ORGANIC
LETTERS

2012
Vol. 14, No. 20
5318–5321

Rhodium-Catalyzed Synthesis of Diaryl Sulfides Using Aryl Fluorides and Sulfur/Organopolysulfides

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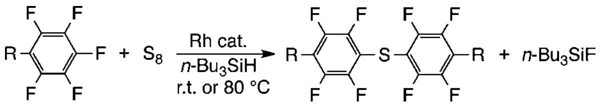
Received September 10, 2012

ABSTRACT



Substituted pentafluorobenzenes react with sulfur to give bis(4-substituted 2,3,5,6-tetrafluorophenyl) sulfides in the presence of RhH(PPh$_3$)$_4$, 1,2-bis(diphenylphosphino)benzene (dppBz), and tributylsilane. The reaction proceeds efficiently between room temperature and 80 °C. A comparative study of the reactivities of an organic trisulfide and a tetrasulfide showed notable substrate specificity. Di-*tert*-butyl tetrasulfide reacted with reactive aryl monofluorides and substituted pentafluorobenzenes. Di-*tert*-butyl trisulfide reacted with aryl monofluorides. The reactivity was explained on the basis of the difference in S–S bond energy.

Diaryl sulfides have different properties from diaryl ethers; they are used as biologically active substances[1] and for high-temperature plastics.[2] They are generally synthesized by the substitution reaction of aromatic halides with inorganic sulfides[3] or aromatic thiolates.[4] The utilization of sulfur in their synthesis is attractive because sulfur is readily available, is easy to handle, and forms no metal waste. Very few examples, however, have been reported for the reaction of aryl halides and sulfur, which proceeds at extremely high temperatures above 200 °C.[5] Bis(pentafluorophenyl) sulfide is obtained by the reaction of iodopentafluorobenzene and sulfur at 230 °C without a solvent; the reaction of chloropentafluorobenzene and sulfur is conducted at 350 °C in the presence of a stoichiometric amount of copper.

Described in this study is the rhodium-catalyzed synthesis of diaryl sulfides from aryl fluorides and sulfur, which proceeds at much lower temperatures (Scheme 1). Previously, we developed a method for the rhodium-catalyzed synthesis of aryl sulfides from aryl fluorides and organic disulfides.[6] Here, we describe the extension of this methodology to the reaction of sulfur.[7] During our study to

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(3) For examples using Na_2S, see: (a) Li, Y.; Nie, C.; Wang, H.; Li, X.; Verpoort, F.; Duan, C. *Eur. J. Org. Chem.* **2011**, 7331. Also see ref 2a. Using thioacetamide: (b) Tao, C.; Lv, A.; Zhao, N.; Yang, S.; Liu, X.; Zhou, J.; Liu, W.; Zhao, J. *Synlett* **2011**, 134. Using thiourea: (c) Argüello, J. E.; Schmidt, L. C.; Peñéñory, A. B. *Org. Lett.* **2003**, *5*, 4133.

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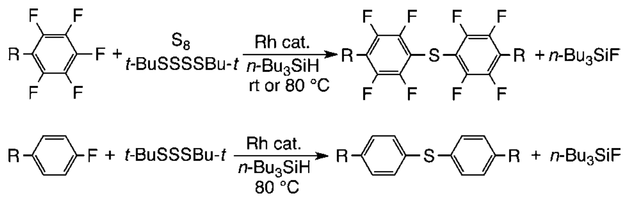
10.1021/ol302497m

develop a sulfur reaction methodology, the reactivities of an organic trisulfide and a tetrasulfide were compared, which showed notable substrate specificity.

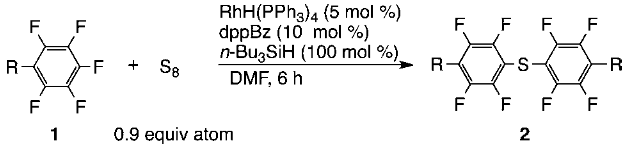
Scheme 1



When (phenylthio)pentafluorobenzene **1e** was reacted with sulfur (0.9 equiv atom) in the presence of $RhH(PPh_3)_4$ (5 mol %), dppBz (10 mol %), and tributylsilane (1 equiv) at 80 °C for 6 h, bis(4-phenylthio-2,3,5,6-tetrafluorophenyl) sulfide **2e** was obtained in 72% yield (Table 1, entry 5). The reaction proceeded effectively using only a small excess of sulfur. The added tributylsilane was converted to tributylsilyl fluoride in 59% yield, which was confirmed by ^{19}F NMR d −174.6 (quintet, $J = 6.0$ Hz) and HRMS 218.1852 (calcd for $C_{12}H_{27}FSi$ 218.1866).[8] A trace amount of **2e** was obtained without using tributylsilane. When triphenylphosphine was used as the fluoride acceptor,[6,9b] the yield of **2e** decreased to 8%, accompanied by the formation of triphenylphosphine sulfide (78%). The result indicated that triphenylphosphine reacted with sulfur faster than fluoride. The rhodium complex and dppBz ligand were both essential for the reaction. No reaction occurred in the absence of either substance. The reaction of *p*-fluorobenzophenone **10a** and *p*-fluorobenzonitrile **10c**, however, did not proceed under the conditions; as will be noted later, the use of an organic trisulfide was essential for such a reaction.

