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Tetrahedron Letters 46 (2005) 5669-5671

Tetrahedron Letters

## Rhodium-catalyzed thiophosphinylation and phosphinylation reactions of disulfides and diselenides

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Received 20 May 2005; revised 16 June 2005; accepted 17 June 2005 Available online 11 July 2005

**Abstract**—Alkyl and aryl dithiophosphinates were synthesized by the reaction of disulfides with biphosphine disulfides in the presence of  $RhH(PPh_3)_4$  and 1,2-diphenylphosphinoethane (dppe). The catalyst also promoted synthesis of thiophosphinates and selenothiophosphinates from disulfides and diselenides. © 2005 Elsevier Ltd. All rights reserved.

The manipulation of sulfur and phosphorous functional groups is an important subject in synthetic organic chemistry. Dithiophosphinates and thiophosphinates, esters of phosphinic acids and thiols, are a group of compounds containing both phosphorous and sulfur atoms. Their synthesis in general employed condensation reactions of thiols with various phosphinylating reagents.<sup>1</sup> It was considered interesting if disulfides could be used in place of thiols, since disulfides are more stable toward oxidation, and are in general less smelling. Such methodology, however, has been rare. The thermal reaction of biphosphine disulfides with disulfides was conducted at 210-230 °C giving alkyl dithiophosphinates.<sup>2</sup> The electrochemical reaction of a biphosphine and disulfides gave mixtures of dithiophosphinates and thiophosphinates.<sup>3</sup> Several reactions, which treat phosphine sulfides possessing P-H bonds and disulfides, were conducted under photochemical or basic conditions.<sup>4</sup>

We have been investigating methods to utilize transition metal catalysis for the synthesis of organosulfur and organophosphorous compounds, and previously developed metathesis reactions of S–S/S–S,<sup>5</sup> C–H/S–S,<sup>6</sup> and C–S/S–S bonds.<sup>6</sup> Described in this study are syntheses of dithiophosphinates, selenothiophosphinates, and thiophosphinates from disulfides or diselenides, which employ the metathesis reactions of S–S/P–P, Se–Se/ P–P, or S–S/P–S bonds in the presence of RhH(PPh<sub>3</sub>)<sub>4</sub>



Scheme 1.

and 1,2-diphenylphosphinoethane (dppe) (Scheme 1). The catalyzed reaction of biphosphine disulfides with organic disulfides proceeded at a much lower temperature compared to the thermal method noted above. The rhodium complex can be used for the synthesis of compounds containing multiple heteroatoms, phosphorous, sulfur, and selenium.

When an equimolar mixture of tetramethylbiphosphine disulfide and diphenyl disulfide in acetone was heated at reflux for 0.5 h in the presence of RhH(PPh<sub>3</sub>)<sub>4</sub> (1.5 mol%) and dppe (3 mol%), phenyl dimethyldithiophosphinate was obtained in 91% yield (Table 1, entry 1).<sup>7</sup> The use of a bidentate phosphine ligand with  $C_2$  linker was critical, and dppe and dppv gave favorable results, while dppp, dppb, and dppf exhibited very low activities. Monodentate phosphines including PPh<sub>3</sub>, Bu<sub>3</sub>P, and (2-furyl)<sub>3</sub>P were not effective at all. As for solvent, THF and acetone gave comparable results (entries 2 and 8).

The reaction of an aromatic disulfide with an electrondonating group proceeded smoothly giving an aryl dithiophosphinate (entry 3), while that with an electronwithdrawing group required higher catalyst loading

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<sup>0040-4039/\$ -</sup> see front matter @ 2005 Elsevier Ltd. All rights reserved. doi:10.1016/j.tetlet.2005.06.109

<b>Table 1.</b> Rhodium-catalyzed metathesis reaction of biphosphine dis	sulfide and disulfid	e
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	$RSSR + \frac{R'}{R'} \xrightarrow{P-P}^{S} \xrightarrow{R'}_{R'}$	RhH(PPh <sub>3</sub> ) <sub>4</sub> (1.5 mol%) R' SI   dppe (3 mol%) P-SR   acetone, refl., 0.5 h R'	
Entry	R′	R	Yield (%)
1	Me	$C_6H_5$	91
2			86 <sup>a</sup>
3		p-MeC <sub>6</sub> H <sub>4</sub>	98
4		<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	8
5			50 <sup>b</sup>
6		$n-C_8H_{17}$	97
7		$BocNH(CH_2)_2$	98
8			89 <sup>a</sup>
9		$MeO_2C(CH_2)_3$	100
10		MeO(CH <sub>2</sub> ) <sub>4</sub>	99
11	Et	$BocNH(CH_2)_2$	98
12	<i>n</i> -Pr	$BocNH(CH_2)_2$	100

<sup>a</sup> Reacted in refluxing THF.

