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## Thiocyanate as a Versatile Synthetic Unit : Efficient Conversion of ArSCN to Aryl Alkyl Sulfides and Aryl Thioesters.

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Abstract: Treatment of aryl thiocyanates with 2.3 equivalents of  $SmI_2$  results in the formation of an intermediate samarium(III) sulfide which can be trapped with a variety of electrophilic reagents.

The preparation of sulfur-substituted aromatics frequently involves introduction of the sulfur functionality by nucleophilic displacement of the corresponding aryl halide. This may be accomplished by utilizing the cuprous<sup>1</sup> or sodium thiolates, either in polar solvents such as N-methylpyrrolidinone (NMP)<sup>2</sup> or hexamethylphosphoric triamide (HMPA),<sup>3</sup> or under phase-transfer catalysis.<sup>4</sup> Alternatively, the Pd(0) catalyzed reaction of sodium thiolates<sup>5</sup> or tin sulfides<sup>6</sup> with aryl halides has been employed. A frequent drawback of these approaches is that only simple alkyl thiolates can be introduced by these methods, while yields are often particularly poor for aromatic substrates substituted with electron-donating substituents.

It would be advantageous, especially in the case of electron- rich aromatics, to be able to introduce the sulfur moiety as an *electrophile*. For this purpose metallation, especially lithiation,<sup>7</sup> followed by trapping with the appropriate disulfide, has been used in some cases. Again, a drawback of this method is that only simple aryl alkyl sulfides may be prepared. We have recently reported an efficient method for the regioselective preparation of aryl thiocyanates<sup>8</sup> and we felt that it should be possible to transform the sulfur which was introduced as an [S<sup>+</sup>] to an [S<sup>-</sup>] equivalent. We now wish to report the application of the powerful one electron donor SmI<sub>2</sub> for this purpose.<sup>9</sup>

We have investigated the reduction of the aryl thiocyanate 1 with SmI<sub>2</sub> and its subsequent reaction with a number of electrophiles (Table 1). We have been able to successfully employ this methodology for the preparation of aryl alkyl sulfides, aryl thioesters, and (mixed) tin sulfides by trapping the presumed intermediate samarium(III) sulfides with appropriate electrophiles. Elevated temperatures are necessary for efficient trapping with longer chain alkyl halides. Interestingly, 1-hexyl tosylate did not give significant amounts of aryl alkyl sulfide even at higher temperatures. Both acid chlorides and anhydrides react readily with the samarium(III) intermediate. Similarly successful results were obtained when the more complex aryl thiocyanate 2 (Entries 8-10) was used.

Thiocyanate ArSCN	Entry	ElectrophileTime/Temp.Isolated Yield (%)(RX or RCOX)(h) (°C)ArSR, 4 or 6/ArSCOR		Isolated Yield (%) ArSR, 4 or 6/ArSCOR, 5
1	1	CH <sub>3</sub> I	2/25	95 <b>4a</b>
	2	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub> Br	20/65	71 <b>4b</b>
	3	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub> CH <sub>2</sub> I <sup>a</sup>	20/65	72 <b>4</b> c
	4	<sup>n</sup> Bu <sub>3</sub> SnCl	18/25	94 <b>4d</b>
	5	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub> COCl	14/65	62 <b>5a</b>
	6	(CH <sub>3</sub> CO) <sub>2</sub> O <sup>b</sup>	19/25	82 <b>5b</b>
	7	C <sub>6</sub> H <sub>5</sub> COCl	19/65	67 <b>5c</b>
2	8	CH <sub>3</sub> I	2/25	97 <b>6a</b>
	9	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> SCH <sub>2</sub> Cl	2/25	88 <b>6b</b>
	10	<sup>n</sup> Bu <sub>3</sub> SnCl	5/25	96 <b>6c</b>

Table 1: Conversion of ArSCN to ArSR and ArSCOR

<sup>a</sup> The corresponding tosylate and bromide were also used, without success.

<sup>b</sup> Ethyl acetate gave no reaction with the  $SmI_2$  product from 1.



The results which we report in Table 2 are consistent with the mechanism recently proposed by Zhang and coworkers<sup>10</sup> for reactions observed with alkyl thiocyanates. This involves initial formation of a radical anion, which fragments to afford the thiyl radical (Scheme 1). A second equivalent of SmI<sub>2</sub> is then required, to form the samarium(III) sulfide. The corresponding disulfide **3** is produced in quantity if only a single equivalent of SmI<sub>2</sub> is used, while the S-alkylated product is the dominant product when at least 2.3 equivalents are used. A similar mechanism presumably applies to thioester formation.

