Reduction of Aryl Thiocyanates with SmI_2 and Pd-Catalyzed Coupling with Aryl Halides as a Route to Mixed Aryl Sulfides

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A series of aryl iodides, with a range of substituents, has been successfully coupled using 10 mol % Pd catalyst with samarium thiolates, derived from the corresponding aryl thiocyanates upon reductive cleavage with SmI_2. Reactions proceed in THF at 65 °C in yields ranging from good to excellent and are compatible with both electron-donating and electron-withdrawing substituents, except NO_2. The reactions may also be conducted with aryl bromides although with somewhat lower yields.

Many applications of SmI_2 are now known and there have been several recent reviews of this topic.[1] The use of transition metals, notably palladium and nickel, in catalyzing the coupling reaction between various aryl derivatives and aryl halides to produce (mixed) aryl compounds[2−5] has been the subject of several recent papers. Other methods for preparing mixed aryl sulfides and sulfones have also appeared recently.[6−9] There have been two recent reports[10,11] of the preparation of samarium(III) thiolates, although no attempts were made to evaluate their synthetic utility.

We hoped to make use of aryl thiocyanates, readily available by our recently described procedure,[12] to extend their synthetic utility[13−15] to the preparation of mixed aryl sulfides. Several methods already exist for preparing mixed aryl sulfides[7−9,16−21] and alkenyl aryl sulfides.[22−24] While these procedures generally provide acceptable yields, they suffer in several cases from drawbacks such as the use of elevated temperatures or the need for rather specialized and expensive solvents. In some cases also the Pd(0) and Ni(0) catalytic species must be preformed, and they are often difficult to handle. Since we have already shown that samarium(II) iodide is a superior reagent for the reductive cleavage of the S−CN bond, we hoped that the (samarium) thiolates produced in this way would react with aryl iodides in the presence of catalytic Pd(0) species. These might, in turn, be generated during the reaction from their more easily handled Pd (II) progenitors, perhaps aided by the reducing power of the SmI_2 (Scheme 1). The results from this approach are described below.

Results and Discussion

We believe that the Sm(III) thiolates (Scheme 1) generated from the corresponding aryl thiocyanates during the course of this investigation are probably covalent in nature. Marks and co-workers[25] have reported a value of 73.4 kcal/mol for the Sm−S bond dissociation energy, remarkably similar to the value for the Sm−I bond (72.7 kcal/mol).

We initially investigated the reactivity of samarium(III) thiolate with iodobenzene in the presence of several transition metal catalysts (Table 1). The use of a slight excess of SmI_2 during the reduction of aryl thiocyanates to samarium(III) thiolates allows for the reduction of the subsequently added transition metal catalyst to the M(0) oxidation state. Addition of the aryl halide to this reaction mixture, which now contains the samarium(III) thiolate and the Pd(0) (or Ni(0)) complex generated *in situ*, results in oxidative addition of ArX, as shown in Scheme 1. Nucleophilic reaction of the samarium(III) thiolate with the metal complex thus obtained provides the thiolato-palladium(II) complex. Reductive elimination regenerates the Pd(0) catalyst, along with the mixed aryl sulfide product. A similar mechanism presumably operates for the nickel-catalyzed process, although this may be complicated by the fact that nickel complexes tend to equilibrate between tri- and tetracoordinate species.[26] A potential difficulty with the use of palladium-catalyzed reactions involving thiol nucleophiles is the poisoning of the catalyst, which is believed to occur

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Scheme 1

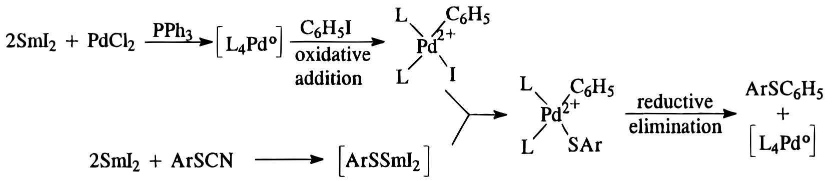
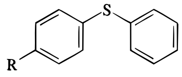


