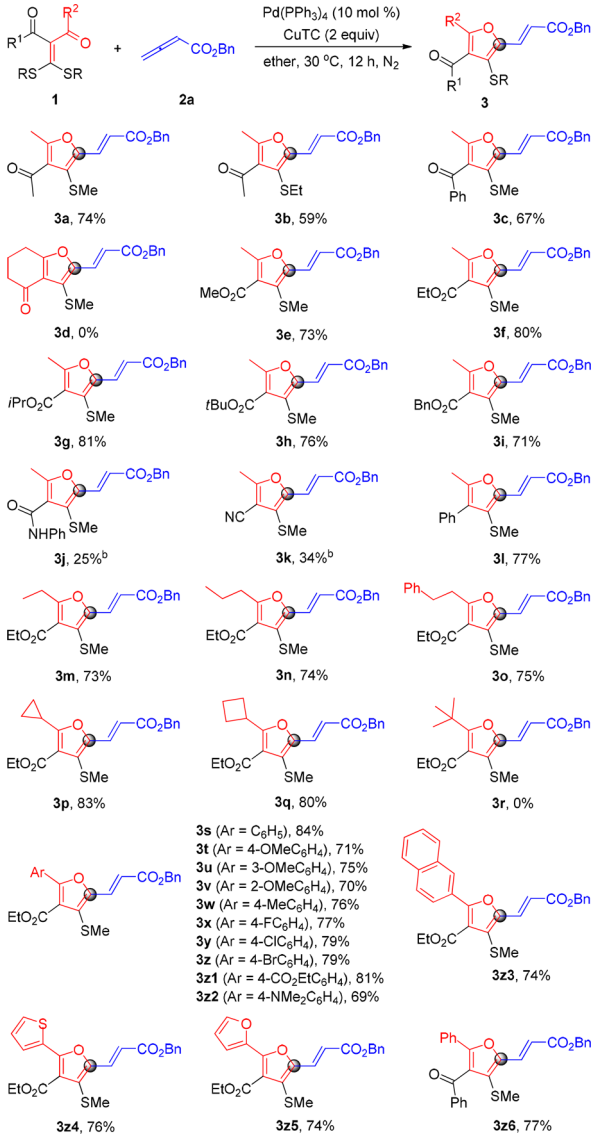
Initially, the reaction of α,α-diacetyl ketene di(methylthio)-acetal (**1a**) with benzyl buta-2,3-dienoate (**2a**) was conducted to screen the reaction conditions (eq 1) (see the Supporting

Information for details). Under a nitrogen atmosphere, in the presence of 10 mol % of $Pd(PPh_3)_4$ catalyst, 2 equiv of copper(I) thiophene-2-carboxylate (CuTC) as the sacrifacial additive, and 2 equiv of Cs_2CO_3 base, the reaction of **1a** with **2a** in a 1:3 molar ratio was undergone in diethyl ether at 25 °C for 12 h, affording tetrasubstituted 2-alkenylfuran **3a** in 71% yield. Elevating the temperature to 30 °C led to more efficient formation of **3a**. It is noteworthy that a base is not necessary for the reaction. Lowering the amount of CuTC diminished the reaction efficiency. The control experiments revealed that the reaction could not efficiently proceed in the absence of $Pd(PPh_3)_4$ or CuTC. On a 0.3 mmol scale the target product **3a** was isolated in 74% yield. The ^1H NMR analysis of the reaction mixture of **1a** and **2a** revealed exclusive formation of the stereospecific product **3a**.

