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One-Pot Syntheses of 2,3-Dihydrothiopyran-4-one Derivatives by Pd/Cu-Catalyzed Reactions of α,β-Unsaturated Thioesters with Propargyl Alcohols

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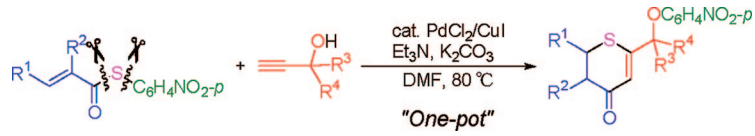
ABSTRACT



2,3-Dihydrothiopyran-4-one derivatives were readily prepared by Pd/Cu-catalyzed reactions between α,β-unsaturated thioesters and propargyl alcohols in the presence of bases. Of note, both carbon−sulfur bonds were cleaved as a result of the single procedure.

Recently, thioesters have been extensively employed as reaction substrates in transition-metal-catalyzed reactions.[1–6] For instance, cross-coupling reactions of organometallic reagents to afford ketones have been studied by several groups.[3–5] In addition, we developed a series of Pt-catalyzed decarbonylative carbothiolations of alkynes that afford vinyl sulfides.[6] Herein we report the syntheses of 2,3-dihydrothiopyran-4-one derivatives **3** by Pd/Cu-catalyzed one-pot cyclization between α,β-unsaturated thioesters **1** and propargyl alcohols **2** in the presence of bases (eq 1). These sulfur-containing six-membered heterocyclic derivatives display a wide range of biological activities.[7]

The reaction of CH_2═C(Me)C(O)S$C_6H_4NO_2$-*p* (**1a**, 0.4 mmol) with 2-methyl-3-butyn-2-ol (**2a**, 0.5 mmol) in the

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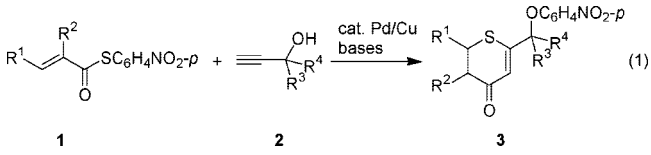
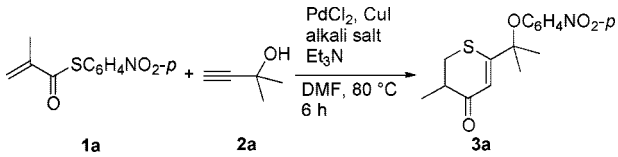


1 2 3

presence of $PdCl_2$ (0.004 mmol), CuI (0.04 mol), and Et_3N (0.4 mmol) in DMF (0.5 mL) at 80 °C for 6 h resulted in the formation of **3a** in 34% yield along with byproduct, including $(ArS)_2$ (10%) (run 1 of Table 1). Single X-ray

Table 1. Pd/Cu-Catalyzed Reaction of **1a** with **2a**[a]



1a 2a 3a

run	M	alkali salt	**3a** (%)[b]
1	$PdCl_2$	none	34
2	$PdCl_2$	Na_2CO_3	40
3	$PdCl_2$	K_2CO_3	68 (60)[c]
4	$PdCl_2$	Cs_2CO_3	60
5	$PdCl_2$	KOAc[d]	23
6	$PdCl_2$	K_2CO_3[e]	49
7[f]	$PdCl_2$	K_2CO_3	19
8[g]	$PdCl_2$	K_2CO_3	16
9[h]	$PdCl_2$	K_2CO_3	28
10	$Pd(OAc)_2$	K_2CO_3	45
11	$PdCl_2(PhCN)_2$	K_2CO_3	61
12	$PdCl_2(PPh_3)_2$	K_2CO_3	48
13	$PdCl_2$ (dppf)	K_2CO_3	25
14	$PtCl_2$	K_2CO_3	14

[a] Unless otherwise noted, **1a** (0.4 mmol), **2a** (0.5 mmol), $PdCl_2$ (1 mol %), CuI (10 mol %), K_2CO_3 (10 mol %), Et_3N (1 equiv), and DMF (0.5 mL) at 80 °C for 6 h. [b] NMR yield. [c] Isolated yield. [d] 20 mol %. [e] 5 mol %. [f] CuI (2 mol %). [g] CuI (100 mol %). [h] Et_3N (20 mol %).

crystallographic analysis of **3a** confirmed the structure to be a 2,3-dihydrothiopyran-4-one derivative (Figure 1).[8] It should be noted that *both* C−S bonds of **1a**, i.e., the C(O)−S and Ar−S bonds, were cleaved and the Ar group migrated from the sulfur of **1a** to the oxygen of **2a**. Among the alkali salts examined (runs 2−5), K_2CO_3 (10 mol %) resulted in the best yield (60% isolated yield) (run 3). Alteration of the amounts of K_2CO_3 (5 mol %) (run 6), CuI (2 mol %, 100 mol %) (runs 7 and 8), or Et_3N (20 mol %) (run 9) decreased the yield of **3a**. Other complexes such as $Pd(OAc)_2$ (run 10), $PdCl_2(PhCN)_2$ (run 11), $PdCl_2(PPh_3)_2$ (run 12), $PdCl_2$(dppf) (run 13), and $PtCl_2$ (run 14) showed inferior catalytic activity. Synthesis of **3a** required both a Pd and Cu catalyst.

