Synthesis of Disulfides from the Palladium(0)-Catalyzed Reactions of Sulfenyl Halides and Organostannanes

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Introduction

Palladium(0 or II)-catalyzed coupling reactions have acquired a well-established status in the synthetic organic repertoire.¹ A recent survey by Farina and coworkers² revealed that a majority of the transition metalmediated cross-coupling reactions reported in 1992 involved palladium catalysis. While most examples involve the formation of carbon–carbon bonds, palladium-catalyzed formation of carbon–silicon, carbon– germanium, and carbon–tin bonds have also been reported. These latter reactions usually involve palladiumcatalyzed additions of an organometallic or organobimetallic species to a carbon–carbon unsaturated system.^{1c}

Labadie,³ in 1989, showed that the palladium-catalyzed cross-coupling process could be extended to reactions between vinylstannanes and sulfonyl chlorides to give vinyl sulfones. The reaction was characterized by short reaction times, high yields, and varied functionality. Similarly, Quintard and co-workers⁴ reported a palladium-catalyzed coupling reaction between acyl chlorides and vinylstannanes to produce α,β -unsaturated ketones. Since the sulfur of the sulfonyl chloride and the carbon of the acyl halide exhibit similar electrophilic character in the displacement of the stannyl group from the vinylstannane, and since the sulfur of sulfenyl halides is electrophilic in cleavage reactions with vinylstannanes,⁵ we chose to determine whether vinyl sulfides could be obtained from the palladium-catalyzed coupling of sulfenyl chlorides and vinylstannanes. To the contrary, the palladium-catalyzed reaction between sulfenyl chlorides and vinylstannanes leads to high yields of the corresponding disulfide, a trialkytin chloride, and vinyl chloride. We show that a tetraalkylstannane or a hexaalkyldistannane is both necessary and as efficacious in the production of the disulfide.

Results and Discussion

The focus of this study is the palladium(0)-catalyzed coupling of sulfenyl halides, resulting in the production of symmetrical disulfides. Stille-type coupling reactions are characterized by a sequence of steps involving first an oxidative addition of the substrate to palladium,

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L = triphenylphosphine

followed by exchange of a ligand on palladium with a new ligand, usually from a stannane, and finally a reductive elimination of two coupled ligands as the product.¹ We envision a similar process for the formation of disulfides, as outlined in Scheme 1. The very reactive sulferyl halide, 1-6a, undergoes an oxidative addition to palladium analogous to that of an aryl halide in the usual Stille reaction. This is followed by a ligand exchange step in which a second sulfur bonds to palladium, releasing a molecule of chlorine. This step is analogous to ligand exchange in which a substituent on tin replaces the halogen and a molecule of tin halide is formed. The two sulfur groups then undergo reductive elimination to form the disulfide, 1-5b (eq 1). The chlorine formed in the ligand exchange step is then available to reverse the process by converting the disulfide back to sulfenyl chloride, a well-known reaction⁶ (eq 2). However, organotin compounds are very reactive to electrophilic cleavage by halogens⁷ and effectively scavenge the chlorine by reaction to give the chlorostannane and an alkyl chloride (eq 3). The results of reactions with several chlorine scavengers are given in Table 1.

$$2\text{RSCl} \xrightarrow{\text{Pd}(0)} (\text{RS})_2 + \text{Cl} \tag{1}$$

$$(RS)_2 + Cl_2 \rightarrow 2RSCl \qquad (2)$$

$$R_4'Sn + Cl_2 \rightarrow R_3'SnCl + R'$$
(3)

Using 2,4-dinitrobenzenesulfenyl chloride as the prototype, the first entry in Table 1 shows that a low but measurable yield of disulfide can be obtained from a THF

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Table 1. Chlorine-Scavenging Reactions