Table 1. Comparison of the Efficiency of Catalysts in the Tandem SmI$_2$ Reduction/Transition Metal-Catalyzed Coupling of ArSCN with C$_6$H$_5$I



2a (R = CH$_3$)
2b (R = NMe$_2$)

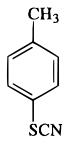
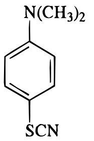
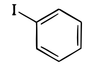
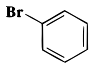
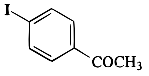
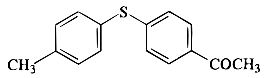
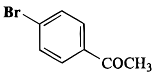
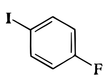
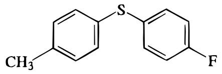
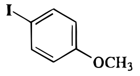
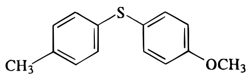
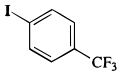
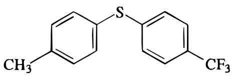
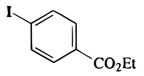
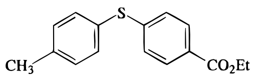
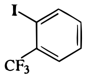
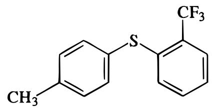
Entry	Aryl Thiocyanate ArSCN	Catalyst (equiv.)	Equivalents of PPh$_3$	Isolated yield (%) of ArSC$_6$H$_5$	
1	**1a** 	None	--.-	0	**2a**
2		PdCl$_2$ (0.1)	0.4	52	
3		(PPh$_3$)$_2$PdCl$_2$ (0.1)	0.2	56	
4		(PPh$_3$)$_2$NiCl$_2$ (0.1)	0.2	36	
5	**1b** 	None	--.-	15	**2b**
6		(PPh$_3$)$_4$Pd (0.05)	0.4	82	
7		PdCl$_2$ (0.1)	0.4	78	
8		(PPh$_3$)$_2$NiCl$_2$ (0.1)	0.2	55	

Table 2. Coupling of the Samarium(III) Thiolate from 1a with Various Aryl Halides, Catalyzed by 10 Mol % (PPh$_3$)$_2$PdCl$_2$/dppe at 65 °C

Entry	Aryl Halide	Product	Isolated Yield (%)
1		**2a**	72
2		**2a**	56
3		 **3a**	92
4		**3a**	69
5		 **3b**	51
6		 **3c**	55
7		 **3d**	83
8		 **3e**	59
9		 **4**	71

during the reductive elimination. Barañano and Hartwig[18] have recently reported that the addition of (diphenylphosphino)ethane (dppe) during the reaction slightly alleviates this problem. In our work, the full role played by the Sm species present is not clear.

The effectiveness of several catalysts in the tandem samarium(II) iodide reduction/transition metal-catalyzed coupling reaction of aryl thiocyanates is detailed in Table 1. In the absence of catalyst very little or no mixed aryl sulfide could be isolated. The palladium(II) catalysts generally appear to be more efficient than the nickel(II) counterparts. These results suggest that palladium may be the transition metal of choice for this reaction, although other types of nickel(II) catalyst were not examined. The yield of sulfide **2b** obtained from the reaction between compound **1b** and iodobenzene, is very similar in the presence of both a Pd(0) catalyst (entry 6) and palladium(II) chloride (entry 7). Although not conclusive proof, this does suggest that a similar mechanism may be operating in each case. This is in accord with our proposal of *in situ* generation of a Pd(0) species resembling (PPh$_3$)$_4$Pd (Scheme 1).

