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Rhodium-Catalyzed Reaction of Thiols with Polychloroalkanes in the Presence of Triethylamine

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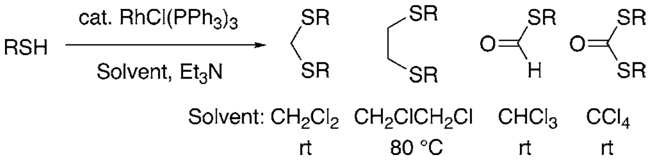
ABSTRACT



$RhCl(PPh_3)_3$ catalyzes a reaction of thiols with polychloroalkanes in the presence of triethylamine. This reaction serves as a convenient new method to produce formaldehyde dithioacetals, ethylenedithioethers, thioformates, and dithiocarbonic esters under mild conditions.

Many methods for the synthesis of formaldehyde dithioacetals ($RSCH_2SR$) are known, including the reaction of thiols with diiodomethane, dibromomethane, or dichloromethane under strongly basic conditions[1] and the reaction of thiols with formaldehyde derivatives under acidic conditions.[2] Demonstrably, the simplest method yet reported is the reaction of thiols with dichloromethane in the presence of *strong organic base* (1,8-diazabicyclo[5,4,0]undec-7-ene, DBU), as reported by Ono et al.[3] The present study explored a rhodium-catalyzed reaction of thiols with polychloroalkanes in the presence of *weak organic base* (Et_3N); the reaction allows both simple operation and mild reaction conditions.

In general, thiols are believed to be poisons of transition metal catalysts. However, several recent reports concerning transition-metal-catalyzed reactions of thiols have explained the utility of transition metal catalysts in synthesis of sulfur compounds.[4–6] Although platinum-catalyzed formaldehyde dithioacetal formation using thiols and CH_2I_2 has been reported,[7] a catalytic method using thiols and CH_2Cl_2 has not. Recently, we reported a cationic rhodium(I)/PPh_3-complex-catalyzed dehydrogenation of alkanethiols to disulfides under inert atmosphere.[8] We found that the formaldehyde dithioacetal was obtained along with the disulfide through reaction of octanethiol with CH_2Cl_2 when dehydro-

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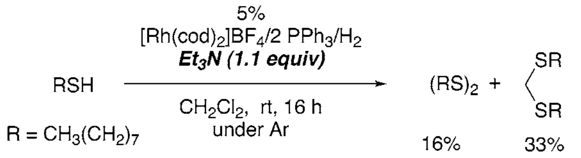
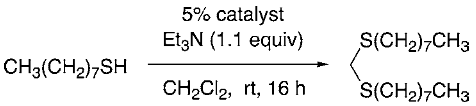
genation of octanethiol was conducted in CH_2Cl_2 at room temperature in the presence of Et_3N (eq 1).



(1)

Table 1 shows various rhodium(I) and iridium(I) catalysts (5% based on thiols) that we examined for their ability to facilitate this transformation. Among the phosphine ligands examined, PPh_3 was the most effective (entries 1−8). The use of $[Ir(cod)_2]BF_4$ or $[Rh(cod)Cl]_2$ and the elimination of treatment of the catalyst with hydrogen engendered very low catalytic activity (entries 9−11). The highest catalytic activity was obtained using $RhCl(PPh_3)_3$ as a catalyst (entry 12). Finally, employing excess amounts of Et_3N furnished the desired methylenedithioether in 81% isolated yield (entry 13).[9] No reaction was observed in the absence of rhodium catalyst (entry 14).

