ORGANIC
LETTERS

2005
Vol. 7, No. 19
4193−4195

Rhodium-Catalyzed Reductive Coupling of Disulfides and Diselenides with Alkyl Halides, Using Hydrogen as a Reducing Agent

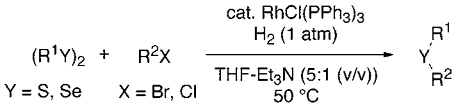
Kaori Ajiki, Masao Hirano, and Ken Tanaka*

Department of Applied Chemistry, Graduate School of Engineering, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184-8588, Japan

tanaka-k@cc.tuat.ac.jp

Received July 7, 2005

ABSTRACT



We have established that $RhCl(PPh_3)_3$ catalyzes a reductive coupling of disulfides and diselenides with alkyl halides in the presence of triethylamine using hydrogen as a reducing agent. This reaction serves as a convenient new method to produce unsymmetrical sulfides and selenides from disulfides and diselenides instead of unstable and odoriferous thiols and selenols.

The reductive coupling of disulfides or diselenides with alkyl or aryl halides is an important reaction in the synthesis of various unsymmetrical sulfides and selenides, which can eliminate the use of unstable and odoriferous thiols and selenols.[1] Although some efficient reductive coupling reactions using dicarcogenides have been reported, they require a stoichiometric amount of metal reducing agents.[2−5] In this paper, we describe a rhodium-catalyzed reductive coupling of disulfides and diselenides with alkyl halides using hydrogen as a reducing agent.

Recently, we reported a rhodium-catalyzed dehydrogenation of thiols to disulfides under an Ar atmosphere[6] and a rhodium-catalyzed coupling reaction of thiols with alkyl halides in the presence of triethylamine.[7,8] The rhodium-catalyzed dehydrogenation reaction is highly dependent on reaction temperature. Although a high yield of disulfides was obtained at 4 °C, raising the reaction temperature to 25 °C decreased the yield of disulfides and regenerated the thiols.[6,9] Furthermore, when dioctyl disulfide was treated with an atmospheric pressure of hydrogen in the presence of 5%

---

[1] For reviews for transition-metal-catalyzed synthesis of carcogenides, see: (a) Ogawa, A. In *Main Group Metals in Organic Synthesis*; Yamamoto, H., Oshima, K., Eds.; Wiley-VCH: Weinheim, Germany, 2004; p 813. (b) Ali, B. E.; Alper, H. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; Chapter VI, section 2.1.1.2. (c) Ogawa, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; Chapter VII. 6. (d) Kuniyasu, H. In *Catalytic Heterofunctionalization*; Togni, A., Grützmacher, H., Eds.; Wiley-VCH: Weinheim, Germany, 2001, p 217. (e) Kuniyasu, H.; Kurosawa, H. *Chem. Eur. J.* **2002**, *8*, 2660. (f) Ogawa, A. *J. Organomet. Chem.* **2000**, *611*, 463. (g) Kondo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205. (h) Han, L.-B.; Tanaka, M. *J. Chem. Soc., Chem. Commun.* **1999**, 395. (i) Beletskaya, I.; Moberg, C. *Chem. Rev.* **1999**, *99*, 3435.

[2] Reductive coupling of disulfides with alkyl halides, see: (a) Chowdhury, S.; Roy, S. *Tetrahedron Lett.* **1997**, *38*, 2149. (b) Nishino, T.; Okada, M.; Kuroki, T.; Watanabe, T.; Nishiyama, Y.; Sonoda, N. *J. Org. Chem.* **2002**, *67*, 8696. (c) Nishino, T.; Nishiyama, Y.; Sonoda, N. *Chem. Lett.* **2003**, 918. (d) Ranu, B. C.; Mandal, T. *J. Org. Chem.* **2004**, *69*, 5793.

[3] Reductive coupling of diphenyl diselenide with alkyl halides, see: (a) Kundu, A.; Roy, S. *Organometallics* **2000**, *19*, 105. (b) Ranu, B. C.; Mandal, T.; Samanta, S. *Org. Lett.* **2003**, *5*, 1439. Also see refs 2b−d.

[4] Reductive coupling of diphenyl ditelluride with alkyl halides, see: Nishiyama, Y.; Okada, M.; Nishino, T.; Sonoda, N. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 341.

[5] Reductive coupling of disulfides and diselenides with aryl halides, see: (a) Taniguchi, N.; Onami, T. *Synlett* **2003**, 829. (b) Taniguchi, N.; Onami, T. *J.* Org. Chem. **2004**, *69*, 915. (c) Taniguchi, N. *J. Org. Chem.* **2004**, *69*, 6904.

[6] Tanaka, K.; Ajiki, K. *Tetrahedron Lett.* **2004**, *45*, 25.

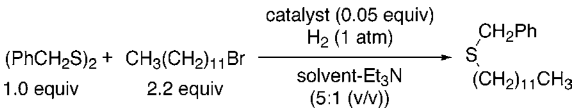
[7] Tanaka, K.; Ajiki, K. *Org. Lett.* **2005**, *7*, 1537.

