ORGANIC
LETTERS

2013
Vol. 15, No. 20
5386–5389

Palladium Catalyzed Oxidative Coupling of α-Enolic Dithioesters: A New Entry to 3,4,5-Trisubstituted 1,2-Dithioles *via* a Double Activation Strategy

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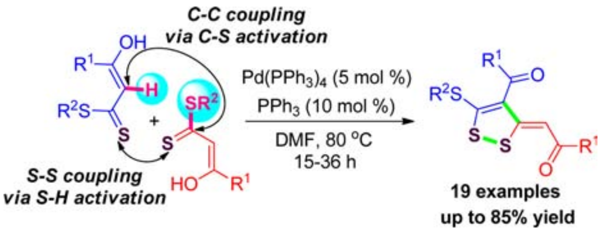
Received September 21, 2013

ABSTRACT



An operationally simple, facile, and convenient one-pot straightforward method for the construction of 3,4,5-trisubstituted 1,2-dithioles has been explored and developed via palladium catalyzed self-coupling of α-enolic dithioesters for the first time. Pd(0) efficiently catalyzes the activation and cleavage of S–H and C–S bonds to achieve cascade coupling, which results in the concomitant formation of new S–S and C–C bonds. Optimization data, substrate scope, and mechanistic insights are discussed.

Oxidative coupling is one of Nature's most commonly used synthetic tools for the structural expression of complex assemblies. Organic scaffolds bearing a disulfide linkage (–S–S–) hold significance due to their presence in various natural and biological frameworks.[1]Among various cyclic disulfides, five-membered skeletons are of high biological importance. For instance, α-lipoic acid is a naturally occurring antioxidant that bears a dithiolane skeleton. Another example is Oltipraz, a schistosomicide containing a 1,2-dithiole-3-thione core that has been found to be a potential chemopreventive agent against *Schistosoma mansoni* and *Schistosoma hematobium*. There are several other derivatives of 1,2-dithiole reported to have a wide spectrum of biological activity.[2] Furthermore, substituted 1,2-dithiole-3-ones have been found as potent inhibitors of FabH (an enzyme which catalyzes the initial step of fatty acid biosynthesis) from both *Escherichia coli* (ecFabH) and *Staphylococcus aureus* (saFabH).[2f]

Due to the pharmacological significance of the aforementioned core, a number of synthetic methods have

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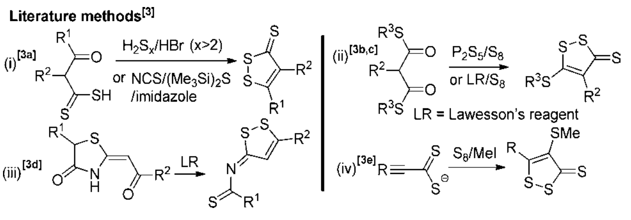
10.1021/ol402728y

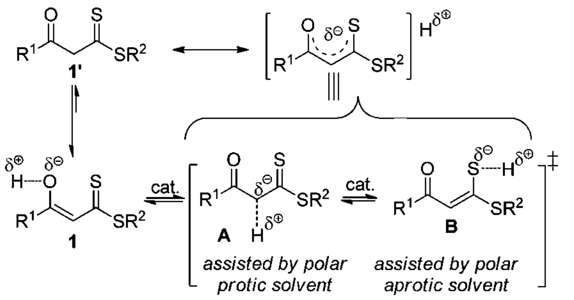
recently been developed for the construction of cyclic disulfides.[3,4] The currently available protocols for the synthesis of cyclic disulfides generally require the external source of sulfur, which is captured from either elemental sulfur or phosphorus containing sulfides or sulfides combined with free radical initiators to form the disulfide linkages (Scheme 1).[3] To the best of our knowledge, the synthesis of cyclic disulfides from α-enolic dithioesters via a coupling approach has not been reported. Herein, we disclose the first example of the synthesis of cyclic disulfides through a cascade S−S and C−C coupling of α-enolic dithioesters.

Scheme 1. Reported Methods for the Synthesis of Five-Membered Cyclic Disulfides



As part of our continuing efforts toward the development of novel methodologies for the construction of various bioactive scaffolds utilizing β-oxodithioesters[5,6] as a key precursor, we were interested in realizing the self-coupling of β-oxodithioesters. The interesting observation about β-oxodithioesters is that unlike β-oxocarboxylate esters prefers to exist exclusively in the enolic form (α-enolic dithioester **1**) both in the solid and in solution phase.[7] From our recent studies on this moiety it is well comprehended that the enolic −OH proton is not fixed with the hydroxyl group and has not been shown to be involved as such in any reaction. Depending upon the reaction conditions the labile proton can be concentrated on either the enolic α-carbon atom (as active methylene in structure **A**, Scheme 2) or on the thiocarbonyl sulfur atom (as thio-enol in structure **B**, Scheme 2). Thus, if the reaction conditions compel our precursor to adopt the structure **B**, an S−S coupling could be achieved by thiometalation of the in situ generated S−H bond. With this overview, we envisioned construction of a disulfide linkage by the self-coupling of β-oxodithioesters.