Interestingly, **1b** provided significantly higher yields of the mixed aryl sulfide coupling products in Table 1. This may be attributed to the increased electron-donating power of the *N*,*N*-dimethylamino group, which presumably results in increased nucleophilicity of the corresponding samarium(III) thiolate. (Although tertiary amines are known to enhance several coupling reactions which involve the generation of HX as a byproduct,[27] a preliminary trial using a stoichiometric amount of *N*,*N*-dimethylaniline in the coupling of **1a** with iodobenzene did not improve the yield of **2a** observed.) In spite of this enhanced reactivity observed for **1b**, however, we decided to use **1a**, as perhaps a more representative prototype, in our study of the synthetic scope of this reaction. A brief study of the effect of varying the ligands employed revealed little difference in effectiveness between triphenylphosphine and triphenylarsine. The addition of 1,2-bis(diphenylphosphino)ethane (dppe), however, produced a significant enhancement in the yields obtained. This is in accord with results obtained by Barañano and Hartwig,[18] although Ortar and co-workers[3] found dppe to be quite ineffective in their catalytic system. The results which we obtained in the study with **1a** and a number of different aryl halides appear in Table 2.

The yields obtained in Table 2 are generally good to very good. While no clear-cut pattern of substituent effects emerges from our results, it is perhaps significant that the best two results were obtained with electron-withdrawing groups (CF$_3$, COCH$_3$) in the *para*-position

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(27) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, 1985.

of the aryl iodide. As expected, no coupling product was obtained when 4-iodonitrobenzene was used: we had earlier observed that nitro groups are incompatible with the use of SmI_2, although they can be used with other types of Pd(0) coupling reactions involving thiolates.[3] No coupling product was obtained from the reaction of N-Boc-protected 4-iodoaniline, perhaps due to deblocking of the protecting group during the reaction.

It appears that both aryl iodides and bromides can be utilized in these reactions. In accord with earlier studies, however, aryl iodides provide higher yields of the diaryl sulfides than the corresponding bromides. Interestingly, in an attempted competition reaction using 4-bromo-1-iodobenzene, the only coupling product isolated was **2a**. This suggests that initial coupling (with the iodide functionality) was accompanied by a dehalogenation step. Aryl halides are known to be reduced by a wide variety of reducing agents, including triphenylphosphine.[28]

This coupling reaction should be capable of extension to a wide variety of aryl thiocyanates and aryl halides. It offers several advantages over earlier literature methods in that it avoids the need to isolate the thiol, the manipulation of air-sensitive transition metal complexes, and the use of special solvents (THF was used throughout), as well as being carried out under relatively mild conditions.

Experimental Section

All the starting aryl iodides and bromides used (with the exceptions noted below) and other intermediates were obtained from the Aldrich Chemical Co. and used without further purification, unless indicated otherwise. 4-Fluoro-1-iodobenzene was obtained from 4-fluoroaniline by diazotization and subsequent reaction with potassium iodide.[29] 4-Methyl-1-thiocyanatobenzene (**1a**) was prepared from 4-methylbenzenethiol by the procedure of Harpp *et al.*[30] and *N*,*N*-dimethyl-4-thiocyanatoaniline (**1b**) by our previously reported procedure.[12] Samarium(II) iodide was generated *in situ* from samarium metal (40 mesh; Alfa Aesar) and either 1,2-diiodoethane or diiodomethane (Lancaster Synthesis Inc.) by literature procedures.[31] Tetrahydrofuran was dried by refluxing over sodium and benzophenone until a permanent purple coloration was present. All reactions were run in oven- or flame-dried glassware under an atmosphere of argon. The products were isolated by evaporation to dryness on the rotary evaporator, redissolving the organic residue in CH_2Cl_2:hexanes (1:1), washing with water, and drying (Na_2SO_4). Purification was conducted by flash chromatography on silica gel, eluting with CH_2Cl_2, unless otherwise stated.

Melting points and boiling points are uncorrected: the latter represent oven temperatures recorded during Kugelrohr (bulb-to-bulb) vacuum distillation. Mass spectra were recorded at an ionizing voltage of 70 eV. FTIR spectra were recorded under the conditions indicated. ^1H NMR spectra were obtained in $CDCl_3$ at 200 MHz and ^{13}C NMR spectra were recorded at 100.6 or 125.7 MHz. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Box 25, DK-2730, Herlev, Denmark.