2 (SCI $\frac{(Ph_3P)_4Pd}{THF} O_2N - \langle V \rangle$	$\left(\begin{array}{c} \\ \\ \end{array} \right) + Cl_2$
	`NO ₂	2	`NO ₂ / 2
	Cl ₂ Scavenger	Molar Ratio ^a	% Yield RSSR
1.	None		7
2.	Argon Sweep		12
3.	Me ₄ Sn 7	2 : 1	95
4.	Me₄Sn 7	1 : 1	85
5.	Et ₄ Sn 8	2 : 1	87
6.	Me ₆ Sn ₂ 9	2 : 1	84
7.	Me ₆ Sn ₂ 9	2 : 1	81
8.	H ₂ C =CHBu ₃ 10	1 : 1	76
9.	Cy ₄ Sn 11	2 : 1	13
10.	Ph ₄ Sn 12	2 : 1	< 10
11		excess	{ 11 ^b 40°
12.	13 Me ₄ Ge 14	2 : 1	15
13.	Me ₄ Ge 14	1 : 1	19

 a Molar ratio of sulfenyl halide to chlorine scavenger. b Disulfide product. c Addition product, mp 116–117 °C [lit.¹³ mp 115–117 °C].

solution of the sulfenyl chloride and the palladium catalyst. This yield is about doubled when argon is bubbled through the reaction mixture. Addition of an organostannane to the system results, in most cases, in a dramatic increase in the yield of disulfide. Compounds investigated are tetramethylstannane (7), tetraethylstannane (8), hexamethyldistannane (9), tributylvinylstannane (10), tetracyclohexylstannane (11), tetraphenylstannane (12), cyclohexene (13), and tetramethylgermane (14). Comparison of the yields in entries 3, 6, and 12 to those in entries 4, 7, and 13, respectively, suggests that an excess of chlorine scavenger has little effect on the yield of disulfide. The low yields in entries 9 and 10 are undoubtedly due to low solubility of stannanes 11 and 12 in THF. With cyclohexene (13), the primary reaction is addition of the sulfenyl chloride to the double bond.⁸ No 1.2-dichlorocyclohexane was detected in the reaction mixture. Also the extent of reaction is considerably diminished when tetramethylgermane (14) is the scavenger compared to tetramethylstannane. This is consistent with their relative reactivities to chlorine.⁹

Several observations are consistent with the stepwise process illustrated in Scheme 1. When the chlorine scavenger is tetramethylstannane (7) or tetramethylger-



Figure 1. Plot of percent reactions of **2a** and **6a** with Me₄Sn and Pd(0) in THF- d_8 vs time. See Experimental Section for details.

mane (14), ¹H NMR spectra of reactions run in THF- d_8 contain a singlet peak at 3.03 ppm, assigned to methyl chloride. This peak disappears from the spectrum when the solvent is removed under vacuum or the solution flushed with argon. Also this peak does not appear in the product spectra when the chlorine scavengers are hexamethyldistannane (9) or tributylvinylstannane (10). Production of the related product, chlorotrimethylstannane, can be directly correlated with the decrease of its precursor, tetramethylstannane or hexamethyldistannane.

The ligand exchange step of the catalytic cycle has been shown to be the rate-determining step.¹⁰ In the Stille coupling reaction this step constitutes a transmetalation by electrophilic cleavage of a carbon-tin bond. The reactivity of groups on tin follows the usual order of ease of electrophilic cleavage.¹¹ In the reactions at hand, this step involves exchange of a chlorine for an RS group from the sulfenyl halide. The chlorine atoms then form a molecule of chlorine. The chlorine is either scavenged by the stannane or converts a molecule of disulfide back to the sulfenyl chloride.