Scheme 2. A Structural Correlation to the Activity of Different Centres of a β-Oxo/α-Enolic Dithioester



For the past few decades palladium catalysis[8,9] has emerged as one of the most intriguing synthetic tools to construct C−C and C−X (X = O, N, S, halogens) bonds for industrial and academic purposes. Further, it has been employed in the syntheses of pharmaceuticals and natural products, which would not otherwise have been possible. We combined the catalytic character of palladium with the particular structural and chemical features of α-enolic dithioesters in a one-pot strategy that ended up with the successful assembly of our novel 1,2-dithiole framework through an unprecedented cascade S−S and C−C coupling. We commenced this project by investigating the reaction of α-enolic dithioesters **1** with $Pd(PPh_3)_4$ in the presence of the PPh_3 ligand in DMF at 80 °C, which led to self-coupling of two molecules of dithioester through S−S and C−C centers resulting in yellow colored 3,4,5-trisubstituted 1,2-dithioles **2** in high yields (Scheme 3).

Initially, to a solution (10 mL) of methyl 3-hydroxy-3-phenylprop-2-enedithioate **1a** (1.0 mmol) in dry CH_3CN, $Pd(PPh_3)_4$ (5 mol %) was added and the mixture was

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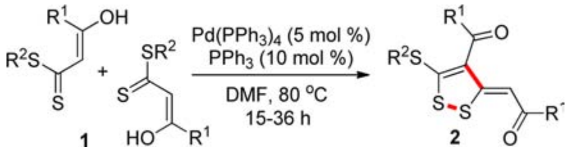
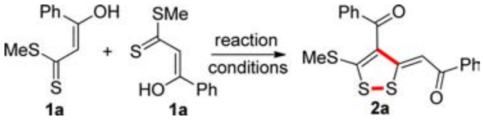
Scheme 3. One-Pot Cascade Coupling Protocol for the Synthesis of Trisubstituted 1,2-Dithioles



heated under reflux. Notably, the envisioned product 4-benzoyl-(*Z*)-3-(1-phenylacetylidene)-5-methylsulfanyl-1,2-dithiole **2a** was obtained in 30% yield after 24 h (Table 1, entry 1).

Table 1. Optimization of Reaction Conditions for the Model Reaction[a]



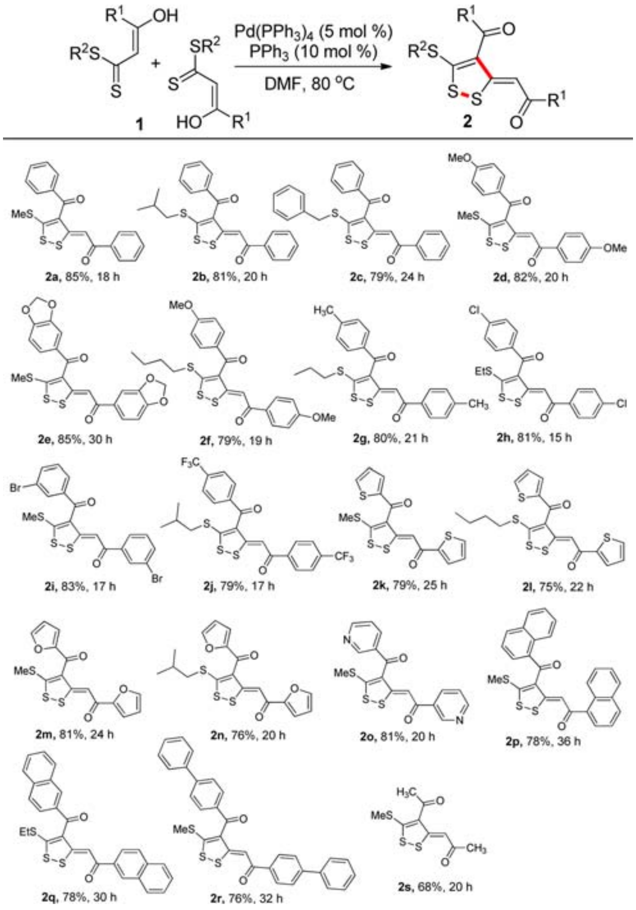
entry	catalyst (mol %)	solvent	temp (°C)	time (h)	yield (%)[b]
1	$Pd(PPh_3)_4$ (5)	CH_3CN	reflux	24	30
2	$Pd(PPh_3)_4$ (5)	DMF	80	24	75
3	$Pd(PPh_3)_4$ (5)	toluene	80	24	45
4	$Pd(PPh_3)_4$ (5)	DCE	reflux	24	15
5	$Pd(PPh_3)_4$ (5)	THF	reflux	24	20
6	$Pd(PPh_3)_2Cl_2$ (5)	DMF	80	24	20
7	$Pd(OAc)_2$ (5)	DMF	80	24	30
8	$Pd(OAc)_2$ (5), AgOAc (1 equiv), PPh_3 (10)	DMF	80	24	70
9	**$Pd(PPh_3)_4$ (5); PPh_3(10)**	**DMF**	**80**	**18**	**85**