Several pentafluorobenzenes possessing cyano, benzoyl, acetyl, and tolylthio groups reacted with sulfur in high yields (Table 1, entries 2–6). Note that pentafluorobenzenes possessing electron-withdrawing groups such as nitro, cyano, and benzoyl groups reacted even at room temperature (entries 1–3).[10] All these reactions occurred at the *p*-position of the substrates irrespective of the nature of the substituents. The same tendency was previously observed in the rhodium-catalyzed thiolation reactions of polyfluorobenzenes with thioesters, the aryloxylation reaction with aryl esters, and the C–C bond-forming reaction with 1,2-diphenylethanone.[9]

Table 1. Reaction of Pentafluorobenzenes and Sulfur

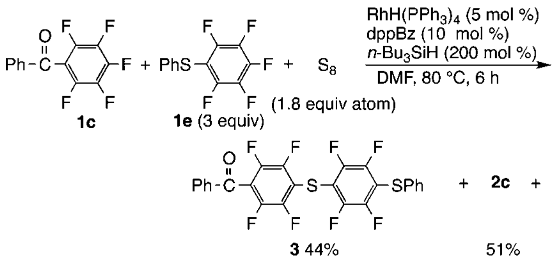


entry	R	yield (%) 80 °C[a]	rt[a]
1	NO_2 (**a**)	42	71
2	CN (**b**)	62	77
3	PhCO (**c**)	67	42
4	CH_3CO (**d**)	66	27
5	PhS (**e**)	72	3
6	4-TolS (**f**)	65	
7	Ph_2N (**g**)	18	

[a] Reaction temperature.

The synthesis of an unsymmetrical diaryl sulfide was examined. When **1c** and **1e** (3 equiv) were reacted with sulfur (1.8 equiv atom), 1-(4-phenylthio-2,3,5,6-tetrafluorophenylthio)-4-benzoyl-2,3,5,6-tetrafluorobenzene **3** (44%) was obtained, which was accompanied by the symmetric sulfides **2c** (51%) and **2e** (20%) (Scheme 2). The sulfur accepting reactivity of **1c** was slightly lower than that of **1e**.

Scheme 2



Substituted pentafluorobenzenes react with sulfur to give bis(4-substituted 2,3,5,6-tetrafluorophenyl) sulfides under rhodium-catalyzed conditions. The reaction proceeds efficiently between room temperature and 80 °C, unlike conventional methods, which proceed only above 200 °C.

The reactivity of sulfur was compared with those of organic polysulfides. Since the reactivity of organic polysulfides with a transition-metal catalyst has rarely been examined,[7] we considered it interesting to study the subject. When **1e** was reacted with di-*tert*-butyl tetrasulfide **4** (0.9 equiv) in the presence of $RhH(PPh_3)_4$ (5 mol %), dppBz (10 mol %), and tributylsilane (1 equiv) in DMF at 80 °C for 6 h, **2e** was obtained in 80% yield along with di-*tert*-butyl trisulfide **5** (41%) and the recovery of **4** (16%) (Scheme 3). No di-*tert*-butyl disulfide was detected. No reaction occurred in the absence of the rhodium complex.

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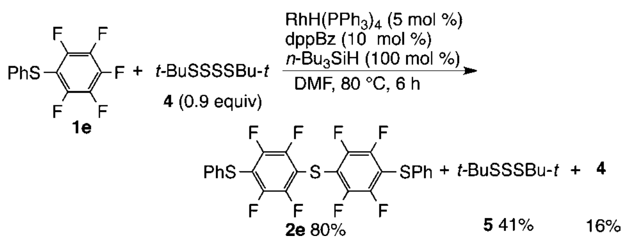
[10] **Typical Experimental Procedures.** In a two-necked flask equipped with a reflux condenser were placed pentafluorobenzonitrile **1b** (0.5 mmol, 61.6 μL), sulfur (0.45 mmol, 7.2 mg), $RhH(PPh_3)_4$ (5 mol%, 28.8 mg), 1,2-bis(diphenylphosphino)benzene (10 mol%, 22.3 mg), and tributylsilane (0.5 mmol, 129 μL) in DMF (0.5 mL) under an argon atmosphere, and the solution was stirred at room temperature for 6 h. The solvent was then removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel giving bis(4-cyano-2,3,5,6-tetrafluorophenyl) sulfide **2b** (73.1 mg, 77%).

