Highly Regioselective Double Hydrothiolation of Terminal Acetylenes with Thiols Catalyzed by Palladium Diacetate

Takenori Mitamura, Masayuki Daitou, Akihiro Nomoto, and Akiya Ogawa*

Department of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University, 1-1 Gakuen-cho, Naka-ku, Sakai, Osaka 599-8531

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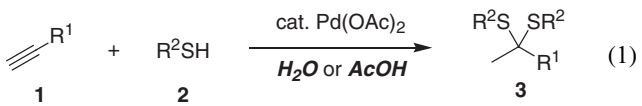
E-mail: ogawa@chem.osakafu-u.ac.jp

Treatment of terminal acetylenes **1** with two equivalents of thiols **2** in the presence of $Pd(OAc)_2$ catalyst and H_2O causes regioselective double hydrothiolation of **1**, leading to the corresponding dithioketals **3** in moderate to good yields.

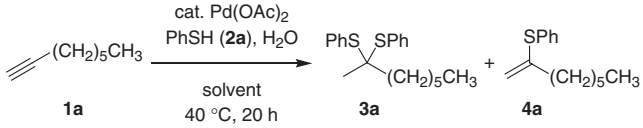
Organosulfur compounds are a useful class of compounds in pharmaceutical science, materials science, and organic synthesis, because of their bioactivity, material functionalities, and synthetic utilities as reaction intermediates.[1] Although transition-metal-catalyzed addition reactions of organosulfur compounds, e.g., thiols, to C–C unsaturated bonds are expected to be efficient methods for the synthesis of organosulfur compounds including the formation of new C–S bonds, the development of these methods is thought to be challenging due to poisoning of transition-metal catalysts by sulfur.[2] We have recently revealed the palladium-catalyzed addition of organic disulfides or thiols to acetylenes[3] or allenes,[4] leading to the corresponding vinyl sulfides selectively. Very recently, we and other groups have also subsequently achieved several addition reactions of organosulfur compounds to unsaturated bonds mediated by transition-metal catalysts.[5,6] During the course of our research extending the transition-metal-catalyzed addition reactions of thiols to unsaturated bonds, we have found that thiols add duplicately to acetylenes. Herein, we wish to report a $Pd(OAc)_2$-catalyzed regioselective double hydrothiolation of terminal acetylenes with thiols to give the corresponding dithioketals in the presence of H_2O or AcOH (eq 1).[7]



(1)

We examined the $Pd(OAc)_2$-catalyzed reaction of 1-octyne (**1a**) with 2 equivalents of benzenethiol (**2a**) in THF at 40 °C in the presence of H_2O (Table 1). 1-Octyne (**1a**) underwent the double hydrothiolation with **2a** to afford dithioketal **3a** selectively (Entries 1 and 2). In addition, the use of AcOH in place of H_2O was effective for this double hydrothiolation

Table 1. The Reaction of 1-Octyne (**1a**) with Benzenethiol (**2a**)[a]



Entry	Solvent	Yield of **3a**/%[b]	Yield of **4a**/%[b]
1	THF	80	ND
2[c]	THF	72	ND
3[d]	THF	71	3
4[e]	THF	ND	69
5[f]	THF	73	3
6	Acetone	83	ND
7	EtOH	84	ND
8	CH_3CN	66	ND
9	$CHCl_3$	66	ND
10	Benzene	17	28

a) Reaction conditions: 1-octyne (**1a**, 0.5 mmol), benzenethiol (**2a**, 1.0 mmol), $Pd(OAc)_2$ (5 mol % based on **1a**), solvent (0.5 mL), H_2O (ca. 1 equiv based on **1a**), 40 °C, 20 h. b) Determined by ^1H NMR. c) The reaction was carried out for 16 h. d) AcOH (1 equiv based on **1a**) was used in place of H_2O. e) The reaction was carried out in the absence of H_2O. f) The reaction was carried out for 40 h in the absence of H_2O.