Preparation of $(PPh_3)_2PdCl_2$. Following the general procedure of Heck,[27] to a solution of palladium(II) chloride (8.85 g, 0.05 mol) and lithium chloride (4.25 g, 0.10 mol) in dry methanol (80 mL) was added triphenylphosphine (27.5 g, 0.11 mol). The resulting reddish brown reaction mixture was heated in a water bath (temp ~80 °C) until a yellow, nearly insoluble solid formed. The reaction mixture was cooled to ambient temperature and the yellow product (32.7 g, 93%) collected by vacuum filtration, washed with methanol (25 mL), and dried overnight in a desiccator prior to use.

Preparation of $(PPh_3)_2NiCl_2$. Following the general procedure of Venanzi,[32] to a deep green solution of nickel(II) chloride hexahydrate (2.38 g, 0.01 mol) in distilled water (3 mL) was added acetic acid (75 mL). The reaction mixture turned from a dark green suspension to a clear light green solution. To this light green solution was added triphenylphosphine (5.25 g, 0.02 mol), resulting in the formation of a dark blue solution, which was stirred for 25 h at 25 °C. After 24 h, the blue solid was collected by suction filtration and washed with acetic acid to afford a greenish-blue solid (5.43 g, 83%).

Representative Procedure for Mixed Aryl Sulfides. 4′-(*N*,*N*-Dimethylamino)phenyl Phenyl Sulfide (2b). To a deep blue solution of SmI_2 (3.09 mmol) in dry THF (45 mL) was added the aryl thiocyanate **1b** (0.25 g, 1.24 mmol), and the resulting reaction mixture was stirred at ambient temperature for 1.5 h. After 1.5 h, the reaction mixture was transferred via a double-ended needle to a refluxing solution of bis(triphenylphosphine)palladium(II) chloride (0.09 g, 0.13 mmol, 10 mol %), diphenylphosphinoethane (0.05 g, 0.13 mmol), and iodobenzene (0.14 mL, 1.25 mmol) in dry THF (10 mL). The addition caused the reaction mixture to immediately become orange and then deep red-brown. After refluxing an additional 16 h, the reaction mixture was cooled to room temperature and the solvent removed under reduced pressure. The residual solid was treated in the usual way and finally afforded a yellow oil. Flash chromatography (R_f = 0.65) afforded a yellow solid (0.19 g, 78%), which was recrystallized from heptane, mp 63−64 °C [lit.[33] mp 66.5−67 °C]. ^1H NMR: δ 7.39 (d, J = 8.9 Hz, 2H), 7.16 (m, 5H), 6.71 (d, J = 8.9 Hz, 2H), 3.02 (s, 6H); EIMS: m/z (%), 229(100), 152(21).

The following diaryl sulfides (see also Table 2) were prepared by the $(PPh_3)_2PdCl_2$/dppe-catalyzed coupling of samarium(III) thiolates and aryl halides, using the procedure detailed above for the preparation of **2b**.

4′-Methylphenyl phenyl sulfide (2a): colorless oil after Kugelrohr distillation at 95−100 °C/12 mm [lit.[34] bp 174 °C/17 mm]. ^1H NMR: δ 7.32 (d, J = 8.0 Hz, 2H), 7.26 (m, 5H), 7.15 (d, J = 8.0 Hz, 2H), 2.36 (s, 3H).

4-[(4′-Methylphenyl)thio]acetophenone (3a): light yellow solid after recrystallization from CH_2Cl_2:hexanes, mp 86−88 °C. ^1H NMR: δ 7.80 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H), 2.55 (s, 3H), 2.40 (s, 3H); EIMS: m/z (%), 242(85), 227(100), 199(9); HR-EIMS calcd for $C_{15}H_{14}OS$ 242.0765, found 242.0759. Anal. Calcd for $C_{15}H_{14}OS$: C, 74.34; H, 5.82. Found: C, 73.88; H, 5.99.