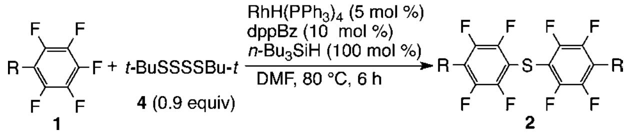
These results showed that only one sulfur atom of **4** was transferred to **1e**, and accordingly, no reaction occurred when **1e** and **5** were reacted. The reactivity of the middle sulfur in **4** is different from that in **5**.

Scheme 3



Several pentafluorobenzenes possessing moderately electron-donating groups (Ph_2N and ArS) and electron-withdrawing groups (PhCO and MeCO) reacted with **4** in high yields (Table 2, entries 3–8). Note that **4** reacted with **1g** possessing a diphenylamino group in a much higher yield than sulfur (entry 8, also see Table 1 entry 7). The yield decreased when **4** was reacted with **1a** and **1b** possessing strong electron-withdrawing groups (entries 1 and 2). The tetrasulfide **4** exhibited a slightly different reactivity with pentafluorobenzenes from sulfur. A notable difference was observed in the reaction of aryl monofluorides possessing two strong electron-withdrawing groups. The reaction of **4** and 4-cyano-(3-trifluoromethyl)fluorobenzene **6a** or 4-cyano-(2-trifluoromethyl)fluorobenzene **6b** gave the sulfides in high yields (Scheme 4). Trace amounts of the products were obtained with sulfur for these substrates. 2-Fluorobenzothiazole **8** also reacted with **4** (0.9 equiv) under the same conditions giving the sulfide **9** in 67% yield. No reaction occurred using sulfur, and the yield of **9** decreased to 13% using the di-*tert*-butyl trisulfide **5** in place of **4**. In contrast to these reactive aryl fluorides, *p*-fluorobenzophenone **10a** and *p*-fluorobenzonitrile **10c** gave no diaryl sulfides using **4**. The difference between the reactivities of **4** and sulfur may originate from the difference in the nature of the middle sulfur, which will be discussed later.

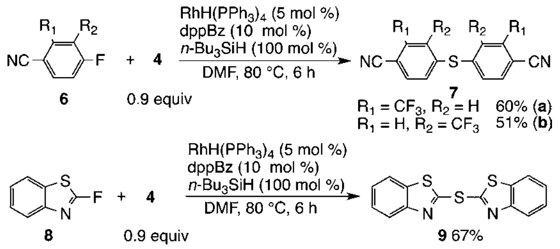
Table 2. Reaction of Pentafluorobenzenes and **4**



entry	R	yield/%
1	NO_2 (**a**)	14
2	CN (**b**)	20
3	PhCO (**c**)	71
4[a]		40
5	CH_3CO (**d**)	66
6	PhS (**e**)	80
7	4-TolS (**f**)	89
8	Ph_2N (**g**)	82

[a] In air atmosphere.

Scheme 4

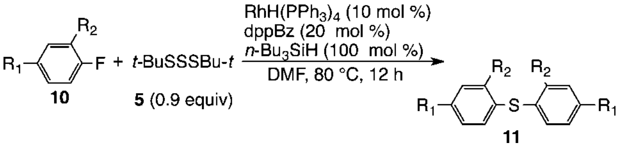


Observing the apparent difference between the reactivities of sulfur and tetrasulfide, it was considered interesting to examine the reactivity of an organic trisulfide. It was found that the reactivity of the middle sulfur in trisulfide was different from those in sulfur and tetrasulfide. When *p*-fluorobenzophenone **10a** and di-*tert*-butyl trisulfide **5** (0.9 equiv) were reacted in DMF at 80 °C for 12 h in the presence of $RhH(PPh_3)_4$ (10 mol %), dppBz (20 mol %), and tributylsilane (100 mol %), bis(4-benzoylphenyl) sulfide **11a** was obtained in 59% yield along with di-*tert*-butyl disulfide (84%) and the recovery of **10a** (35%) (Table 3, entry 1). Using dibutyl trisulfide (0.25 equiv) in place of **5**, no **11a** was detected, and *p*-benzoylphenyl butyl sulfide (89%) was formed, which indicated the bulky substituent of trisulfides to be critical for the selective transfer of the middle sulfur atom in **5**. As noted before, sulfur and the tetrasulfide **4** produced no **11a** from **10a** under the conditions employed. Appropriate combinations of sulfurating reagents and aryl fluorides are required for an effective reaction.