[a] Reaction of 1.0 mmol of **1a** to form **2a**. [b] Isolated pure yields.

Realizing the significant methodological potential in the above observation, we focused on finding optimal reaction conditions for the synthesis of 1,2-dithiole **2a**. Reaction parameters such as solvent, catalyst loading, additional ligands, and temperature were examined (Table 1). The initial change of the solvent from CH_3CN to DMF improved the yield of our desired product from 30% to 75% (Table 1, entry 2). Further, the use of different polarity solvents (toluene, DCE, and THF) did not improve the yield (Table 1, entries 3−5). Next, replacement of Pd(0) with Pd(II) catalysts such as $Pd(PPh_3)_2Cl_2$ and $Pd(OAc)_2$ resulted in poor yields (Table 1, entries 6−7). However, the use of additional ligands such as PPh_3 along with AgOAc improved the yield significantly (Table 1, entry 8) suggesting the superior catalytic efficiency of Pd(0) species over Pd(II).

Keeping in mind that the ligand PPh_3 may accelerate the reaction, we used 10 mol % of additional PPh_3 with 5 mol % of $Pd(PPh_3)_4$. To our delight, the desired product **2a** was obtained in 85% yield within 18 h (Table 1, entry 9). A further assay demonstrated that 5 mol % of $Pd(PPh_3)_4$ with 10 mol % of PPh_3 was the optimum loading of the catalytic system for the reaction (see Supporting Information (SI)). Thus, the optimized reaction conditions were chosen to be 5 mol % of $Pd(PPh_3)_4$ in the presence of 10 mol % PPh_3 in DMF at 80 °C (Table 1, entry 9).

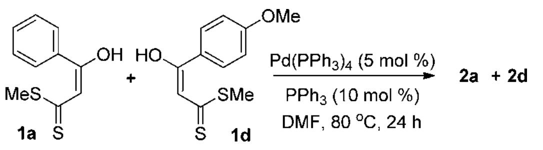
Scheme 4. Substrate Scope for the Synthesis of **2**[a]



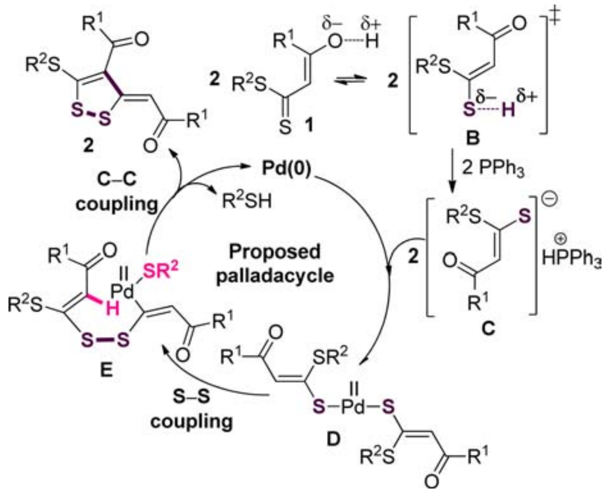
[a] Reaction conditions: **1** (1.0 mmol), $Pd(PPh_3)_4$ (5 mol %), PPh_3 (10 mol %), DMF (5.0 mL), 80 °C.