(Entry 3). When we examined the $Pd(OAc)_2$-catalyzed reaction of **1a** with **2a** in the absence of H_2O, the $Pd(OAc)_2$-catalyzed reaction provided only vinyl sulfide **4a** as a single hydrothiolation product (Entry 4). However, when the $Pd(OAc)_2$-catalyzed reaction of **1a** with **2a** in the absence of H_2O was conducted for 40 h, dithioketal **3a** was obtained in 73% yield (Entry 5). Thus, these results suggest that the addition of H_2O or AcOH promotes the double hydrothiolation of terminal acetylenes. The $Pd(OAc)_2$-catalyzed double hydrothiolation of **1a** was also examined in several solvents. In the cases of acetone and ethanol, the corresponding dithioketal **3a** was obtained in 83% and 84% yields, respectively (Entries 6 and 7). In acetonitrile or chloroform, **3a** was also produced in moderate yields (Entries 8 and 9). In contrast, when benzene was used as a nonpolar solvent, a mixture of vinyl sulfide **4a** and dithioketal **3a** was formed with lower conversion (Entry 10).

We next examined the $Pd(OAc)_2$-catalyzed reaction of several terminal acetylenes **1** with thiols **2** (Table 2). 1-Hexyne (**1b**) and 5-methyl-1-hexyne (**1c**) provided the corresponding dithioketals **3b** and **3c** in good to high yields (Entries 2 and 3). Hydroxy, carboxy, and chloro substituents were tolerated under these double hydrothiolation conditions, affording **3d**, **3e**, and **3f** in moderate to good yields, respectively (Entries 4–6). In the cases of 5-hexynenitrile (**1g**) and methyl propargyl ether (**1h**), moderate yields of **3g** and **3h** were obtained (Entries 7 and 8). Unfortunately, propargyl chloride (**1i**) or bromide (**1j**) were not suitable substrates for this double hydrothiolation, and instead, the oligomerization of **1i** or **1j** took place (Entries 9 and 10). In the case of phenylacetylene (**1k**), the reaction led to **3k** successfully when the reaction mixture was treated in two steps (Entry 11).[8] We also attempted using several arenethiols. 4-Fluorobenzenethiol (**2b**) and 4-chlorobenzenethiol (**2c**) produced dithioketals **3l** and **3m** in 70% and 55% isolated yields, respectively (Entries 12 and 13). In contrast, the reactions with

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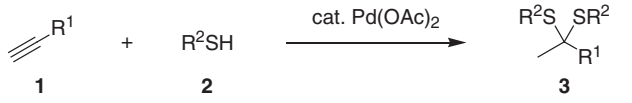
Table 2. Double Hydrothiolation of Terminal Acetylenes **1** with Thiols **2**[a)]



1 **2** **3**

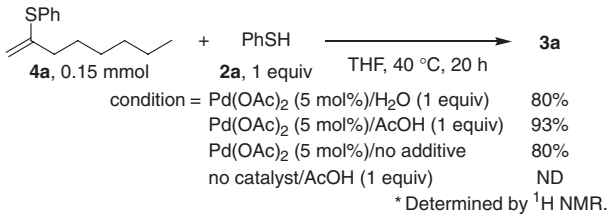
Entry	**1**	R^1	**2**	R^2	**3**	Yield/%[b)]
1	**1a**	$CH_3(CH_2)_5$–	**2a**	Ph–	**3a**	72 (67)
2	**1b**	$CH_3(CH_2)_3$–	**2a**	Ph–	**3b**	67 (57)
3	**1c**	$(CH_3)_2CH(CH_2)_2$–	**2a**	Ph–	**3c**	82 (73)
4	**1d**	$HO(CH_2)_2$–	**2a**	Ph–	**3d**	60 (43)
5	**1e**	$HO_2C(CH_2)_3$–	**2a**	Ph–	**3e**	69 (33)
6	**1f**	$Cl(CH_2)_3$–	**2a**	Ph–	**3f**	54 (45)
7	**1g**	$NC(CH_2)_3$–	**2a**	Ph–	**3g**	36 (21)
8	**1h**	CH_3OCH_2–	**2a**	Ph–	**3h**	36 (28)
9	**1i**	$ClCH_2$–	**2a**	Ph–	**3i**	5
10	**1j**	$BrCH_2$–	**2a**	Ph–	**3j**	ND
11[c)]	**1k**	Ph–	**2a**	Ph–	**3k**	53 (52)
12	**1a**	$CH_3(CH_2)_5$–	**2b**	4-F–C_6H_4–	**3l**	93 (70)
13	**1a**	$CH_3(CH_2)_5$–	**2c**	4-Cl–C_6H_4–	**3m**	70 (55)
14[d)]	**1a**	$CH_3(CH_2)_5$–	**2d**	4-CH_3–C_6H_4–	**3n**	20 (8)
15[d)]	**1a**	$CH_3(CH_2)_5$–	**2e**	2-CH_3–C_6H_4–	**3o**	23 (—)
16[e)]	**1a**	$CH_3(CH_2)_5$–	**2f**	C_6H_{11}–	**3p**	25 (25)
17	**1a**	$CH_3(CH_2)_5$–	**2g**	$CH_3(CH_2)_{11}$–	**3q**	ND