The results of Pd/Cu-catalyzed reactions between various thioesters (**1**) and propargyl alcohols (**2**) under optimized conditions are summarized in Table 2. The treatment of **1a**

(8) Crystal data of **3a**: space group monoclinic, *P*21/*a* (No. 14) with $a = 11.1771(4)$, $b = 14.9463(5)$, $c = 11.0961(6)$ Å, $\beta = 1212.578(1)°$, $Z = 4$, $\rho = 1.307$ g/cm^3, $R = 0.074$, and $R_w = 0.184$. See Supporting Informaion for crystal data for **3a**.

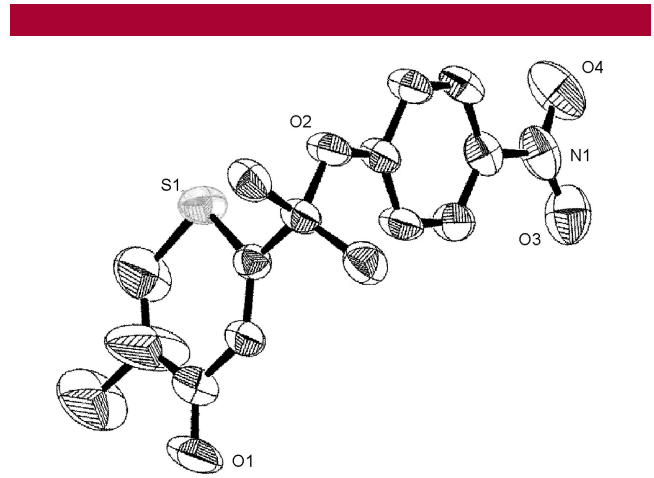
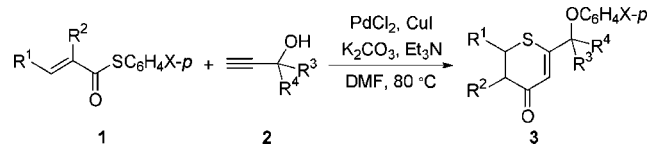


Figure 1. ORTEP diagram of **3a**.

with tertiary propargyl alcohols (**2b**, $R^3 = R^4 = -(CH_2)_4-$; **2c**, $R^3 = R^4 = -(CH_2)_5-$; **2d**, R^3 = Me, R^4 = Ph) provided

Table 2. Pd/Cu-Catalyzed One-Pot Syntheses of 2,3-Dihydro-thiopyran-4-one Derivatives[a]



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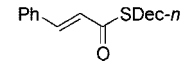
run	**1**	R^1	R^2	X	**2**	R^3	R^4	time (h)	**3** (%)[b]
1	**1a**	H	Me	NO_2	**2a**	Me	Me	6	**3a** 60
2	**1a**	H	Me	NO_2	**2b**	$-(CH_2)_4-$		6	**3b** 48
3	**1a**	H	Me	NO_2	**2c**	$-(CH_2)_5-$		16	**3c** 37
4	**1a**	H	Me	NO_2	**2d**	Me	Ph	9	**3d** 37
5	**1a**	H	Me	NO_2	**2e**	H	*n*-Pen	6	**3e** 35
6	**1a**	H	Me	NO_2	**2f**	H	H	6	**3f** nd
7	**1b**	H	*i*-Pr	NO_2	**2a**	Me	Me	6	**3g** 60
8[c]	**1c**	Ph	H	NO_2	**2a**	Me	Me	19	**3h** 55
9[c]	**1d**	Me	Me	NO_2	**2a**[d]	Me	Me	16	**3i** 64
10	**1d**	Me	Me	NO_2	**2c**[d]	$-(CH_2)_5-$		18	**3j** 62
11	**1e**	H	C_6H_4Me-*p*	Me	**2a**	Me	Me	6	**3k** nd
12	**1f**				**2a**	Me	Me	6	**3l** nd

