gel column was eluted successively with 9:1 and 85:15 $CHCl_3$–MeOH, and then with 85:15 $CHCl_3$–MeOH containing 5% Et_3N: total yield 208 mg (62%). Anal. Calcd for $C_{66}H_{84}N_{14}O_{14}\cdot 3H_2O$: C, 58.65; H, 6.71; N, 14.51. Found: C, 58.45; H, 6.63; N, 14.12.

Acknowledgment. This work was supported in part by a grant (CA30897) from the National Cancer Institute, DHHS.

Registry No. 1, 89106-02-5; 2, 19741-14-1; 3·TsOH, 89106-04-7; 4·TsOH, 89121-06-2; 5, 89106-05-8; 6, 89106-06-9; 7, 89106-07-0; 8, 89106-08-1; 9, 89106-09-2; Boc-Lys(Cbz)-OH, 2389-45-9; Boc-Lys(Cbz)-OTmse, 89121-14-2; Boc-Lys(Cbz)-Lys(Cbz)-OTmse, 89121-15-3; H-Glu-OBzl, 13030-09-6; Me_3Si-Glu($OSiMe_3$)-OBzl, 89106-10-5; Boc-Lys-OH, 13734-28-6; Boc-Lys($SiMe_3$)-$OSiMe_3$, 89106-11-6; 2-(trimethylsilyl)ethanol, 2916-68-9.

Preparation of Alkyl Aryl Sulfides via Phase-Transfer Catalyzed Displacement of Aromatic Chloride by Alkyl Thiolates

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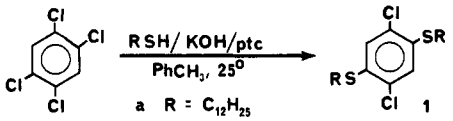
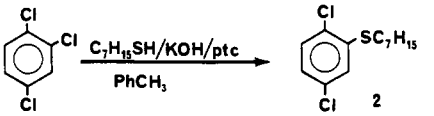
Although a number of procedures have been developed for the preparation of alkyl aryl sulfides, displacement of unactivated aryl chlorides with alkyl mercaptans was not reported until recently.[1-4] Tiecco et al. have utilized nucleophilic displacement of aromatic chlorides with alkyl sodium thiolates in hexamethylphosphoric triamide (HMPA) solution.[5] A recent report by Rolla et al.[6] on the reaction of alkyl thiolates with dichlorobenzenes in water, catalyzed by dicyclohexano-18-crown-6 prompts us to disclose results in a similar area. We have found that reaction occurs between alkyl thiolates and aromatic di-, tri-, and tetrachlorides with surprisingly high regioselectivity under phase transfer catalysis (PTC) conditions in toluene solution, thus allowing high yield preparation of alkyl aryl sulfides from a variety of chloro aromatics and alkyl thiols.



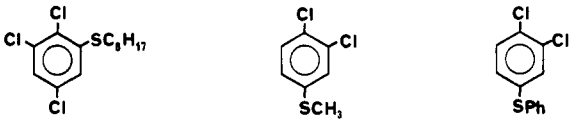
We became interested in PTC reactions of aryl chlorides because of the difficulties associated with the reaction: unactivated aryl halides normally require reaction at high temperatures in polar solvents (e.g., 200 °C in dimethylformamide[7]) or special solvents such as HMPA. Our results with a variety of phase-transfer catalysts are summarized in Table I. Phosphonium salts, crown ethers, and polyethylene glycols were effective catalysts for the conversion. Furthermore, we found it was not necessary to use strong bases, such as KH or *t*-BuOK, to form the thiolate; ground 85% KOH pellets were equally effective.

Reaction of 1,2,4,5-tetrachlorobenzene provides the para disulfide 1 in 89% yield; 1–4% of the 2,4- and 4,5-disulfides were also detected by VPC. Preparation of the monosulfide is possible by use of 1 equiv of thiol. Reaction of 1,2,4-trichlorobenzene provides almost exclusive substitution at the 2-position, providing sulfide 2 in 92% yield.



Reaction of the trichlorobenzene is substantially slower than that of the tetrachlorobenzene and requires reaction at ambient temperature for 24 h or warming to 50 °C for 3 h to effect complete reaction.