[8] Platinum-catalyzed formaldehyde dithioacetal formation using thiols and diiodomethane, see: (a) Page, P. C. B.; Klair, S. S.; Brown, M. P.; Smith, C. S.; Maginn, S. J.; Mulley, S. *Tetrahedron* **1992**, *48*, 5933. (b) Page, P. C. B.; Klair, S. S.; Brown, M. P.; Harding, M. M.; Smith, C. S.; Maginn, S. J.; Mulley, S. *Tetrahedron Lett.* **1988**, *29*, 4477.

10.1021/ol051588n CCC: \$30.25

$[Rh(cod)_2]BF_4/8PPh_3$ at room temperature for 5 h, octanethiol was generated in 7% yield.[6] These phenomena prompted us to investigate the rhodium-catalyzed reductive coupling of disulfides with alkyl halides in the presence of triethylamine under a hydrogen atmosphere.

Table 1. Rhodium-Catalyzed Reductive Coupling of Dibenzyl Disulfide with 1-Bromododecane: Screening of Reaction Conditions[a]

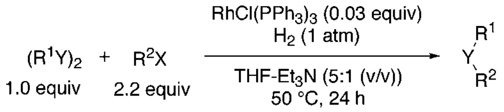


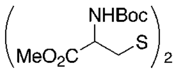
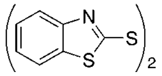
entry	catalyst	solvent	temp (°C)	time (h)	yield (%)
1	$[Rh(cod)_2]BF_4/2PPH_3$	toluene	25	16	50
2	$[Rh(cod)_2]/4PPh_3$	toluene	25	16	0
3	$RhCl(PPh_3)_3$	toluene	25	16	51
4	$RhCl(PPh_3)_3$(0.3 equiv)	toluene	50	24	86[b]
5	$RhCl(PPh_3)_3$(0.3 equiv)	THF	50	24	88[b]
6	none	THF	50	24	0
7[c]	$RhCl(PPh_3)_3$	THF	50	24	0

[a] NMR yield based on disulfide. [b] Isolated yield based on disulfide. [c] Under Ar.

Table 1 shows screening of reaction conditions to promote the rhodium-catalyzed reductive coupling of dibenzyl disulfide with 1-bromododecane in the presence of triethylamine under a hydrogen atmosphere. Among the catalysts (5% based on dibenzyl disulfide) examined, the commercially available rhodium catalyst, $RhCl(PPh_3)_3$, shows a high catalytic activity (entries 1−3). Raising the reaction temperature to 50 °C furnished benzyl dodecyl sulfide in 86% isolated yield by using 3% $RhCl(PPh_3)_3$ (entry 4). The reaction proceeded not only in toluene but also in THF (entry 5). No reaction was observed in the absence of rhodium catalyst or hydrogen (entries 6 and 7).

Table 2. Rhodium-Catalyzed Reaction of Disulfides and Diselenides with Alkyl Halides in the Presence of Triethylamine and Hydrogen[a]

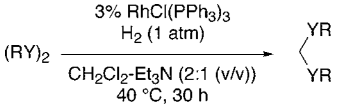


entry	$(R^1Y)_2$	R^2–X	yield (%)[a]
1	$(n\text{-}C_{12}H_{25}S)_2$	$CH_3(CH_2)_{11}Br$	91
2	$(PhCH_2S)_2$	$CH_3(CH_2)_{11}Br$	88
3[b]		$CH_3(CH_2)_{11}Br$	72
4	$(p\text{-TolS})_2$	$CH_3(CH_2)_{11}Br$	100
5	$(4\text{-ClC}_6H_4S)_2$	$CH_3(CH_2)_{11}Br$	98
6	$(4\text{-MeOC}_6H_4S)_2$	$CH_3(CH_2)_{11}Br$	98
7		$CH_3(CH_2)_{11}Br$	99
8	$(p\text{-TolS})_2$	$PhCH_2Cl$	90
9[b,c]	$(p\text{-TolS})_2$	EtO_2CCH_2Br	59
10[b,c]	$(p\text{-TolS})_2$	PhCOCl	98
11	$(PhSe)_2$	$CH_3(CH_2)_{11}Br$	97
12	$(PhSe)_2$	$PhCH_2Cl$	100
13[c]	$(PhSe)_2$	PhCOCl	94

[a] Isolated yield based on disulfide or diselenides. [b] The reactions were conducted with catalyst (0.05 equiv) in toluene at 100 °C. [c] Reaction time: 30 h.

A series of disulfides and alkyl halides were subjected to the above optimal reaction conditions (Table 2).[10] The reactions of alkyl (entries 1 and 2), aryl (entries 4−6), and heteroaryl (entry 7) disulfides with 1-bromododecane proceeded in high yield. Highly functionalized disulfides, a protected cystine, reacted with 1-bromododecane at 100 °C to furnish the corresponding sulfides in good yield (entry 3). Not only 1-bromododecane but also benzyl chloride could be employed (entry 8). Although high catalyst loading (5%), high reaction temperature (100 °C), and prolonged reaction time (30 h) were required, the reactions of ethyl bromoacetate and benzoyl chloride proceeded in good to high yield (entries 9 and 10). Importantly, this reductive coupling protocol can be applicable to the synthesis of various selenides. The reactions of diphenyl diselenide with 1-bromododecane, benzyl chloride, and benzoyl chloride proceeded in high yield (entries 11−13).