4-Fluorophenyl 4′-methylphenyl sulfide (3b): colorless oil after Kugelrohr distillation at 135−140 °C/12 mm [lit.[35] bp 100−104 °C/0.3 mm]. ^1H NMR: δ 7.29 (m, 2H), 7.24 (d, J = 9.1 Hz, 2H), 7.12 (d, J = 9.1 Hz, 2H), 6.99 (m, 2H), 2.33 (s, 3H); EIMS: m/z (%), 218(100), 203(29), 91(31); HR-EIMS calcd for $C_{13}H_{11}FS$ 218.0565, found 218.0562.

4-Methoxyphenyl 4′-methylphenyl sulfide (3c): light yellow solid after recrystallization from hexanes, mp 43−45 °C [lit.[36] mp 43−45 °C, from 95% EtOH]. ^1H NMR: δ 7.37 (d, J = 8.9 Hz, 2H), 7.14 (d, J = 8.3 Hz, 2H), 7.07 (d, J = 8.9 Hz, 2H), 6.87 (d, J = 8.3 Hz, 2H), 3.81 (s, 3H), 2.30 (s, 3H); EIMS: m/z (%), 230(100), 215(49), 91(10). Anal. Calcd for $C_{14}H_{14}OS$: C, 73.00; H, 6.13; S, 13.92. Found: C, 72.68; H, 6.15; S, 13.58.

4′-Methylphenyl 4-(trifluoromethyl)phenyl sulfide (3d): light yellow solid after recrystallization from hexanes, mp 93−95 °C. ^1H NMR: δ 7.45 (d, J = 8.5 Hz, 2H), 7.40 (d, J = 8.4

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Hz, 2H), 7.22 (d, $J = 8.4$ Hz, 2H), 7.20 (d, $J = 8.5$ Hz, 2H), 2.39 (s, 3H); EIMS: *m/z* (%), 268(100), 249(9), 199(14), 184(18), 91(40); HR-EIMS calcd for $C_{14}H_{11}F_3S$ 268.0534, found 268.0531. Anal. Calcd for $C_{14}H_{11}F_3S$: C, 62.67; H, 4.13; S, 11.95. Found: C, 62.94; H, 4.30; S, 11.80.

Ethyl 4-[(4′-Methylphenyl)thio]benzoate (3e): low melting solid from cold hexanes, mp 22–24 °C. ^{1}H NMR: δ 7.88 (d, $J = 8.5$ Hz, 2H), 7.40 (d, $J = 7.9$ Hz, 2H), 7.22 (d, $J = 7.9$ Hz, 2H), 7.15 (d, $J = 8.5$ Hz, 2H), 4.34 (q, $J = 7.2$ Hz, 2H), 2.40 (s, 3H), 1.37 (t, $J = 7.2$ Hz, 3H); EIMS: *m/z* (%), 272(100), 244(26), 227(68), 199(20), 184(54), 91(33); HR-EIMS calcd for $C_{16}H_{16}O_2S$ 272.0871, found 272.0872.

4′-Methylphenyl 2-(trifluoromethyl)phenyl sulfide (4): pale yellow oil after Kugelrohr distillation at 230 °C/15 mm. ^{1}H NMR: δ 7.66 (dd, $J = 7.2$, 1.2 Hz, 1H), 7.37 (d, $J = 8.2$ Hz, 2H), 7.30 (m, 2H), 7.19 (d, $J = 8.2$ Hz, 2H), 7.08 (dd, $J = 7.9$, 1.2 Hz, 1H), 2.38 (s, 3H); EIMS: *m/z* (%) 268(100), 199(10), 184(14), 91(39); HR-EIMS calcd for $C_{14}H_{11}F_3S$ 268.0534, found 268.0521.

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Supporting Information Available: FT-IR spectral details for the mixed aryl sulfides obtained are listed, along with a table of ^{13}C-NMR chemical shift data for these compounds and reproductions of the individual ^{13}C-NMR (and APT) spectra for each (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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