With the optimized reaction conditions in hand, we next investigated the scope and generality of our newly developed protocol utilizing various α-enolic dithioesters (Scheme 4). Notably, the catalytic system proved broadly applicable, and the method tolerated well a wide range of substituents: aromatic, heteroaromatic, or aliphatic groups at R^1 and different aliphatic substituents at R^2 of our precursor moiety. Steric and electronic effects of the substituents had no obvious impact on the yield of the reaction. Even R^1 groups such as the extended aromatics 1-naphthyl, 2-naphthyl, and biphenyl were well tolerated taking slightly longer reaction times (**2p**−**2r**). Moreover, in the case of α-enolic dithioesters where R^1 is an aliphatic group the yield is lowered, probably due to the lower heat stability of dithioesters derived from aliphatic ketones (**2s**).

Scheme 5. Preferential Formation of Homocoupled Product during the Reaction of **1a** and **1d**



Scheme 6. Proposed Palladacycle for the Cascade Coupling



Having demonstrated a broad scope for self-coupling of dithioesters bearing different substitution patterns, next we coupled two different dithioesters **1a** and **1d** under the optimized reaction conditions to check the possibility of heterocoupling. Workup of the reaction led to the formation of homocoupled dithioles **2a** and **2d** as major products with some additional faint spots on the TLC plate, which could not be isolated (Scheme 5). Similar results were obtained when three other sets of reactions were carried out with different dithioesters (see SI).

Although we have not established the mechanism of the reaction experimentally, based on the above results and previous reports regarding palladium catalysis, a plausible mechanism is outlined in Scheme 6.

The coupling is initiated by the oxidative addition of thioenolate **C** (generated by PPh$_3$ assisted deprotonation of isomeric form **B** of dithioester **1**) to the Pd(0) catalyst to give complex **D**. In this manner, the two dithioester molecules are assembled on the same Pd(II) atom via Pd–S bonds and then undergo S–S coupling followed by C–S activation to form organopalladium(II) intermediate **E**. Ultimately, **E** undergoes intramolecular C–C coupling to form our desired product **2** with the elimination of one molecule of thiol and the eventually regenerated Pd(0) catalyst to complete the Pd^0–Pd^{II}–Pd^0 catalytic cycle. Thus, the reaction sequence involves the activation and rupture of two S–H bonds and one C–S bond, as well as the formation of one S–S bond and one C–C bond.

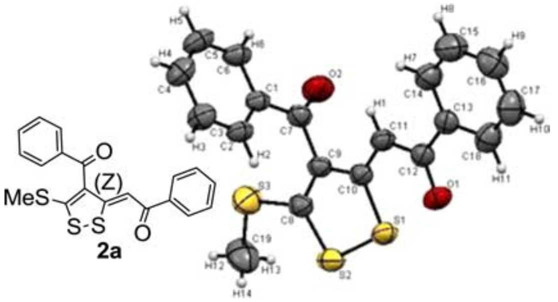


Figure 1. ORTEP diagram of compound **2a**.

All of the isolated products were identified by satisfactory spectral (IR, ^{1}H, and ^{13}C NMR) data and HRMS analyses. The structure of one representative compound 4-benzoyl-(*Z*)-3-(1-phenylacetylidene)-5-methylsulfanyl-3*H*-1,2-dithiole **2a** was confirmed unambiguously by single crystal X-ray diffraction analysis (see the SI) (Figure 1).

In summary, we have demonstrated an efficient homocoupling of α-enolic dithioesters for the synthesis of 3,4,5-trisubstituted 1,2-dithioles through tandem palladium-catalyzed consecutive S–S and C–C coupling for the first time in a single synthetic operation. This cascade transformation of the coupling/intramolecular cyclization reaction proceeds smoothly in DMF and demonstrates broad substrate scope and good functional group tolerance. The reaction outcomes provide a new strategy for the synthesis of densely functionalized 1,2-dithioles with high atom economy and high catalytic efficiency, which offers an efficient approach for the preparation of synthetic and medicinally relevant 1,2-dithiole derivatives. We believe that the present study not only provides an attractive procedure to access the highly substituted 1,2-dithioles but also broadens the scope of catalytic activity of the Pd(0) reagents. Further studies regarding photophysical properties and biological activities of the newly synthesized 1,2-dithiole derivatives are currently under investigation in our laboratory.

Acknowledgment. We gratefully acknowledge the financial support from SERB, the Department of Science and Technology (Grant No. SR/S1/OC-66/2009), the Council of Scientific and Industrial Research (Grant No. 02(0072)/12/EMR-II), and the UGC-UKIERI (Grant No. 184-16/2013(IC), New Delhi. Spectral help from Prof. Ganesh Pandey, CBMR, Lucknow is highly appreciated.

Supporting Information Available. Full experimental details; analytical and spectroscopic data (copies of ^{1}H and ^{13}C NMR for compounds (**2a**–**s**); X-ray data and structure for compound **2a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.