The reaction of disulfides and diselenides with volatile dichloromethane was also investigated. When the reactions were carried out at 40 °C for 30 h, the corresponding formaldehyde dithioacetals and diselenoacetal were obtained in good to high yield (eq 1).



(1)

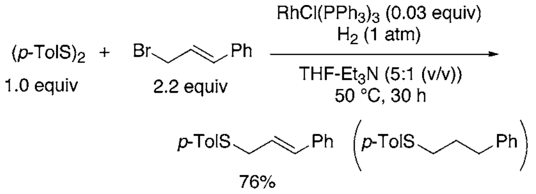
Y = S, R = p-Tol 84%
Y = S, R = n-$C_{12}H_{25}$ 75%
Y = Se, R = Ph 93%

Because $RhCl(PPh_3)_3$ is a highly active catalyst for the hydrogenation of olefins, the tolerance of olefins in the reductive coupling of disulfides with alkyl halides with hydrogen as a reducing agent is of interest. The reaction of $(p\text{-TolS})_2$ with cinnamyl bromide under a hydrogen atmosphere furnished the desired cinnamyl sulfide in 76% yield and almost no hydrogenated phenylpropyl sulfide was generated (eq 2).

---

[9] Rhodium-catalyzed equilibrating disulfide exchange reaction, see: (a) Arisawa, M.; Yamaguchi, M. *J. Am. Chem. Soc.* **2003**, *125*, 6624. (b) Tanaka, K.; Ajiki, K. *Tetrahedron Lett.* **2004**, *45*, 5677.

[10] **Representative procedure (Table 2, entry 4):** Under an Ar atmosphere, a THF (0.2 mL) solution of $RhCl(PPh_3)_3$ (5.6 mg, 0.0060 mmol) was added to a THF (0.2 mL) solution of di-p-tolyl disulfide (49.3 mg, 0.200 mmol), 1-bromododecane (109.7 mg, 0.440 mmol), and Et_3N (0.2 mL) by using THF (0.6 mL). H_2 was introduced to the resulting solution in a Schlenk tube. The mixture was stirred at 50 °C for 24 h. The resulting solution was concentrated and purified by preparative TLC (hexane), which furnished dodecyl p-tolyl sulfide (117.0 mg, 0.400 mmol, 100%) as a colorless oil.



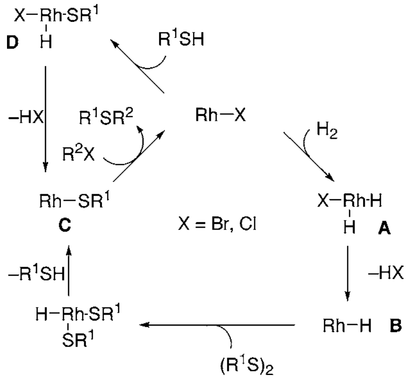
(2)

To confirm whether thiols were generated in this reductive coupling reaction or not, the hydrogenation of disulfides was investigated.[11] When didodecyl disulfide was treated with hydrogen in the presence of 3% $RhCl(PPh_3)_3$ at 100 °C, dodecanethiol was generated in 94% yield (eq 3).

$$(n\text{-}C_{12}H_{25}S)_2 \xrightarrow[\text{toluene, 100 °C, 2 h}]{\text{3\% }RhCl(PPh_3)_3,\ H_2\text{ (1 atm)}} \underset{94\%}{n\text{-}C_{12}H_{25}SH} \quad (3)$$

Scheme 1 depicts a plausible mechanism of this reaction. The reaction of a rhodium(I) catalyst with H_2 affords a rhodium(III) complex **A**. Elimination of HY with Et_3N furnishes a rhodium(I) hydride **B**, which reacts with disulfides followed by elimination of a thiol furnishing a rhodium(I) thiolate **C**. The reaction of **C** with alkyl halides in an S_N2 fashion furnishes sulfides, regenerating the rhodium(I) catalyst. In addition to this catalytic cycle, the previously reported catalytic cycle via a rhodium(III) complex **D** may also be included.[7]

Scheme 1



In conclusion, we have established that $RhCl(PPh_3)_3$ catalyzes the reductive coupling of disulfides or diselenides with alkyl halides in the presence of triethylamine using the most atom economical reducing agent, hydrogen. This reaction serves as a convenient new method to produce unsymmetrical sulfides and selenides from disulfides and diselenides instead of unstable and odoriferous thiols and selenols.

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

OL051588N

---

[11] Although metal complexe-catalyzed hydrogenation of disulfides to thiols has not been reported, some heterogeneous catalyses were reported, see: (a) Kessler, P.; Servent, D.; Hirth, C. *Tetrahedron Lett.* **1994**, *35*, 7237. (b) Calais, C.; Lacroix, M.; Geantet, C.; Breysse, M. *J. Catal.* **1993**, *144*, 160.