[a] Unless otherwise noted, **1** (0.4 mmol), **2** (0.5 mmol), $PdCl_2$ (1 mol %), CuI (10 mol %), K_2CO_3 (10 mol %), Et_3N (1 equiv), and DMF (0.5 mL) at 80 °C. [b] Isolated yield. [c] 60 °C. [d] 1.0 mmol.

the corresponding cyclization products **3b**−**3d** in moderate yields (runs 2−4). Cyclization with secondary propargyl alcohol (**2e**, R^3 = H, R^4 = *n*-Pen) also gave **3e** in 35% yield (run 5). Propargyl alcohol (**2f**) gave a complicated mixture and **3f** was not synthesized (run 6). In the thioesters, replacement of the Me group at R^2 with an *i*-Pr group did not interfere with cyclization (run 7). **1c** (R^1 = Ph, R^2 = H) was also converted into **3h** in 55% yield (run 8). The thioester with an Me group at R^1 and a second Me at R^2 (**1d**) underwent a similar transformation as a result of reaction

with either **2a** or **2c** (runs 9 and 10). In marked contrast, the thioester with a *p*-tolyl group on the sulfur (**1e**, X = Me) gave a complicated mixture (run 11). No reaction took place with substrate **1f**, which had a $SC_{10}H_{21}$-*n* group rather than $SC_6H_4NO_2$-*p* (run 12). These results demonstrate that the $SC_6H_4NO_2$-*p* group of thioester **1** is required for the formation of **3**.

To elucidate the reaction pathway, the reaction of **1a** with **2a** in DMF-d_7 at 80 °C was monitored by ^{1}H NMR spectroscopy (Figure 2). The results suggest that both alkynyl

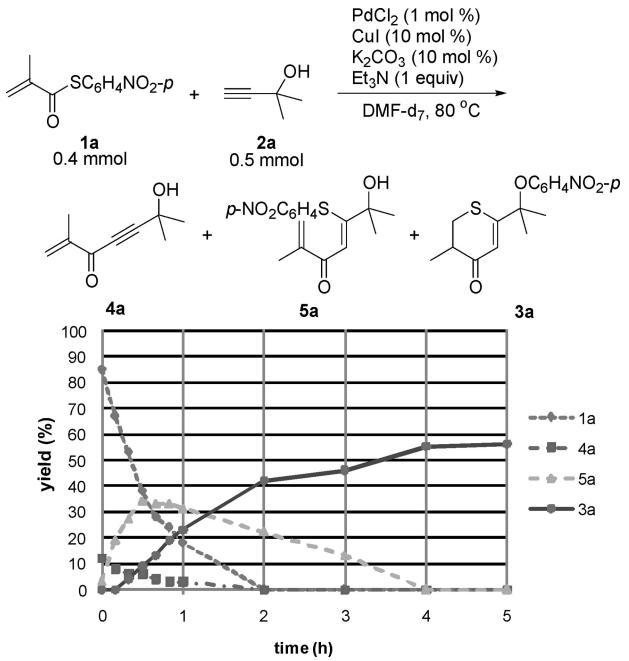
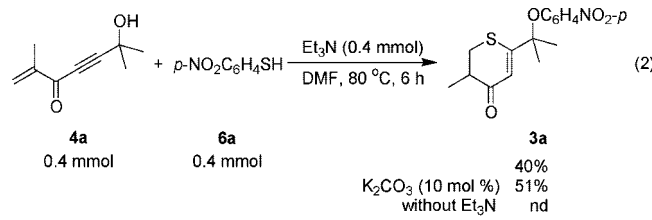
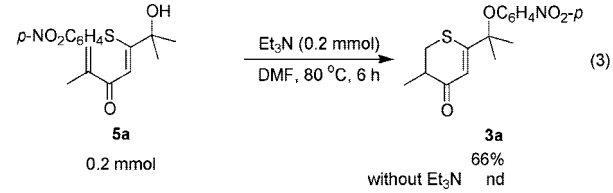


Figure 2. Time course of the Pd/Cu-catalyzed reaction of **1a** with **2a**.

ketone **4a** and vinyl sulfide **5a** were converted into **3a**. After 4 h, both **4a** and **5a** disappeared and **3a** was the major product detected, in addition to unidentified byproduct.

