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Rhodium-Catalyzed Disulfide Exchange Reaction

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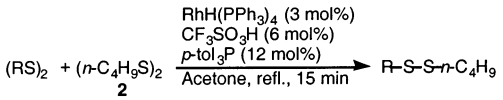
A disulfide bond plays an important role in the construction of the secondary and the tertiary structures of polypeptides and proteins. Industrially important polymers such as rubber contain polysulfide bonds.[1] The cleavage and recombination of organodisulfides and polysulfides, resulting in the disulfide exchange is, therefore, an important process for the production, modification, and degradation of such biologically active substances and materials. The cleavage of sulfur−sulfur bonds is known to occur either homolytically or heterolytically: (a) short-lived sulfenyl radicals are generated by homolytic scission via photolysis,[2] oxidation,[3] or heating;[4] and (b) ionic scission generates mercaptides (XS^-) under basic/nucleophilic conditions[5] or sulfenium cation (XS^+) under acidic/electrophilic conditions.[6,7] The sulfur radical, anion, or cation then reacts with another disulfide, resulting in exchange reactions. These reactions, however, often require harsh reaction conditions such as high temperature and strong acids or bases, and are generally slow in solution, particularly in the case of alkyl disulfides. We considered that the disulfide exchange process, which proceeds rapidly under neutral conditions and at ambient temperature, would provide a new methodology, which has broad applications to biosciences and material sciences. Described here is a novel exchange reaction of disulfides catalyzed by a transition metal complex:[8] A rapid and mild disulfide exchange reaction takes place in the presence of $RhH(PPh_3)_4$, a phosphine, and trifluoromethanesulfonic acid, which can be used for the peptide disulfide exchange. In addition, the metal system catalyzes the disproportionation of diselenide or ditelluride with disulfide.

When bis(2-benzoyloxyethyl) disulfide **1** (0.5 mmol) was treated with dibutyl disulfide **2** (0.5 mmol) in the presence of $RhH(PPh_3)_4$ (1.5 mol %), tris(*p*-tolyl)phosphine (6 mol %), and trifluoromethanesulfonic acid (3 mol %) in refluxing acetone for 15 min, 2-benzoyloxyethyl butyl disulfide **3** (0.49 mmol, 49% yield based on the $BzO(CH_2)_2S$ group) was obtained with the recovery of **1** (0.21 mmol, 41%) and **2** (0.20 mmol, 40%), which is the statistical product ratio (Table 1, entry 1). When another portion of **2** (0.5 mmol) was added to the refluxing mixture, the yield of **3** increased to 71% after 10 min. Addition of **2** twice (1.0 and 1.0 mmol) at 10 min intervals further increased the yields to 86% and 92%, respectively. This catalyst system was found to be active after the equilibrium was attained. The exchange reaction of **1** and **2** in a 1:4 initial ratio gave **3** in 86% yield with recovery of **1** (12%) and **2** (76%) (entry 2). The rhodium complex, trifluoromethanesulfonic acid, and phosphine are essential; no reaction occurs in the absence of the rhodium complex (entry 3), and there was low conversion in the absence of the phosphine or acid (entries 4 and 5). The effect of added phosphine was examined by reacting for 3 min, and triarylphosphines, particularly those with electron-donating substituents were found to be effective (entries 6, 7, 8, and 9). Bidentate phosphines (entries 10 and 11) and tributylphosphine (entry 12) were less effective. This reaction was effectively promoted by trifluoromethanesulfonic acid, and the yield of **3** decreased with methanesulfonic acid or *p*-toluenesulfonic acid. The rhodium-catalyzed exchange reactions of **2** (4 equiv) and several symmetrical dialkyl disulfides were rapid, completing within 15 min in refluxing acetone (entries 13, 14, and 15). Bis(*sec*-butyl) disulfide **4** and **2**, however, did not undergo the exchange reaction under these conditions. The reaction of a diaryl disulfide and a dialkyl disulfide took place more rapidly than that of dialkyl disulfides, when 1,2-bis(diphenylphosphino)ethane (dppe) was used instead of tris(*p*-tolyl)phosphine (entries 16, 17, and 18). The ligand effect is an interesting aspect of the transition metal-catalyzed exchange.

Since, the present disproportionation is considerably affected by the substituent on the disulfide, selective exchange of symmetrical disulfides can be conducted. Treatment of equimolar amounts (0.5 mmol) of **4**, diphenyl disulfide **5**, and di(*p*-tolyl) disulfide **6** gave phenyl *p*-tolyl disulfide **7** (0.49 mmol), **5** (0.25 mmol), and **6** (0.25 mmol) at room temperature for 1 min in the presence of 1 mol % of the rhodium complex and 2 mol % of dppe, with the unchanged

Table 1. Rhodium-Catalyzed Exchange of Symmetrical Disulfides[a]