Next, the scope of tetrasubstituted α-oxo ketene dithioacetals **1** was investigated under the optimized conditions (Scheme 2). The ethylthio-featuring α,α-diacetyl ketene di(ethylthio)acetal (**1b**) reacted less efficiently than **1a** to form the target product **3b** (59%). Although two different carbonyl groups, i.e., acetyl and benzoyl, were present in ketene dithioacetals **1c**, only the acetyl group was involved in the reaction with **2a**, and the reaction exclusively gave product **3c** (67%). 2-(Bis(methylthio)methylene)cyclohexane-1,3-dione (**1d**) exhibited no reactivity to **2a**. The α-acetyl-α-ester ketene dithioacetals **1e–i** efficiently underwent the reactions with **2a**, affording products **3e–i** in 71–81% yields, while α-amide and α-cyano-functionalized α-acetyl ketene dithioacetals **1j** and **1k** could not efficiently react to yield **3j** (25%) and **3k** (34%), respectively. α-Phenyl-α-acetyl ketene dithioacetals **1l** also reacted efficiently with **2a** to form **3l** (77%). It is noteworthy that α-ester-functionalized α-alkanoyl ketene di(methylthio)acetals **1m–q** reacted well with **2a** to produce products **3m–q** in 73–83% yields. Cyclopropyl and cyclobutyl moieties facilitated the formation of **3p** (83%) and **3q** (80%), respectively, whereas the *tert*-butyl group in α-ester-α-pivaloyl ketene dithioacetal (**1r**) completely inhibited the reaction with **2a**, exhibiting a remarkable steric effect.

Then, the protocol generality was explored by extending the substrate scope to α-aroyl ketene dithioacetals of type **1**. Notably, α-ester-functionalized α-benzoyl ketene dithioacetal **1s** efficiently underwent the reaction to generate **3s** (84%). The analogues of **1s**, that is, substituted α-benzoyl ketene dithioacetals **1t–z2**, exhibited various reactivities to form the target furan products **3t–z2** in 69–81% yields. Bulky α-(2-naphthoyl) ketene dithioacetal **1z3** reacted well with **2a** to give **3z3** (74%), showing no obvious steric effect from the 2-naphthyl group. α-Heteroaroyl (2-furoyl and 2-thienoyl) ketene dithioacetals **1z4** and **1z5** also reacted efficiently with **2a** to form **3z4** (76%) and **3z5** (74%), respectively. It should be noted that reacting α,α-dibenzoyl ketene dithioacetal **1z6** with allenoate **2a** led to the target product **3z6** in 77% yield.

Scheme 2. Scope of Tetrasubstituted α-Oxo Ketene Dithioacetals (1)[a]



[a]Conditions: **1** (0.3 mmol), **2a** (0.9 mmol), $Pd(PPh_3)_4$ (0.03 mmol), CuTC (0.6 mmol), ether (3 mL), 0.1 MPa N_2, 30 °C, 12 h. Yields refer to the isolated products. [b]$Pd(PPh_3)_4$ (0.06 mmol).

The protocol generality was further explored by using various allenoates **2** as the coupling partners (Scheme 3). α-Benzoyl-α-ester ketene dithioacetal **1s** reacted with ethyl buta-2,3-dienoate (**2b**) to afford the target product **4a** in 73% yield. Compound **1s** also efficiently reacted with allenoates **2b–f** to give tetrasubstituted 2-alkenylfurans **4b–e** (70–76%), and variation of the alkyl ester groups in the allenoates had no obvious impact on the reaction efficiency. Phenyl buta-2,3-dienoate (**2g**) exhibited a moderate reactivity, and its reaction with **1s** gave product **4f** in 50% yield. Both ethyl 2-methylbuta-2,3-dienoate (**2h**) and 2-benzylbuta-2,3-dienoate (**2i**) showed an obvious steric effect on the formation of the target products **4g** (50%) and **4h** (44%). The ^1H NMR analysis of the crude product **4g** or **4h** before separation was made, but the proton NMR signals were too complicated to distinguish the product stereoselectivity. We only obtained the stereospecific products **4g** and **4h** by silica gel column chromatography. Both the