Table 1. Screening of Catalysts for Reaction of Octanethiol with Dichloromethane[a]

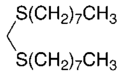
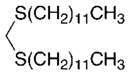
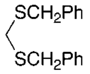
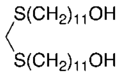
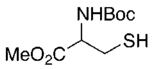
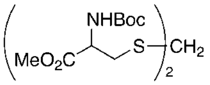
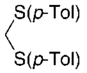
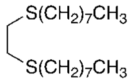
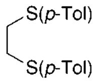
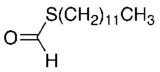
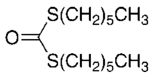


entry	catalyst	yield (%)[b]
1[c]	$[Rh(cod)_2]BF_4$/2 PPh_3	33
2[c]	$[Rh(cod)_2]BF_4$/2 n-Bu_3P	3
3[c]	$[Rh(cod)_2]BF_4$/dppe	5
4[c]	$[Rh(cod)_2]BF_4$/dppb	1
5[c]	$[Rh(cod)_2]BF_4$/dcpe	3
6[c]	$[Rh(cod)_2]BF_4$/dppf	24
7[c]	$[Rh(cod)_2]BF_4$/Tol-BINAP	8
8[c]	$[Rh(cod)_2]BF_4$/XANTPHOS[d]	17
9[c]	$[Ir(cod)_2]BF_4$/2 PPh_3	<1
10[c]	$[Rh(cod)Cl]_2$/4 PPh_3	<1
11	$[Rh(cod)_2]BF_4$/2 PPh_3	<1
12	$RhCl(PPh_3)_3$	39
13[e]	$RhCl(PPh_3)_3$	81[f]
14	none	0

[a] Rh or Ir catalyst (0.010 mmol), phosphine (0−0.020 mmol), Et_3N (0.22 mmol), thiol (0.20 mmol), and CH_2Cl_2 (1.0 mL) were employed. [b] Determined by ^1H NMR. [c] The catalysts were treated with hydrogen (1 atm, rt, 0.5 h). [d] 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene. [e] $RhCl(PPh_3)_3$ (0.025 mmol), Et_3N (0.5 mL), thiol (0.50 mmol), and CH_2Cl_2 (2.0 mL) were employed. Reaction time: 24 h. [f] Isolated yield.

Table 2 shows the rhodium-catalyzed reactions of various thiols with polychloroalkanes, as investigated in polychloroalkane solvents.[10] The reactions of both alkyl and aryl thiols with CH_2Cl_2 in the presence of 5% $RhCl(PPh_3)_3$ proceeded at room temperature to furnish the corresponding formaldehyde dithioacetals in good yield (entries 1−6). A hydroxy-substituted alkanethiol and a cysteine derivative can

Table 2. Rhodium-Catalyzed Reaction of Thiols with Polychloroalkanes[a]

entry	thiol	polychloro-alkane	product	yield (%)[b]
1	$CH_3(CH_2)_7SH$	CH_2Cl_2		81
2	$CH_3(CH_2)_{11}SH$	CH_2Cl_2		80
3	$PhCH_2SH$	CH_2Cl_2		82
4	$HO(CH_2)_{11}SH$	CH_2Cl_2		63
5		CH_2Cl_2		73
6	p-TolSH	CH_2Cl_2		99
7[c]	$CH_3(CH_2)_7SH$	CH_2ClCH_2Cl		84
8[c]	p-TolSH	CH_2ClCH_2Cl		87
9[d]	$CH_3(CH_2)_{11}SH$	$CHCl_3$		69
10[d]	$CH_3(CH_2)_5SH$	CCl_4		61

[a] Reactions were conducted using $RhCl(PPh_3)_3$ (0.025 mmol), Et_3N (0.5 mL), thiol (0.50 mmol), and polychloroalkane (2.0 mL) at room temperature for 24 h. [b] Isolated yields based on thiols. [c] At 80 °C. [d] $RhCl(PPh_3)_3$ (0.10 mmol) and polychloroalkane (10 mL) were used.

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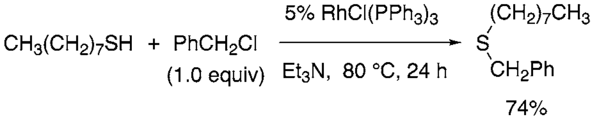
(8) Tanaka, K.; Ajiki, K. *Tetrahedron Lett.* **2004**, *45*, 25.