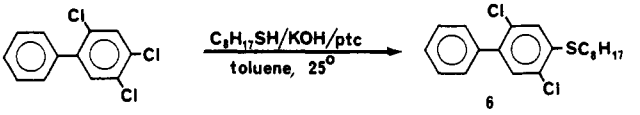
We have found, contrary to literature predictions,[8] that chlorine acts primarily as a meta and ortho activator. Thus, a competition experiment using limited thiolate in reaction with the three isomeric trichlorides showed 73% reaction of the 1,3,5-isomer, 50% reaction of the 1,2,3-isomer, and only 37% reaction of the 1,2,4-isomer. Additionally, we have found that reaction occurs predominantly at positions that have no para chloride. Thus, 1,2,3,5-tetrachlorobenzene provides sulfide 3 as the major



product; displacement at the 1-position is activated by two meta chlorides and has no deactivating para chlorides. Chloride is a more efficient activator than a sulfide or a phenyl group. Thus, sulfides 4 and 5 react to only about 5% completion under conditions that consume 1,2,4-trichlorobenzene.

All the dichlorobenzenes react significantly more slowly than the more highly chlorinated compounds, and reflux in toluene is necessary. These conditions roughly parallel those used by Rolla et al.[6] for the reaction of dichlorobenzenes in water.

We have found that polychlorinated biphenyls (PCB's) are quite reactive under our conditions. For example, 2,4,5-trichlorobiphenyl is converted to sulfide 6 in 90%



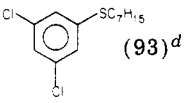
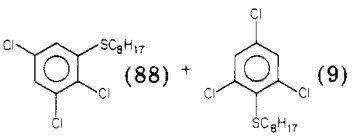
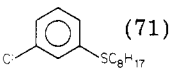
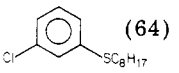
yield at ambient temperature in 5 h. The unsymmetrical PCB 2,3,4,5,6-pentachlorobiphenyl reacts to form a 40:60 mixture of di- and trisulfides.[9]

The most efficient PTC was a hindered phosphonium salt, (tricyclohexyl-*n*-dodecyl)phosphonium bromide.[10] Use of 0.1 equiv of this catalyst at 25 °C afforded complete reaction of tetrachlorobenzene in 2 h. A hindered phosphonium salt is preferred, to prevent destruction of the salt via S_N2 reaction by thiolate (butyl alkyl sulfides have

(1) Reid, E. E. "Organic Chemistry of Bivalent Sulfur"; Chemical Publishing Co.: New York, 1960; Vol. 2, p 13.
(2) For several examples, see: Keller, W. E., Ed. "Compendium of Phase-Transfer Reactions and Related Synthetic Methods"; Fluka AG: CH-9470 Buchs, Switzerland, 1979; pp 136–137, and references cited therein.
(3) Ferreira, J. T. B.; Comasseto, J. V.; Braga, A. L.; *Synth. Commun.* **1982**, *12*, 595.
(4) Jacob, P.; Shulgin, A. T. *Synth. Commun.* **1981**, *11*, 957.
(5) (a) Testaferri, L.; Tingoli, M.; Tiecco, M. *J. Org. Chem.* **1980**, *45*, 4376. (b) Cogolli, P.; Maiolo, F.; Testaferri, L.; Tingoli, M.; Tiecco, M. *Ibid.* **1979**, *44*, 2642. (c) Testaferri, L.; Tingoli, M.; Tiecco, M. *Tetrahedron Lett.* **1980**, 3099.
(6) Landini, D.; Montanari, F.; Rolla, F. *J. Org. Chem.* **1983**, *48*, 604.
(7) Campbell, J. R. *J. Org. Chem.* **1964**, *29*, 1830.
(8) March, J. "Advanced Organic Chemistry", 2nd ed.; McGraw-Hill: New York, 1977; pp 591–593, and references cited therein.
(9) For further examples, see: Brunelle, D. J. *Chemosphere* **1983**, *12*, 167.
(10) This salt has been used for the alkylation of ketones: Tamai, Y.; Nishida, Y.; Fujita, Y.; Ohmura, Y.; Hosogai, T.; Ninagawa, Y.; Itoi, K. Japan Kokai 75 96 514, 1976; *Chem. Abstr.* **1976**, *84*, 4483s.