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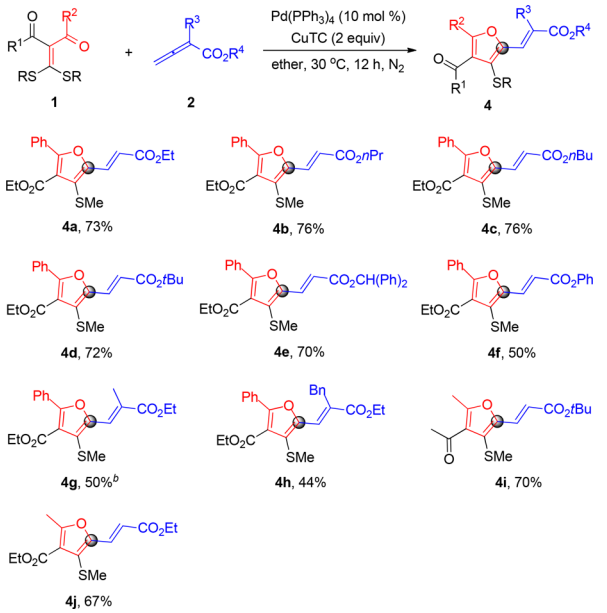
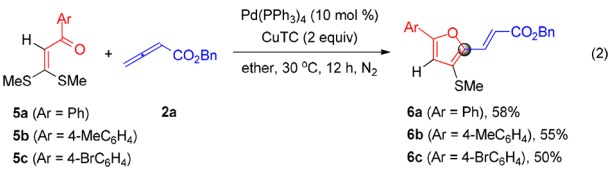
Scheme 3. Scope of Allenoates (2)[a]



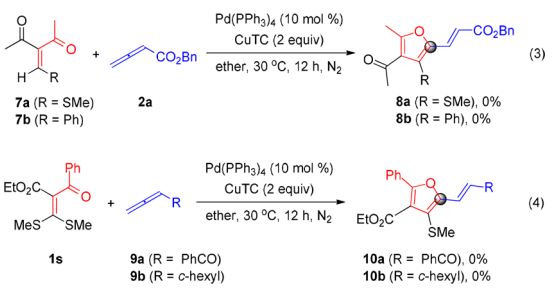
[a]Conditions: **1** (0.3 mmol), **2** (0.9 mmol), $Pd(PPh_3)_4$ (0.03 mmol), CuTC (0.6 mmol), ether (3 mL), 0.1 MPa N_2, 30 °C, 12 h. Yields refer to the isolated products. [b]60 °C, in a 25 mL sealed tube.

reactions of α-acetyl ketene dithioacetals **1a** with **2e** and **1f** with **2b** proceeded smoothly to form products **4i** (70%) and **4j** (67%), respectively. The molecular structures of compounds **3e** and **4g** were further confirmed by the X-ray single-crystal crystallographic determinations (see the SI for details).

A comparative evaluation of the reactivities was made between the tetra- and trisubstituted α-oxo ketene dithioacetals **1** and **5**. It was found that trisubstituted α-benzoyl ketene di(methylthio)acetals **5a–c** exhibited a reactivity lower than their tetrasubstituted analogues **1s**, **1w**, and **1z**, and their reactions with allenoate **2a** formed the corresponding trisubstituted 2-alkenylfurans **6a–c** in 50–58% yields (eq 2).

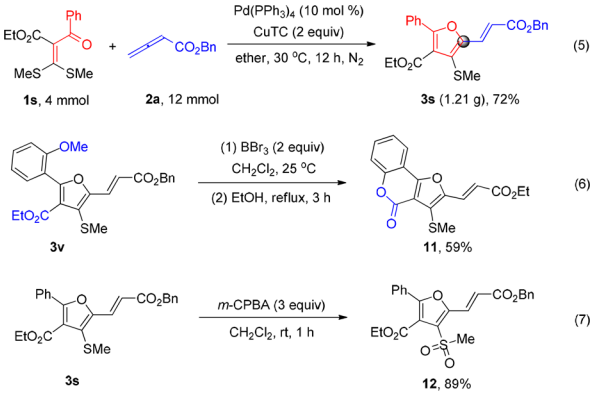


In order to verify the role of the dialkylthio functionality in **1**, 3-((methylthio)methylene)pentane-2,4-dione (**7a**) and 3-benzylidenepentane-2,4-dione (**7b**) were reacted with **2a** under the standard conditions. No reaction was observed to form the desired products **8a** and **8b** (eq 3), while the