a) Reaction conditions: acetylene (**1**, 0.5 mmol), thiol (**2**, 1.0 mmol), $Pd(OAc)_2$ (5 mol % based on **1**), THF (0.5 mL), H_2O (ca. 1 equiv based on **1**), 40 °C, 16 h. b) Yields were determined by ^1H NMR. Values in parentheses are isolated yields. c) This reaction was conducted by the following two steps: (1) phenylacetylene (**1k**, 0.25 mmol), benzenethiol (**2a**, 0.25 mmol), $Pd(OAc)_2$ (5 mol %), acetone (0.25 mL), 40 °C, 16 h; (2) benzenethiol (**2a**, 0.25 mmol), AcOH (0.25 mmol), 40 °C, 16 h. The yield shown in Entry 11 was calculated after the two steps reaction. d) The corresponding vinyl sulfide **4** was obtained mainly. e) Most of the starting material **1a** was recovered unchanged.

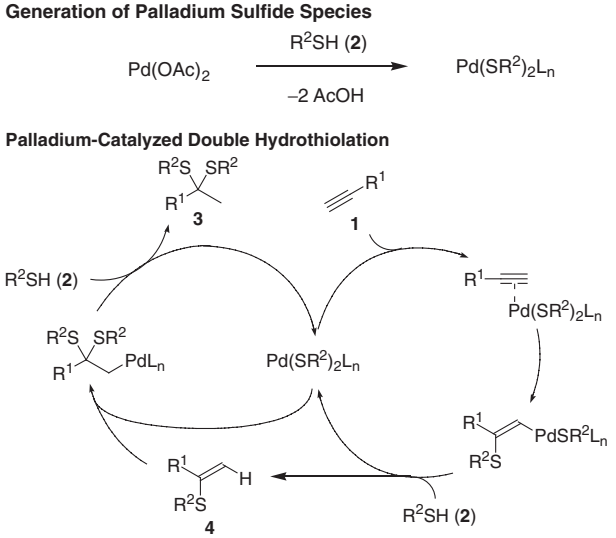
4-toluenethiol (**2d**), 2-toluenethiol (**2e**), and cyclohexanethiol (**2f**) afforded low yields of **3n**, **3o**, and **3p** (Entries 14–16), and dodecanethiol (**2g**) did not give **3q** (Entry 17).

To elucidate the reaction pathway for the palladium diacetate-catalyzed double hydrothiolation of terminal acetylenes with thiols, we focused on vinyl sulfides as a plausible intermediate. When vinyl sulfide **4a** was treated with **2a** and H_2O in the presence of $Pd(OAc)_2$ as a catalyst, hydrothiolation of **4a** proceeded to afford the dithioketal **3a** in 80% yield (Scheme 1). AcOH was also efficient for the hydrothiolation of **4a**, providing an excellent yield of **3a**. In addition, the reaction of **4a** in the absence of additives also provided **3a** in 80% yield. On the other hand, no reaction took place by use of AcOH in the absence of $Pd(OAc)_2$. These results strongly suggest that the double hydrothiolation proceeds via the formation of vinyl sulfides and is catalyzed by palladium species in both first addition of thiols to terminal acetylenes and second addition to vinyl sulfides.

A plausible reaction pathway for the reaction is proposed in Scheme 2. Ligand exchange of acetate groups of $Pd(OAc)_2$ with R^2S groups generated $Pd(SR^2)_2L_n$ and AcOH (Scheme 2). The coordination of alkyne to the palladium sulfide complex and *syn*-thiopalladation of alkyne formed *β-cis*-thio-substituted



Scheme 1. Reactions of vinyl sulfide **4a**.



Scheme 2. A plausible reaction pathway.