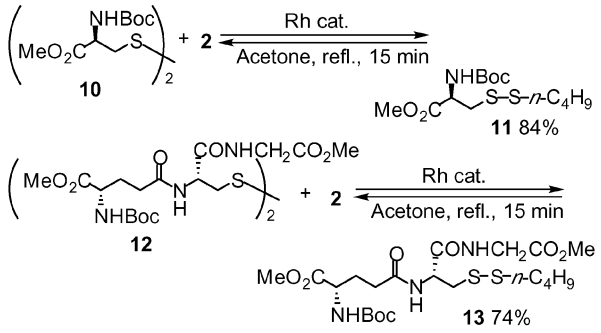


run	R	phosphine	yield/%[b]
1[c]	$BzO(CH_2)_2S$	*p*-tol_3P	49
2		*p*-tol_3P	86
3[c,d]		*p*-tol_3P	N.D.[e]
4[c]		none	3
5[c,f]		*p*-tol_3P	8
6[c,g]		(*p*-$MeOC_6H_4)_3P$	19
7[c,g]		*p*-tol_3P	24
8[c,g]		PPh_3	14
9[c,g]		(*p*-$ClC_6H_4)_3P$	6
10[c,g]		dppe[h]	N.D.
11[c,g]		dppf[i]	10
12[c,g]		Bu_3P	5
13[j]	n-C_8H_{17}	*p*-tol_3P	77
14	$PhCH_2$	*p*-tol_3P	81
15	*t*-$BuMe_2SiO(CH_2)_6$	*p*-tol_3P	84
16[k]	Ph	*p*-tol_3P	19
17[l]		dppe	90
18[m]	Ph	dppe	85

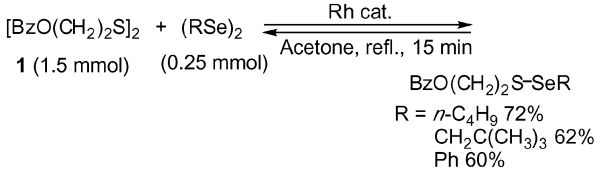
[a] See Supporting Information for reaction conditions. [b] Yield based on the RS group. [c] The reaction was conducted using **1** (0.5 mmol) and **2** (0.5 mmol) in the presence of $RhH(PPh_3)_4$ (1.5 mol %), *p*-tol_3P (6 mol %), and trifluoromethanesulfonic acid (3 mol %). [d] In the absence of Rh complex. [e] N.D.: not detected by ^1H NMR. [f] In the absence of CF_3SO_3H. [g] The reaction time: 3 min. [h] 1,2-Bis(diphenylphosphino)ethane. [i] 1,1′-Bis(diphenylphosphino)ferrocene. [j] The reaction was conducted using dioctyl disulfide (2.5 mmol) and **2** (12.5 mmol) in refluxing acetone for 30 min, and the product was isolated by distillation. [k] The reaction was conducted in acetone at room temperature for 5 min in the presence of $RhH(PPh_3)_4$ (0.75 mol %) and *p*-tol_3P (3 mol %). [l] The reaction was conducted in acetone at room temperature for 5 min in the presence of $RhH(PPh_3)_4$ (0.75 mol %) and dppe (1.5 mol %). [m] The reaction was conducted using diphenyl disulfide **5** (1.0 mmol) and bis(*sec*-butyl) disulfide **4** (0.25 mmol) in refluxing acetone for 10 min in the presence of $RhH(PPh_3)_4$ (1 mol %) and dppe (2 mol %).

10.1021/ja035221u CCC: $25.00

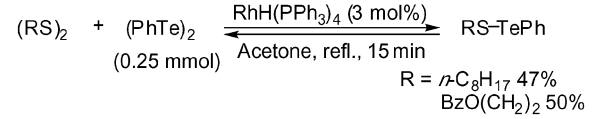
Scheme 1



Scheme 2



Scheme 3



4 (0.48 mmol). Random disproportionation takes place giving statistical amounts of **7** (0.32 mmol), *sec*-butyl phenyl disulfide **8** (0.34 mmol), and *sec*-butyl *p*-tolyl disulfide **9** (0.34 mmol) at acetone reflux for 5 min with the recovery of **4** (0.14 mmol), **5** (0.16 mmol), and **6** (0.16 mmol). Such property may be used for the selective disulfide formation in polymercapto compounds such as proteins.

A cystine derivative **10** exchanged with **2** to give the unsymmetrical disulfide **11** without racemization (Scheme 1). It should be noted that a tripeptide glutathione derivative **12** also undergoes the reaction giving a disulfide **13** in 74% yield after recrystalization.

The exchange reactions of dialkyl disulfides and dialkyl diselenides are also catalyzed by the same complex (Scheme 2).[9] When dibutyl diselenide (0.25 mmol) was treated with **1** (1.5 mmol) in the presence of $RhH(PPh_3)_4$ (5 mol %), tris(*p*-tolyl)phosphine (20 mol %), and trifluoromethanesulfonic acid (5 mol %) in refluxing acetone for 15 min, butylselenyl 2-benzoyloxyethyl sulfide was obtained (0.36 mmol, 72% yield based on the *n*-C_4H_9Se group). It was confirmed that the rhodium complex is essential for the reaction.

Exchange reaction of disulfides and ditellurides gives tellurinosulfides (Scheme 3). No reaction takes place without the rhodium complex under the conditions.

We describe here a novel Rh-catalyzed exchange reaction of disulfides. Compared with the conventional exchange reaction, this reaction takes place rapidly under mild conditions and is applicable to peptide disulfide exchange. In addition, the reaction can be controlled by changing the ligand or acid, and the application of this methodology to polysulfides including elemental sulfur is now under investigation. This is a novel combination of transition metal chemistry and organosulfur chemistry.

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Supporting Information Available: Detailed experimental procedures, characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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