corresponding α,α-diacetyl ketene di(methylthio)acetal (**1a**) reacted with **2a** to give the target product **3a** in 74% yield (Scheme 2). These results have unambiguously revealed that such a di(alkylthio) functionality is crucial for α-oxo ketene dithioacetals of type **1** to undergo the palladium-catalyzed [4 + 1] annulation with allenoates. Allene derivatives **9a** and **9b** were used to replace **2a** in the annulation reaction, but they could not undergo the same annulation reactions, implicating the crucial role of an ester group at the terminus of the allene backbone (eq 3).

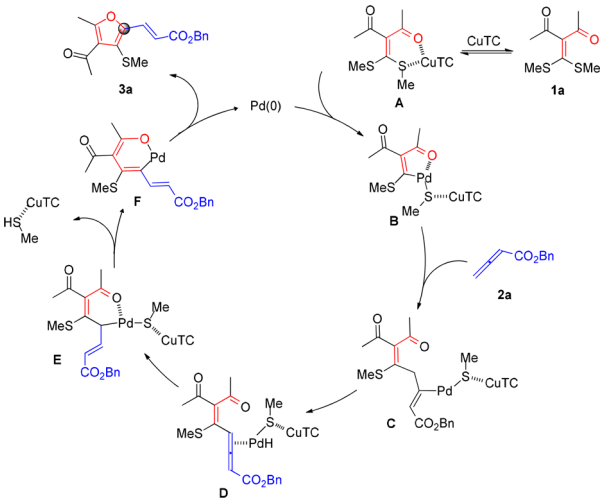
To demonstrate the utility of the synthetic protocol, a gram-scale reaction of **1s** with **2a** was performed, and the target product **3s** was obtained in 72% yield (eq 5). A two-step



procedure was developed to transform 2-alkenylfuran **3v** to lactone **11**[22] (59%), which has been proved to be a key structural motif in some bioactive molecules, natural products, and pharmaceuticals (eq 6).[23] With *meta*-chloroperoxybenzoic acid (*m*-CPBA) as the oxidant, 2-alkenylfuran **3s** was readily oxidized to the corresponding sulfone **12** in 89% yield (eq 7).

A plausible mechanism is proposed in Scheme 4. The copper(I) additive initially activates one of the C–S bonds in

Scheme 4. Proposed Reaction Mechanism



1a through coordination with the sulfur atom by assistance of the directing α-acetyl group, forming species **A**. Pd(0) species is then inserted into the activated C–S bond to yield Pd(II) species **B** in which both Pd–C and Pd–S bonds are formed. Interaction of species **B** with allenoate **2a** generates Pd(II) species **C** through insertion of the terminal alkenyl of the

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allene substrate into the Pd−C bond. β-H elimination occurs to produce intermediate **D**[24] and is followed by C=C insertion into the Pd−H bond, resulting in species **E**.[24b] Loss of the CuTC methylthiol adduct generates cyclopalladate species **F** which then undergoes reductive elimination to afford the target product **3a** and regenerate the catalytically active Pd(0) species, accomplishing a catalytic cycle.

In summary, efficient palladium-catalyzed, copper-mediated [4 + 1] annulation of tetrasubstituted α-oxo ketene dithioacetals and allenoates has been realized to synthesize tetrasubstituted 2-alkenylfurans under mild conditions. In the process, allenoates acted as effective C1 synthons. The present protocol provides a convenient route to tetrasubstituted 2-alkenylfurans.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02253.

Experimental materials and procedures, NMR of compounds, and X-ray crystallographic analysis for compounds **3e** and **4g** (PDF)

Accession Codes

CCDC 1813518 and 1842016 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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