0022-3263/84/1949-1309$01.50/0

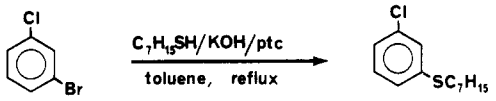
Table I. Phase-Transfer Catalyzed Reactions of Chlorobenzenes with Alkyl Thiolates in Toluene[a]

chlorobenzene	thiol (equiv)	PTC (equiv)	time, h	temp, °C	product (yield, %)
1,2,4,5-Cl_4Ph	n-$C_{12}H_{25}$ (3)	none	24	50	NR
1,2,4,5-Cl_4Ph	n-$C_{12}H_{25}$ (3)	Bu_4NBr (0.2)	24	25	NR
1,2,4,5-Cl_4Ph	n-$C_{12}H_{25}$ (3)	Bu_4PBr (0.2)	2	25	**1a** (42)[b,c]
1,2,4,5-Cl_4Ph	n-$C_{12}H_{25}$ (3)	Bu_4PBr (0.4)	2	25	**1a** (78)[b,c]
1,2,4,5-Cl_4Ph	n-C_7H_{15} (3)	18-cr-6 (0.2)	2	25	**1b** (70)[d]
1,2,4,5-Cl_4Ph	n-C_7H_{15} (3)	PEG 300 (10)	2	25	**1b** (62)[d]
1,2,4,5-Cl_4Ph	n-C_7H_{15} (3)	Cy_3PC_{12} (0.2[e])	2	25	**1b** (99)[d]
1,2,4,5-Cl_4Ph	n-C_7H_{15} (3)	Cy_3PC_{12} (0.1)	2	25	**1b** (88)[d]
1,2,4-Cl_3Ph	n-C_7H_{15} (1.5)	Cy_3PC_{12} (0.2)	3	50	**2** (92)[d,f]
1,3,5-Cl_3Ph	n-C_7H_{15} (1.5)	Cy_3PC_{12} (0.2)	3	50	 (93)[d]
1,2,3,5-Cl_4Ph	n-C_8H_{17} (1.2)	18-cr-6 (0.2)	2	25	
m-Cl_2Ph	n-C_8H_{17} (1.5)	Cy_3PC_{12} (0.2)	24	110	 (71)
m-Cl_2Ph	n-C_8H_{17} (1.5)	Cy_3PC_{12} (0.2)	24	110	 (64)

[a] A 1.1-fold excess (over thiol) of powdered 85% KOH was used in all cases. [b] n-Dodecyl disulfide forms as a byproduct. [c] Butyl dodecyl sulfide forms as a byproduct. [d] Diheptyl disulfide forms as a byproduct. [e] (Tricyclohexyl-n-dodecyl)-phosphonium bromide. [f] 5% of a second product, unidentified, also formed.

been detected in reactions using tetrabutylphosphonium bromide as catalyst). Alternatively, crown ethers, such as 18-crown-6 or dicyclohexano-18-crown-6, may be used. Reactions were not successful using quaternary ammonium salts, presumably due to competing S_N2 reaction.[11]

Aromatic bromides were found to react substantially faster than the aromatic chlorides. For example, m-dibromobenzene formed 88% of the monosubstitution product after 3 h in refluxing toluene with n-octyl thiolate. m-Chlorobromobenzene reacted cleanly to form the chloro sulfide **7** in 86% yield.[12]



7

Experimental Section

General. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Proton NMR were recorded on a Varian EM-390 NMR spectrometer in $CDCl_3$. Carbon-13 NMR were recorded on a Varian CFT-80 spectrometer. IR spectra were recorded on a Perkin-Elmer 457 or a Beckman Microlab 250 MX spectrophotometer in $CHCl_3$. Vapor-phase chromatography was carried out on a Varian 3700 gas chromatograph, using flame detection. Separations were performed on a 6-ft 3% OV-17 column (Chrom W support). High-resolution mass spectra were recorded on a MAT 731 mass spectrograph at 95 eV, using electron-impact mode, with a source temperature of 200 °C; mass calculations used ^{35}Cl. All solvents and reagents were reagent grade and used without purification, unless noted otherwise.

General Reaction Procedure. The chlorobenzene (1.0 equiv), phase-transfer catalyst (0.05–0.2 equiv), and powdered 85% KOH pellets (1.3 equiv) were placed in a flask and stirred in toluene under nitrogen. The mercaptan (1.2 equiv) was added via syringe, and stirring was continued under nitrogen for 1–24 h, until complete reaction occurred (as evident by VPC analysis). The reaction was diluted with water and toluene and then washed with Claisen's alkali[13] to remove unreacted thiol. The crude product was eluted through a short pad of silica gel with 1:1 hexane/CH_2Cl_2 to remove the phase-transfer catalyst. VPC analysis of this crude product generally showed 90–95% desired sulfide. Recrystallization or microdistillation afforded the pure sulfides; derivatization via oxidation to the sulfone was carried out in some cases. Specific examples follow.

