ORGANIC LETTERS

2008
Vol. 10, No. 12
2469−2472

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

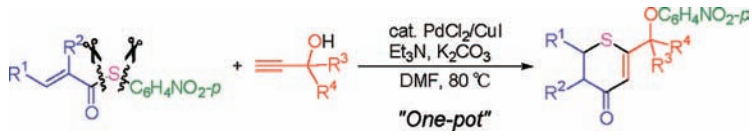
Yasunori Minami, Hitoshi Kuniyasu,* and Nobuaki Kambe*

Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

kuni@chem.eng.osaka-u.ac.jp

Received April 3, 2008

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

(1) (a) Osakada, K.; Yamamoto, T.; Yamamoto, A. *Tetrahedron Lett.* **1987**, *28*, 6321. (b) Kato, T.; Kuniyasu, H.; Kajiura, T.; Minami, Y.; Ohtaka, A.; Kinomoto, M.; Terao, J.; Kurosawa, H.; Kambe, N. *Chem. Commun.* **2006**, 868.

(2) (a) Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050. (b) Kuniyasu, H.; Ogawa, A.; Sonoda, N. *Tetrahedron Lett.* **1993**, *34*, 2491.

(3) (a) Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189. (b) Tokuyama, H.; Miyazaki, T.; Yokoshima, S.; Fukuyama, T. *Synlett* **2003**, 1512.

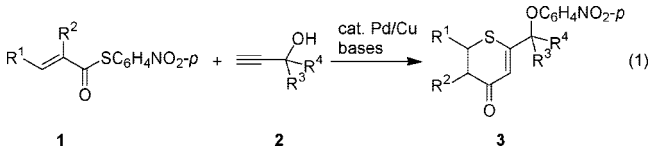
(4) (a) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260. (b) Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 3033. (c) Yang, H.; Li, H.; Wittenberg, R.; Egi, M.; Huang, W.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 1132. (d) Yang, H.; Liebeskind, L. S. *Org. Lett.* **2007**, *9*, 2993. (e) Villalobos, J. M.; Srogl, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 15734.

(5) (a) Ikeda, Z; Hirayama, H.; Matsubara, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 8200. (b) Ooguri, A.; Ikeda, Z.; Matsubara, S. *Chem. Commun.* **2007**, 4761.

(6) (a) Kuniyasu, H.; Kurosawa, H. *Chem. Eur. J.* **2002**, *8*, 2660. (b) Sugoh, K.; Kuniyasu, H.; Sugae, T.; Ohtaka, A.; Takai, Y.; Tanaka, A.; Machino, C.; Kambe, N.; Kurosawa, H. *J. Am. Chem. Soc.* **2001**, *123*, 5108. (c) Hirai, T.; Kuniyasu, H.; Kambe, N. *Chem. Lett.* **2004**, *33*, 1148. (d) Hirai, T.; Kuniyasu, H.; Kambe, N. *Tetrahedron Lett.* **2005**, *46*, 117. (e) Hirai, T.; Kuniyasu, H.; Asano, S.; Terao, J.; Kambe, N. *Synlett* **2005**, 1161. (f) Kuniyasu, H.; Yamashita, F.; Hirai, T.; Ye, J.-H.; Fujiwara, S.; Kambe, N. *Organometallics* **2006**, *25*, 566. (g) Kuniyasu, H.; Kambe, N. *Chem. Lett.* **2006**, *35*, 1320. (h) Yamashita, F.; Kuniyasu, H.; Terao, J.; Kambe, N. *Org. Lett.* **2008**, *10*, 101.

(7) (a) Ingall, A. H. In *Comprehensive Heterocyclic Chemistry II*; Boulton, A. S., McKkillop, A., Eds.; Pergamon Press: Oxford, 1996; Vol. 5, p 501. (b) Schneller, S. W. *Adv. Heterocycl. Chem.* **1975**, *18*, 59. (c) Katrizky, A. R.; Bonlton, A. J. *Adv. Heterocycl. Chem.* **1975**, *18*, 76. (d) Al-Nakib, T.; Bezjak, V.; Meegan, M.; Chandy, R. *Eur. J. Med. Chem.* **1990**, *25*, 455. (e) Al-Nakib, T.; Bezjak, V.; Rashid, S.; Fullam, B.; Meegan, M. *Eur. J. Med. Chem.* **1991**, *26*, 221. (f) van Vliet, L. A.; Rodenhuis, N.; Dijkstra, D.; Wikstrom, H.; Pugsley, T. A.; Serpa, K. A.; Meltzer, L. T.; Heffner, T. G.; Wise, L. D.; Lajiness, M. E.; Huff, R. M.; Svensson, K.; Sundell, S.; Lundmark, M. *J. Med. Chem.* **2000**, *43*, 2871.

10.1021/ol800754w CCC: $40.75
Published on Web 05/20/2008

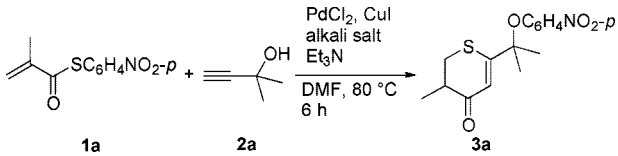


1 2 3

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 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** 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 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

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 %).