The sulfuration of **5** could be applied to the synthesis of aryl fluorides possessing *p*-benzoyl, *o*- or *p*-cyano, and nitro groups (Table 3, entries 1–6). When triphenylphosphine was used as the fluoride acceptor in the reaction of *o*-nitrofluorobenzene **10d** and **5**, **11d** was obtained in 43% yield (entry 5). Since both triphenylphosphine and tributylsilane worked effectively, the formation of silyl sulfide intermediates from trisulfide and silane reagent may not be likely for the present reactions. 3,4-Difluorobenzonitrile **10g** reacted at the *p*-fluoride atom (entry 8). No reaction of *m*-cyanofluorobenzene and 4-fluorotoluene occurred. Di-*tert*-butyl trisulfide reacted efficiently at 80 °C with aryl monofluorides, which have electron-withdrawing groups at the *o*- and *p*-positions.

A possible mechanism of the reaction of **4** follows (Figure 1). The high-oxidation-state rhodium complex **A** is formed by the oxidative addition of an aryl fluoride and **4** at the SS–SS bond. Then, a sulfur atom inserts at the Rh–C bond with the liberation of **5**. The resulting rhodium fluoride **B** reacts with another aryl fluoride and transfers fluoride atoms to tributylsilane or

Table 3. Reaction of Aryl Monofluorides and **5**



entry	R$_1$	R$_2$	yield (%)
1	PhCO	H (**a**)	59
2	H	CN (**b**)	48
3	CN	H (**c**)	64
4	H	NO_2 (**d**)	66
5[a]			43
6	NO_2	H (**e**)	64
7	CN	Cl (**f**)	53
8	CN	F (**g**)	41

[a] Using PPh_3 in place of n-Bu_3SiH.

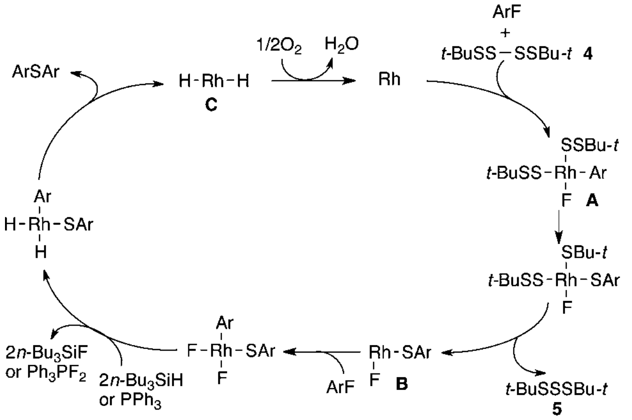


Figure 1

triphenylphosphine giving tributylsilyl fluoride or triphenylphosphine difluoride. A diaryl disulfide is liberated by reductive elimination, and the rhodium catalyst is regenerated by the oxidation of the rhodium dihydride **C** with a trace amount of oxygen-forming water. It was previously reported that the rhodium-catalyzed oxidation of thiols is quite rapid, giving disulfides in an oxygen atmosphere.[11] The reaction of **1c** and **4** gave **2c** (40%) in air atmosphere as well as in argon atmosphere (Table 2, entry 4), indicating that oxygen does not inhibit the catalytic cycle.

Sulfur, **4**, and **5** showed different reactivities with aryl fluorides. Trisulfide **5** sulfurated aryl monofluorides; Tetrasulfide **4** sulfurated reactive aryl monofluorides and substituted pentafluorobenzenes with moderately electron-donating and electron-withdrawing groups. Sulfur reacted with only substituted pentafluorobenzenes. The difference in reactivity may be due to the difference in S–S bond energy [trisulfide (46 kcal/mol) > tetrasulfide (37 kcal/mol) > sulfur (33 kcal/mol)][12] and the difference in reactivity between the aryl fluorides (pentafluorobenzenes > aryl monofluorides with two electron-withdrawing groups and 2-fluorobenzothiazole > aryl monofluorides with one electron-withdrawing group). These results support the idea that less reactive sulfurating reagents should be used for less reactive substrates. Similar correlations were previously observed in the thiolation reaction of various organic compounds.[13] The need for suitable combinations of substrates and sulfurating reagents is important for the catalyzed sulfuration of organic compounds.

In summary, sulfur was reacted with substituted pentafluorobenzenes to give bis(4-substituted 2,3,5,6-tetrafluorophenyl) sulfides in the presence of a rhodium catalyst and tributylsilane. The reaction proceeded efficiently between room temperature and 80 °C. The reactivities of organic polysulfides under transition-metal catalyzed conditions were compared, and these sulfur reagents showed differences in reactivity between sulfur, trisulfide, and tetrasulfide.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research (No. 21229001) from JSPS and the GCOE program. M.A. expresses her thanks for financial support from the Grant-in-Aid for Scientific Research from MEXT (No. 22689001), Japan Science Technology Agency, and also to the Asahi Glass Foundation.

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

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