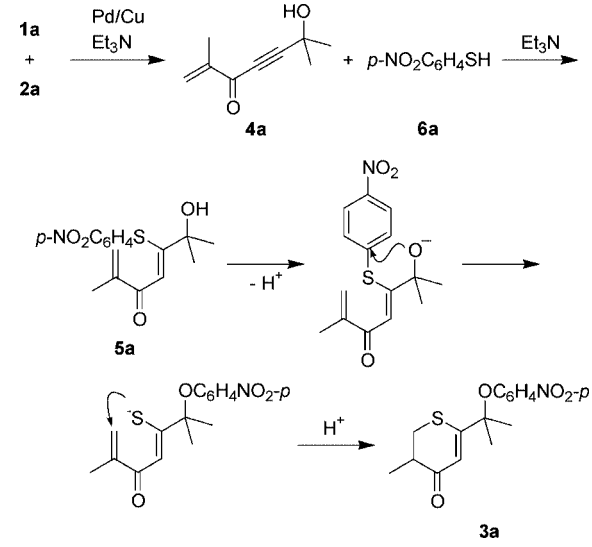
Thus, authentic **4a** and **5a**[9] were prepared and the reaction mechanism was examined in greater detail. Alkynyl ketone **4a** (0.4 mmol) reacted with *p*-$NO_2C_6H_4SH$ (**6a**, 0.4 mmol) to give **3a** in the presence of Et_3N (0.4 mmol) at 80 °C even without Pd/Cu catalysts, albeit in low yield (40%) (eq 2). Addition of a catalytic amount of K_2CO_3 (0.04 mmol) to the reaction mixture improved the yield of **3a** (51%). However, the yields for both the catalyst-free and K_2CO_3-catalyzed reaction of **1a** with **2a** were lower than that obtained by the Pd/Cu-catalyzed reaction as a result of formation of complicated byproduct (compare with run 1 of Table 2). Without Et_3N, neither **3a** nor **5a** formed. Intramolecular cyclization of **5a** (0.2 mmol) proceeded in the presence of Et_3N (0.2 mmol) at 80 °C to afford **3a** in 66% yield, whereas no reaction took place in the absence of Et_3N (eq 3). These results show that Et_3N is essential for the synthesis of **5** and **3**.





The reaction pathway proposed for the formation of **3** is shown in Scheme 1, with **1a** and **2a** as representative

Scheme 1. Proposed Reaction Pathway



substrates. First, a Pd/Cu-catalyzed Sonogashira-type reaction between **1a** and **2a** gives **4a** and **6a**,[3b] and the subsequent *trans*-addition of **6a** to the yne moiety of **4a** affords **5a**.[10,11] Intramolecular aromatic nucleophilic substitution by the oxygen anion induces migration of the *p*-$NO_2C_6H_4$ group

(9) The NOE experiment showed that the *cis*-isomer was exclusively produced. See Supporting Information for more details.

(10) For addition of thiol to eynone, see: (a) Perlmutter, P. In *Conjugate Addition Reactions in Organic Synthesis*; Baldwin, J. E., Magnus, P. D., Eds.; Pergamon Press: Oxford, U.K., 1992; Vol. 9, pp 310−322. (b) Blanco, L.; Bloch, R.; Bugnet, E.; Deloisy, S. *Tetrahedron Lett.* **2000**, *41*, 7875. (c) Gardiner, J. M.; Giles, P. E.; Martin, M. L. M. *Tetrahedron Lett.* **2002**, *43*, 5415. (d) Maezaki, N.; Yagi, S.; Yoshigami, R.; Maeda, J.; Suzuki, T.; Ohsawa, S.; Tsukamoto, K.; Tanaka, T. *J. Org. Chem.* **2003**, *68*, 5550. (e) Hollowood, C. J.; Yamanoi, S.; Ley, S. V. *Org. Biomol. Chem.* **2003**, *1*, 1664. (f) Ding, F.; Jennings, M. P. *Org. Lett.* **2005**, *7*, 2321.

(11) For copper-catalyzed acylselenation and telluration of alkynes, see: (a) Zhao, C.-Q.; Huang, X.; Meng, J.-B. *Tetrahedron Lett.* **1998**, *39*, 1933. (b) Zhao, C.-Q.; Li, J.-L.; Meng, J.-B.; Wang, Y.-M. *J. Org. Chem.* **1998**, *63*, 4170.

from sulfur to oxygen.[12] Finally, nucleophilic addition of the resultant S anion to the terminal ene moiety and the subsequent protonation yield **3a**. Maintenance of low concentrations of **4a** and **6a** during the course of the reaction improve the yield of **3a** relative to that obtained by the reaction of **4a** with **6a**.

In summary, this study realized the synthesis of 2,3-dihydrothiopyran-4-one derivatives by Pd/Cu-catalyzed reactions between α,β-unsaturated thioesters and propargyl alcohols in the presence of bases. The reactions proceed through a one-pot sequence as follows: Sonogashira-type reaction, Michael-addition of thiol to yne moiety, intramolecular aromatic nucleophilic substitution, and cyclization.

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Supporting Information Available: Experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) It has been reported that 2-arylthio-pyridine undergoes nucleophilic substitution by phenol: (a) Inoue, S. *Phosphorus Sulfur* **1985**, *22*, 141.