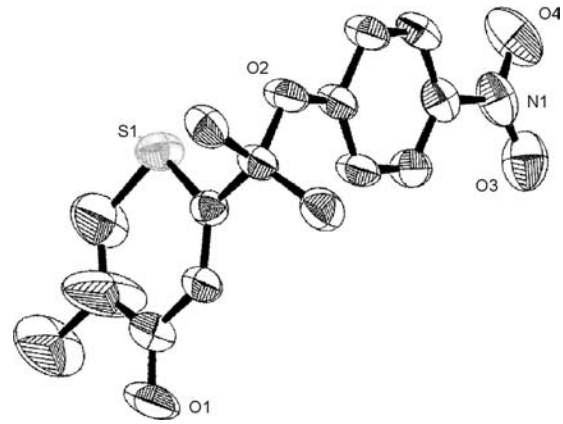
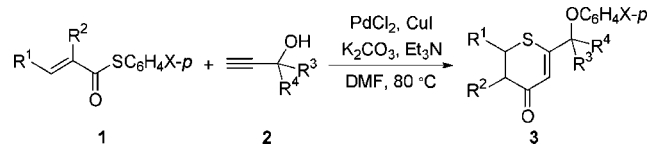


Figure 1. ORTEP diagram of **3a**.

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



1 2 3

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**	Ph, SDec-*n*			**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.

(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, β = 1212.578(1)°, Z = 4, ρ = 1.307 g/cm^3, R = 0.074, and R_w = 0.184. See Supporting Informaion for crystal data for **3a**.

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

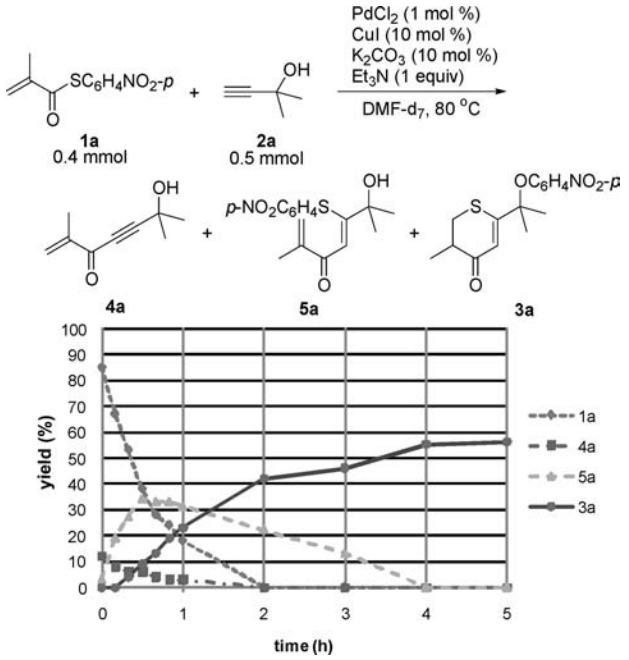
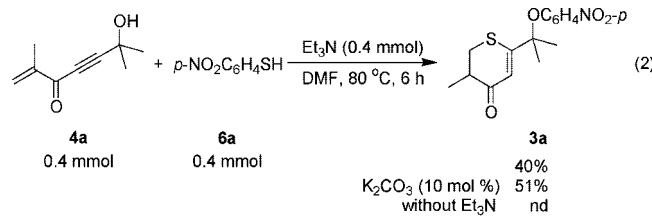
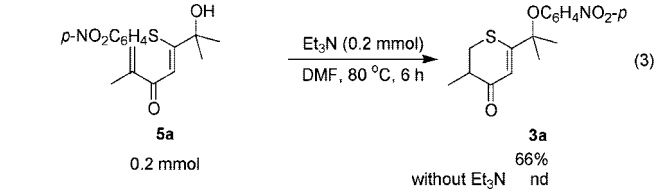


Figure 2. Time course of the Pd/Cu-catalyzed reaction of **1a** with **2a**.

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.

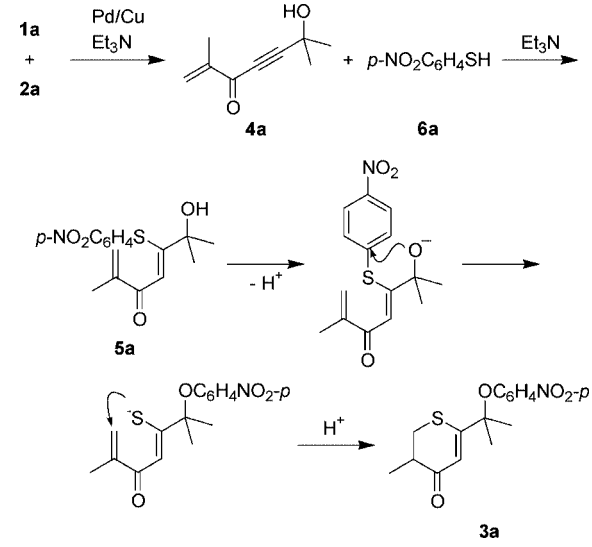
Thus, authentic **4a** and **5a**[9] were prepared and the reaction mechanism was examined in greater detail. Alkynyl ketone **4a** (0.4 mmol) reacted with *p*-$NO_2C_6H_4SH$ (**6a**, 0.4 mmol) to give **3a** in the presence of Et_3N (0.4 mmol) at 80 °C even without Pd/Cu catalysts, albeit in low yield (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.

Acknowledgment. Thanks are due to the Instrumental Analysis Center, Faculty of Engineering, Osaka University, for assistance in obtaining mass spectra with the JEOL JMS-DX303 instrument. Y.M. would like to thank The Global COE (center of excellence) Program "Global Education and Research Center for Bio-Environmental Chemistry" of Osaka University.

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.

OL800754W

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