Scheme 1

Equv. SmI <sub>2</sub>	Additive	Time (h)	ArSCH <sub>3</sub> (%)	(ArS) <sub>2</sub> (%)
1.0		1.5	0	48
2.1		1.5	60	5
2.1	NMP	0.67	20	78
2.1	HMPA	0.25	37	61
2.3		1.5	97	0

Table 2. Effect of Varying Ratio of  $SmI_2$  to ArSCN, with 2 as substrate and  $CH_3I$  as the Electrophile.

The SmI<sub>2</sub> reduction here described offers several advantages over more traditional hydride reductions<sup>11</sup> of thiocyanates. The mild, non-basic conditions allow for the preparation of base-sensitive functional groups such as thioesters. The reactions described in Table 1 allow for the easy formation of RS-substituted aromatic substrates in high yields, in a two-stage process initiated by regioselective electrophilic thiocyanation.<sup>8</sup> For a large number of of electron-rich aromatic compounds, this will therefore allow the regioselective introduction of RS<sup>+</sup> with high efficiency and reproducibility. Applications of this methodology to total synthesis will be published in due course.

General Procedure. To a well stirred solution of  $\text{SmI}_2^{12}$  (2.3 mmol) in dry THF (23 mL) at ambient temperature under argon was added the aryl thiocyanate (1.0 mmol). The resulting blue solution, which may slowly become green, was stirred for 1-1.5 h. The reaction mixture was then treated with the appropriate electrophile RX or RCOX (5.0 mmol) and the reaction mixture subjected to the conditions detailed in Table 1. When the reaction was complete, the THF solution was washed with 20% K<sub>2</sub>CO<sub>3</sub> (2 x 25 mL), satd. NaCl (25 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Chromatography, distillation or recrystallization afforded the pure product.<sup>13,14</sup>

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## **REFERENCES AND NOTES**

- 1. Adams, R.; Reifshneider, W.; Ferretti, A. Org. Synth. Coll. Vol. V, 1973, 107-110.
- 2. Shaw, J. J. Org. Chem. 1991, 56, 3728-3729.
- 3. Testaferri, L.; Tingoli, M.; Tiecco, M. Tetrahedron Lett. 1980, 21, 3099-3100.
- 4. Reeves, W. P.; Bothwell, T. C.; Rudis, J. A.; McClusky, J. V. Synth. Commun. 1982, 12, 1071-1079.