(9) Not only tertiary amines but also secondary and primary amines (n-Bu_2NH and n-$BuNH_2$) can be used for this reaction, although the reaction rate is low.

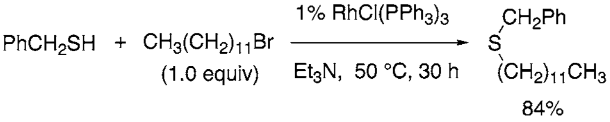
(10) In all entries, <5% conversions were observed in the absence of rhodium catalyst.

be used (entries 4 and 5).[11] The reaction of a vicinal dichloride (CH_2ClCH_2Cl) proceeded at 80 °C to furnish the corresponding ethylenedithioethers in good yield (entries 7 and 8). Importantly, although high catalyst loading and diluted condition were required, the reaction of $CHCl_3$ and CCl_4 also proceeded at room temperature to give a thioformate and a dithiocarbonic ester, respectively, presumably through hydrolysis of corresponding polythiomethanes by silica gel chromatography (entries 9 and 10). The reaction of $CHCl_3$ and CCl_4 serves as a convenient new method for preparation of a thioformate and a dithiocarbonic ester starting from a thiol.

Next, we investigated the rhodium-catalyzed reaction of thiols with alkyl halides. The reaction proceeded cleanly in Et_3N without using excess alkylating reagents when a reactive primary alkyl chloride (benzyl chloride, eq 2) or a primary alkyl bromide (dodecyl bromide, eq 3) was used as an alkylating reagent. No reaction was observed in the absence of rhodium catalyst.



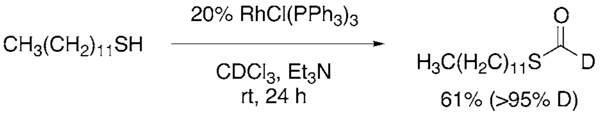
(2)



(3)

The reaction of dodecanethiol with $CDCl_3$ was investigated to gain mechanistic insight into this reaction (eq 4). Deuterium of $CDCl_3$ was quantitatively incorporated into the formyl group. Furthermore, the reaction of benzyl mercaptan with (*R*)-(1-chloroethyl)benzene (78% ee) furnished the corresponding sulfide with complete inversion of configuration (78% ee, eq 5).

Scheme 1 depicts a plausible mechanism of this reaction. We believe that the rhodium(I) catalyst oxidatively inserts into the thiol S−H bond, affording a rhodium(III) complex **A**. Elimination of HX with Et_3N furnishes rhodium(I) thiolate **B**, which reacted with alkyl halides in an S_N2 fashion, thereby furnishing sulfides and regenerating the rhodium(I) catalyst.



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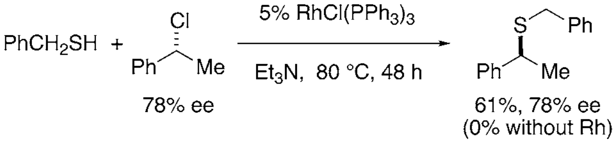
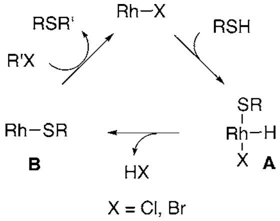


(5)

Scheme 1



In conclusion, we have established that $RhCl(PPh_3)_3$ catalyzes a reaction of thiols with polychloroalkanes in the presence of triethylamine. This reaction serves as a convenient new method to produce formaldehyde dithioacetals, ethylenedithioethers, thioformates, and dithiocarbonic esters under mild conditions.

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

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[11] For synthesis of methylenedithioethers from cysteine derivatives using tetrabutylammonium fluoride hydrate, see: Ueki, M.; Ikeo, T.; Hokari, K.; Nakamura, K.; Saeki, A.; Komatsu, H. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 829.