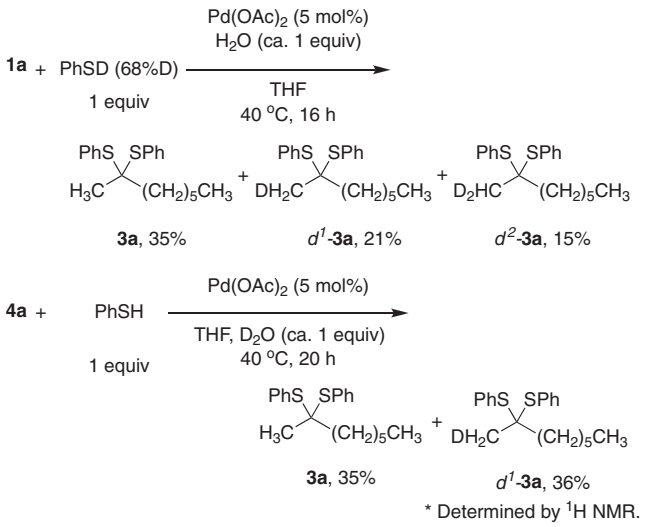
vinylpalladium species. Protonolysis of vinylpalladium species with thiols produced the vinyl sulfide **4** with regeneration of the palladium sulfide complex. Further thiopalladation and protonolysis with thiols afforded dithioketals **3**. H_2O or AcOH may contribute to accelerating the addition of thiols to unsaturated bonds by protonolysis or coordinate to the catalyst to prevent the clustering of palladium complex with sulfur species.

We also examined the reaction using PhSD or D_2O to gain mechanistic insights (Scheme 3).[9] When **1a** was treated with PhSD (68%D) in the presence of H_2O, the reaction formed **3a**, d_1-**3a**, and d_2-**3a** in 35%, 21%, and 15% yields. In addition, the reaction of **4a** with PhSH in the presence of D_2O was also carried out, which afforded **3a** and d_1-**3a** in 35% and 36% yields. These observations suggest that H_2O (or AcOH) promotes protonation in the generation of dithioketals.

In summary, we have developed the palladium diacetate-catalyzed double hydrothiolation of terminal acetylenes with thiols in the presence of H_2O or AcOH, leading to the corresponding dithioketals selectively. We also revealed that this palladium-catalyzed double hydrothiolation took place via the formation of vinyl sulfides and the additives, i.e., H_2O or AcOH, promoted the addition of thiols to unsaturated bonds.

Experimental

General Procedure for the Palladium Diacetate-Catalyzed Double Hydrothiolation of Terminal Acetylenes. To a solution of 1-octyne (**1a**, 0.5 mmol) and palladium diacetate (5 mol %) in THF (0.5 mL) were added benzenethiol (**2a**, 1.0 mmol) and H_2O (ca. 1 equiv based on **1a**), and the mixture



Scheme 3. The reaction using PhSD or D_2O.

was stirred at 40 °C for 16 h. After the reaction, the mixture was filtered through a Celite pad (eluent: AcOEt) and the filtrate was concentrated under reduced pressure. The crude mixture was purified by PTLC (Hex:AcOEt = 99:1) to give 2,2-bis(phenylsulfanyl)octane (**3a**, 0.335 mmol, 67%) as slightly yellow oil.

2,2-Bis(phenylsulfanyl)octane (3a): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, $J = 6.6$ Hz, 3H), 1.15–1.34 (m, 6H), 1.37 (s, 3H), 1.55–1.74 (m, 4H), 7.27–7.39 (m, 6H), 7.58–7.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.5, 24.7, 28.1, 29.2, 31.7, 41.5, 64.2, 128.4, 128.9, 132.1, 136.8; MS (EI) m/z 330 (M^+, 100).

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Supporting Information

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for dithioketals. This material is available free of charge on the web at http://www.csj.jp/journals/bcsj/.

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8 When the reaction of phenylacetylene (0.1 mmol) with benzenethiol (0.2 mmol) in the presence of $Pd(OAc)_2$ (5 mol %) and H_2O (ca. 0.1 mmol) in THF was conducted, a complex mixture of 1,1-bis(phenylsulfanyl)ethylbenzene, 2-phenylsulfanylstyrene, and 1-phenylsulfanylstyrene was obtained.

9 For the monohydrothiolation using deuterated thiol, see Ref. 3b.