The proposal of the ligand exchange step is based, experimentally, on two considerations. Figure 1 shows a plot of ¹H NMR peak areas for chlorotrimethylstannane and bromotrimethylstannane as a function of time. These products arise from the coupling of 2-nitrobenzenesulfenyl chloride (**2a**) and 2-nitrobenzenesulfenyl bromide (**6a**), respectively, in the presence of tetramethylstannane. The plot shows that the sulfenyl chloride is both more reactive and proceeds to a higher yield than the bromide. Since bromine is a softer ligand, it is to be expected that the ligand exchange step would be slower in the case of the sulfenyl bromide. Second, a comparison

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Table 2.Yields of Disulfides

$2RSX + Me_4Sn \frac{(Ph_3P)_4I}{THF}$	⊃d ➡ RSSR + Me ₃ :	SnX + MeX
RSX	Time/Temp	% Yield
	4h/25 ⁰ C	95
	4h/25 ⁰ C	88
$O_2N \longrightarrow SCI$	4h/25 ⁰ C	84
	4h/25 ⁰ C	86
$\left(\begin{array}{c} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$	24h/40 ⁰ C	73 ^a
SBr 6a NOc	4h/25 ⁰ C	83 ^b

 a Yield as based on recovery of starting sulfenyl chloride **5a**. b The coproducts are Me₃SnBr (¹H NMR 0.72 ppm, s, $^2J_{SnH}$ = 65.1/ 62.3 Hz) and MeBr (¹H NMR 2.68 ppm, s).

of entries 3 or 4 with 8 in Table 1 shows that the vinylstannane (**10**) gives a slightly lower yield than tetramethylstannane (**7**). Vinyl groups, bonded to tin, are about 700 times more reactive in transmetalation than are alkyl groups.¹¹ Thus if the tin compound is involved in the ligand exchange process, as opposed to acting as a chlorine scavenger, **10** should give a comparable yield to **7**, which it does not.

Table 2 list yields for the six sulfenyl halides using **7** as the halogen scavenger. It is clear that the reaction is facilitated by electron withdrawing groups operating near the sulfenyl halide. Triphenylmethanesulfenyl chloride was significantly less reactive, and to obtain a decent yield, a longer reaction time and higher temperature were necessary.

Finally it should be noted that the ¹H NMR spectrum of each crude reaction product, except **5b**, gave a singlet peak at about 3.5 ppm. This peak is attributed to a MeS group and constitutes less than 3% of the product mixture. The presence of this peak suggests that the normal Stille coupling reaction (eq 4) is present but competes poorly with the disulfide coupling process. This peak was absent when the palladium(0) catalyst was withheld and also did not appear in reactions with **9** as the stannane.

$$RSCl + Me_4Sn \xrightarrow{Pd(0)} RSMe + Me_3SnCl \qquad (4)$$

In summary, we report a unique coupling process in which sulfenyl halides are converted to disulfides in excellent yield. The overall process is similar to a Stille coupling reaction but differs in the function of the stannane.

Experimental Section

General. Tetrakis(triphenylphosphine)palladium(0), THF d_8 , tributylvinylstannane, hexamethyldistannane, tetraphenylstannane, 2,4-dinitrobenzenesulfenyl chloride, triphenylmethanesulfenyl chloride, 2,4,5-trichlorophenyl disulfide, 2-nitrophenyl disulfide, and 2-nitrobenzenesulfenyl chloride were obtained from Aldrich and used without further purification. Tetramethylstannane, tetraethylstannane, and tetramethylgermane were obtained from Gelest and used without further purification. Tetracyclohexylstannane was prepared from the Grignard reagent of chlorocyclohexane and tin(IV) chloride. THF was distilled from sodium/benzophenone ketyl. Carbon tetrachloride was dried over molecular sieves. ¹H and ¹³C NMR spectra were obtained on a Bruker AC-250 spectrometer at 250 and 62.9 MHz, respectively, and referenced to TMS and $CDCl_3$ or acetone- d_6 , respectively. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. All melting points are uncorrected.