<sup>b</sup> RhH(PPh<sub>3</sub>)<sub>4</sub> (3 mol%) and dppe (6 mol%) were used, and the reaction was conducted for 2 h.

and longer reaction time (entries 4 and 5). Aliphatic disulfides also underwent the metathesis reaction giving alkyl dithiophosphinates (entries 6–10). Tetraethyl- and tetrapropylbiphosphine disulfide effectively gave the corresponding metathesis products (entries 11 and 12).

The reaction of dialkyl diselenides provided *Se*-alkyl selenothiophosphinates, although a higher catalyst loading was needed to obtain the products in high yields (Scheme 2). The yield decreased with diphenyl diselenide probably because of the catalyst deactivation. This synthesis of selenothiophosphinates<sup>8</sup> employs organic diselenides for the substrate, which are one of the most convenient sources of organoselenium compounds.

The reaction of a biphosphine dioxide and disulfides gave S-alkyl or S-aryl thiophosphinates using the same rhodium catalyst (Scheme 3). The treatment of tetraphenylbiphosphine dioxide and diphenyl disulfide in refluxing THF for 0.5 h in the presence of RhH(PPh<sub>3</sub>)<sub>4</sub> (1 mol%) and dppe (2 mol%) gave S-phenyl diphenylthiophosphinate in 97% yield. Dialkyl disulfides also reacted under the same conditions.

Utility of this methodology is shown by the synthesis of peptide derivatives (Scheme 4).

Recently, we reported an alkylthio exchange reaction of a thioacetylene and disulfides in the presence of RhH(PPh<sub>3</sub>)<sub>4</sub> complex.<sup>6</sup> The reaction was considered to involve S–C bond cleavage by the rhodium complex, and it was wondered whether dithiophosphinates can undergo the alkylthio exchange reaction with cleavage of the P–S bond. Such reaction is an alternative method



Scheme 2.



## Scheme 5.

Scheme 4.

to synthesize dithiophosphinates from disulfides. The treatment of phenyl dimethyldithiophosphinate and di(*p*-chlorophenyl) disulfide (1 equiv) in the presence of RhH(PPh<sub>3</sub>)<sub>4</sub> (2 mol%) and dppe (4 mol%) in refluxing acetone for 0.5 h gave *p*-chlorophenyl dimethyl-dithiophosphinate in 68% yield (Scheme 5). Several dialkyl disulfides also underwent the exchange reaction.

To summarize, a rhodium complex catalyzes thiophosphinylation and phosphinylation of disulfides or diselenides by S–S/P–P, Se–Se/P–P, or S–S/P–S bond metathesis. Use of disulfides in the synthesis of organosulfur compounds in place of thiols would have synthetic potential, when a suitable catalyst is developed.

## Acknowledgments

This work was supported by JSPS (Nos. 16109001 and 17689001). M.A. expresses her thanks for financial support from the New Energy and Industrial Technology Development Organization (NEDO) of Japan (No. 02A44003d) and the Takeda Science Foundation.

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- 7. In a two-necked flask equipped with a reflux condenser were placed RhH(PPh<sub>3</sub>)<sub>4</sub> (1.5 mol%, 13.8 mg), 1,2-bis(diphenylphosphino)ethane (dppe, 3.0 mol%, 9.6 mg), tetramethylbiphosphine disulfide (0.8 mmol, 149.0 mg), and diphenyl disulfide (0.8 mmol, 174.4 mg) in acetone (3.0 mL) under an argon atmosphere, and the solution was heated at reflux for 0.5 h. Then, the solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel giving phenyl dimethyldithiophosphinate (295.2 mg, 91%).
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