- 5. Migita, T.; Shimizu, T.; Asaini, Y.; Shiobara, J.; Kato, Y.; Kosugi, M.; Bull. Chem. Soc. Jpn. 1980, 53, 1385-1389.
- 6. Kosugi, M.; Ogata, T.; Terada, M.; Sano, H.; Migita, T. Bull. Chem. Soc. Jpn. 1985, 58, 3657-3658.
- 7. Jabob, P.; Shulgin, T. Synth. Commun. 1981, 11, 957-968.
- 8. Toste, F. D.; DeStefano, V; Still, I. W. J. Synth. Commun. 1995, 25, 1277-1286.
- For reviews see: Kagan, H. B.; Namy, J. L. Tetrahedron 1986, 42, 6573-6614; Molander, G. A. Chem. Rev. 1992, 92, 29-68.
- 10. Jia, X.; Zhang, Y; Zhou, X. Tetrahedron Lett. 1994, 35, 8833-8834.
- 11. Still, I. W. J.; Sayeed, V. A. Synth. Commun. 1983, 13, 1181-1192.
- Prepared from 1,2-diiodoethane and samarium mesh by the method of Kagan and coworkers: Namy, J. L.; Girard, P.; Kagan, H. B. Nouv. J. Chim. 1977, 1, 5-7.
- All products obtained in Table 1 were characterized either by satisfactory high resolution mass measurements on the purified samples or by elemental analysis.
- Physical and <sup>1</sup>H-NMR<sup>15</sup> data for 4a-d, 5a-c, 6a-c: 4a, mp 104-107°C; 8 7.30 (d, J=8.0 Hz, 2H, H-2, H-6), 6.70 (d, 14. J=8.0 Hz, 2H, H-3, H-5), 3.00 (s, 6H, N(CH, j), 2.40 (s, 3H, SCH, j). 4b, bp 170-175 °C (15 mm); 8 7.35 (d, J=8.0 Hz, 2H, H-2, H-6), 6.70 (d, J=8.0 Hz, 2H, H-3, H-5), 2.95 (s, 6H, N(CH, J, ), 2.75 (t, J=5.0 Hz, 2H, SCH, ), 1.35 (m, 4H), 0.90 (t, J=4.0 Hz, 3H). 4c, mp 101-103 °C; § 7.35 (d, J=8.0 Hz, 2H, H-2, H-6), 6.70 (d, J=8.0 Hz, 2H, H-3, H-5), 2.95 (s, 6H, N(CH)), 2.75 (t, J=5.0 Hz, 2H, SCH2), 1.35 (m, 8H), 0.90 (t, J=4.0 Hz, 3H). 4d, mp 95-100°C; δ 7.35 (m, 2H, H-2, H-6), 6.65 (d, J=8.0 Hz, 2H, H-3, H-5), 3.00 (s, 6H, N(CH<sub>2</sub>), 1.70 (m, 27H). 5a, bp 237.5-238°C (15 mm); IR(film): v 1738 (C=O) cm<sup>-1</sup>; 8 7.25 (d, J=8.0 Hz, 2H, H-2, H-6), 6.60 (d, J=8.0 Hz, 2H, H-3, H-5), 3.00 (s, 6H, N(CHy)), 2.50 (t, J=6.0 Hz, 2H, COCH<sub>2</sub>), 1.70 (m, 2H), 1.30 (m, 4H) 0.85 (t, J=4.0 Hz, 3H). **5b**, mp 71.5-72°C; IR(film): v 1690 (C=O) cm<sup>-1</sup>; **b** 7.50 (d, J=8.0 Hz, 2H, H-2, H-6), 6.80 (d, J=8.0 Hz, 2H, H-3, H-5), 3.00 (s, 6H, N(CH<sub>2</sub>)<sub>2</sub>), 2.40 (s, 3H, COCH<sub>1</sub>). Sc, mp 125-126.5°C; IR(film): v 1669 (C=O) cm<sup>-1</sup>; 8.05 (m, 2H, H-2', H-6'), 7.50 (m, 3H, H-3', H-4', H-5'), 7.33 (d, J=8.0 Hz, 2H, H-2, H-6), 6.70 (d, 2H, J=8.0 Hz, H-3, H-5), 3.00 (s, 6H, N(CH)), 6a, mp 89-90.5°C; IR(KBr): v 3329(NH), 1695(C=O) cm<sup>-1</sup>; 8 6.90 (s, 1H, H-6), 6.71 (s, 1H, H-3), 4.62 (br s, 1H, NH, exch.), 3.88, 3.86 (each s, 3H, OCH<sub>3</sub>), 3.38 (collapsed dt, J=13.3, 6.5 Hz, 2H, CH<sub>2</sub>NH), 2.93 (t, J=7.2 Hz, 2H, ArCH<sub>2</sub>), 2.41 (s, 3H, SCH<sub>3</sub>), 1.44 (s, 9H, OC(CH<sub>3</sub>)<sub>3</sub>). **6b**, mp 82-83°C; IR(KBr): v 3344 (NH), 1682 (C=O) cm<sup>-1</sup>;  $\delta$  7.26 (s, 5H,  $C_{e}H_{s}$ ), 7.05 (s, 1H, *H*-6), 6.74 (s, 1H, *H*-3), 4.62 (br s, 1H, *NH*, exch.), 3.88 (s, 5H, OCH, and SCH<sub>2</sub>S), 3.85 (s, 3H, OCH<sub>1</sub>), 3.74 (s, 2H, CH<sub>2</sub>Ph), 3.36 (collapsed dt, J=13.2, 6.6 Hz, 2H, CH<sub>2</sub>NH), 2.93 (t, J=7.2 Hz, 2H, ArCH<sub>2</sub>), 1.44 (s, 9H, OC(CH<sub>2</sub>),). 6c, oil; IR(film): v 3369 (NH), 1695 (C=O) cm<sup>-1</sup>; 8 6.91 (s, 1H, H-6), 6.66 (s, 1H, H-3), 4.63 (br s, 1H, NH, exch.), 3.82, 3.81 (each s, 3H, OCH<sub>3</sub>), 3.33 (collapsed dt, J=13.2, 6.6 Hz, 2H, CH,NH), 2.96 (t, J=7.2 Hz, 2H, ArCH<sub>2</sub>), 1.45 (m, 6H, SnCH<sub>2</sub>), 1.42 (s, 9H, OC(CH<sub>3</sub>)<sub>3</sub>), 1.28 (m, 6H), 1.06 (m, 6H), 0.85 (t, J=7.2 Hz, 9H).
- 15. All 'H-NMR spectra were run in CDCl, at 60 or 200 MHz and referenced to TMS.

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