2,4,5-Trichlorobenzenesulfenyl Chloride (4a). In a 250 mL flask, fitted with a reflux condenser and gas dispersion tube, were placed 1.53 g (3.60 mmol) of 2,4,5-trichlorophenyl disulfide, 30 mg of iodine and 100 mL of dry carbon tetrachloride. Chlorine gas was bubbled through the solution until the color turned to a pale yellow. The excess chlorine and the carbon tetrachloride were removed on a rotary evaporator. The resulting solid was purified by column chromatography on silica gel using methylene chloride as the eluent. The sulfenyl chloride was eluted after unreacted disulfide. The yield was 1.45 g (5.85 mmol, 81%): mp 35.5–37.0 °C; ¹H NMR (CDCl₃) δ 7.50 (s, 1H), 7.65 (s, 1H); ¹³C NMR (CDCl₃) δ 128.97, 129.10, 130.66, 132.51, 133.67, 135.03. Anal. Calcd for C₆H₂SCl₄: C, 29.06; H, 0.81. Found: C, 29.12; H, 0.80. The sample was protected from light during workup and on storage.

2-Nitrobenzenesulfenyl Bromide (6a). In a 500 mL flask, fitted with a reflux condenser, addition funnel, and magnetic stirrer, were placed 5.00 g (16.2 mmol) of 2-nitrophenyl disulfide and 200 mL of dry carbon tetrachloride. To this mixture were added, at room temperature, 2.60 g (16.2 mmol) of bromine in 50 mL of dry carbon tetrachloride and a catalytic amount of iodine (30 mg). The mixture was heated to reflux. After 24 h, a sample was removed and evaporated to dryness. An ¹H NMR spectrum indicated about 40% conversion to product. After 72 h, the reaction was stopped and the volatile components were removed on a rotary evaporator. The resulting solid was recrystallized from carbon tetrachloride yielding unreacted disulfide. The mother liquor was evaporated to dryness and yielded 5.40 g (71%) of 2-nitrobenzenesulfenyl bromide: ¹H NMR (CDCl₃) δ 7.44 (t, 1 H), 7.73 (t, 1 H), 8.04 (d, 1 H), 8.31 (d, 1 H); ¹³C NMR (CDCl₃) δ 125.50, 126.68, 129.09, 134.52, 135.37, 137.70; mp 85.5–87 °C (lit.¹² mp 83–85 °C).

Synthetic Coupling Reactions. Compounds 1–4. General. In a 10 mL pear-shaped flask were mixed 1.00 mmol of the sulfenyl halide, 0.500 mmol of tetramethylstannane, 2 mol % of tetrakis(triphenylphosphine)palladium(0), and 4 mL of dry THF. The catalyst was added last, and an argon atmosphere was maintained in the flask. The contents of the flask were stirred for 4 h at room temperature. Further workup is described below.

2,4-Dinitrophenyl Disulfide (1b). During the reaction period a yellow precipitate appeared. After 4 h the reaction mixture was cooled to -2 °C for 0.5 h. The product was filtered on a sintered glass funnel and dried to constant weight, yielding 188 mg (95%) of **1b**: ¹H NMR (DMSO- d_6) δ 8.17 (d, 2H), 8.43 (dd, 2H), 9.01 (d, 2H); ¹³C NMR (DMSO- d_6) δ 121.45, 128.43, 128.70, 140.71, 145.42, 145.97; mp 307 °C dec [lit.¹³ mp 280 °C dec].

Isolation and Characterization of Compounds 2–4b. After 4 h the THF was removed on a rotary evaporator and the resulting solid dissolved in methylene chloride. This solution was washed twice with 2 mL portions of water and dried over magnesium sulfate, and the methylene chloride was removed on a rotary evaporator.

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2-Nitrophenyl Disulfide (2b). Removal of the methylene chloride in a tared flask yielded 135 mg (88%) of 2b. Further purification was obtained by recrystallization from benzene: 1H NMR (CDCl₃) & 7.41 (dd, 2H), 7.61 (dd, 2H), 7.86 (d, 2H), 8.34 (d, 2H); ¹³C NMR (CDCl₃) & 126.37, 127.00, 127.17, 134.52, 134.88, 146.10; mp 193-194 °C [lit.12 mp 192.5-193.5 °C]. The yield of 2b from 2-nitrobenzenesulfenyl bromide (6a) was 83%.

4-Nitrophenyl Disulfide (3b). Removal of the methylene chloride in a tared flask yielded 129 mg (84%) of 3b. Further purification was obtained by recrystallization from absolute ethanol: ¹H NMR (CDCl₃) δ 7.62 (d, 4H, J = 9.00 Hz), 8.20 (d, 4H, J = 8.98 Hz); ¹³C NMR (CDCl₃) δ 124.39, 126.32, 143.99, 146.90; mp 182-182.5 °C [lit.14 mp 182-183 °C].

2,4,5-Trichlorophenyl Disulfide (4b). Removal of the methylene chloride in a tared flask yielded 180 mg (86%) of 4b. Further purification was obtained by recrystallization from benzene: ¹H NMR (CDCl₃) δ 7.50 (s, 2H), 7.61 (s, 2H); ¹³C NMR (CDCl₃) δ 128.78, 130.91, 131.07, 132.29, 132.49, 134.07; mp 144.5–145 °C [lit.¹⁵ mp 146.5–147.5 °C].

Triphenylmethyl Disulfide (5b). A solution of 311 mg (1.00 mmol) of triphenylmethanesulfenyl chloride, 89 mg (0.500 mmol) of tetramethylstannane, 23 mg (~2 mol %) of tetrakis-(triphenylphosphine)palladium(0), and 4 mL of dry THF was mixed in a 10 mL flask fitted with a magnetic stirrer and septum cap. An atmosphere of argon was maintained. The flask was heated in a water bath to 40 °C for 24 h and then the THF removed on a rotary evaporator. The black solid was dissolved in methylene chloride and chromatographed on a silica gel column (3 \times 20 cm) using methylene chloride as the eluent. Fifteen 7.5 mL samples were collected and analyzed by TLC.

Samples 5-7 contained starting sulfenyl chloride 5a and samples 10-13 contained the product triphenylmethyl disulfide (5b). The solvent from the pooled samples 10–13 was evaporated to constant weight in a tared flask and yielded 170 mg (62%) of product. On the basis of recovered sulfenyl chloride, the yield was 73%: ¹H NMR (CDCl₃) δ 7.29 (m, 36 H); ¹³C NMR (acetone- d_6) δ 69.94, 128.35, 129.12, 129.63, 149.48; mp 158-159 °C [lit.¹⁶ mp 156-157 °C].

Palladium-Catalyzed Reactions of 2,4-Dinitrobenzenesulfenyl Chloride with Chlorine Scavengers 7-14. A solution of 1.00 mmol of 1a, 1.00 or 0.500 mmol of chlorine scavenger, 7-14, 2 mol % of tetrakis(triphenylphosphene)palladium(0), and 4 mL of dry THF were mixed in a flask. The mixture was stirred overnight, and the solid disulfide (1b) was filtered on a Hirsch funnel. The solid was washed with THF and dried in a vacuum desiccator. Yields are listed in Table 2. The THF filtrates were evaporated to dryness, and the ¹H NMR spectrum of the solid showed the presence of the alkyltin or germanium halide.

Reactivity Studies of 2a and 6a. In an NMR tube were mixed 0.100 mmol of 2a or 6a, 0.0500 mmol of tetramethylstannane, 2 mol % of tetrakis(triphenylphosphine)palladium(0), and 0.5 mL of THF- d_8 . The reaction was monitored by ¹H NMR over a period of 4 h. The reaction mixture was maintained at 25 °C. The extent of reaction was determined by the normalized areas of the tetramethylstannane, chlorotrimethylstannane, and bromotrimethylstannane peaks at 0.10, 0.62, and 0.72 ppm, respectively. The results are shown in Figure 1.

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