2,5-Bis(dodecylthio)-1,4-dichlorobenzene: recrystallized from $CHCl_3$; mp 88–88.5 °C; NMR δ 0.9 (t, 6 H), 1.2–1.9 (m, 40 H), 2.93 (t, J = 7 Hz, 4 H), 7.28 (s, 2 H); high resolution MS calcd fof $C_{30}H_{52}Cl_2S_2$, 546.2888; found, 546.2862. Anal. Calcd for $C_{30}H_{52}Cl_2S_2$: C, 65.78; H, 9.57; S, 11.71; Cl, 12.94. Found: C, 65.84; H, 9.66; S, 11.95; Cl, 13.04.

2,5-Bis(heptylthio)-1,4-dichlorobenzene: recrystallized from $CHCl_3$/hexane; mp 99–100 °C; NMR δ 0.9 (t, 6 H), 1.2–1.9 (m, 20 H), 2.90 (t, J = 7 Hz, 4 H), 7.29 (s, 2 H); high-resolution MS calcd for $C_{20}H_{32}Cl_2S_2$, 406.1322; found, 406.1352. Anal. Calcd for $C_{20}H_{32}Cl_2S_2$: C, 58.95; H, 7.92; Cl, 17.40; S, 15.74; Found: C, 59.28; H, 7.96; Cl, 17.71; S, 16.00.

Heptyl 2,4,5-trichlorophenyl sulfide: recrystallized from hexane; mp 38–39 °C; NMR δ 0.9 (t, 3 H), 1.2–1.9 (m, 10 H), 7.28 (s, 1 H), 7.45 (s, 1 H); high-resolution MS calcd for $C_{13}H_{17}Cl_3S$, 310.0112; found, 310.0122.

Heptyl 2,5-dichlorophenyl sulfide: bp 120–123 °C (0.025 mm); NMR δ 0.9 (t, 3 H), 1.1–1.9 (m, 10 H), 2.90 (t, J = 7 Hz, 2 H), 7.02 (d of d, J = 8.5 and 2.4 Hz, 1 H, proton meta to sulfide), 7.15 (d, J = 2.4 Hz, 1 H, proton para to sulfide), 7.26 (d, J = 8.5 Hz, proton ortho to sulfide); high-resolution MS Calcd for $C_{13}H_{18}Cl_2S$, 276.0506; found, 276.0505. Anal. Calcd for $C_{13}H_{18}Cl_2S$: C, 56.32; H, 6.54; Cl, 25.57; S, 11.57. Found: C, 56.13; H, 6.72; Cl, 25.63; S, 11.69. The compound was identical (by VPC and by ^1H and ^{13}C NMR) with a sample prepared from commercially available 2,5-dichlorothiophenol via reaction with heptyl bromide.

Octyl 2,3,5-trichlorophenyl sulfide: product was a viscous oil and showed an 8:1 mixture of isomers by VPC. Oxidation to the sulfone (25% peracetic acid/acetic acid in CH_2Cl_2) and column chromatography using 10% EtOAc/hexane provided the sulfone

(11) (a) Shamma, M.; Deno, N. C.; Remar, J. F. *Tetrahedron Lett.* **1966**, 1376. (b) Jenden, D. J.; Hanin, I.; Lamb, S. I. *Anal. Chem.* **1968**, *40*, 125.

(12) This work was presented in part: see "Abstracts of Papers", 185th National Meeting of the American Chemical Society, Seattle, WA, Mar 20–25, 1983, American Chemical Society: Washington, DC, 1983, Abstr. 254.

(13) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. 1, p 153.

corresponding to **3** in 80% yield: mp 43–44 °C; NMR δ 0.85 (t, 3 H), 1.2–1.9 (m, 12 H), 3.42 (t, J = 6 Hz, 2 H), 7.73 (d, J = 2.7 Hz, 1 H), 8.06 (d, J = 2.7 Hz, 1 H); high-resolution MS calcd for $C_{14}H_{19}Cl_3O_2S$, 356.0171; found, 356.0179. Anal. Calcd for $C_{14}H_{19}Cl_3O_2S$: C, 47.01; H, 5.35; Cl, 29.73; S, 8.96. Found: C, 46.77; H, 5.36; Cl, 30.13; S, 9.39. Nine percent of a product, tentatively identified as octyl 2,4,6-trichlorophenyl sulfone by NMR, was also isolated.

Octyl 2-chlorophenyl sulfide: product was an oil; NMR δ 0.85 (t, 3 H), 1.2–1.9 (m, 12 H), 2.85 (t, J = 7.5 Hz, 2 H), 7.0–7.5 (m, 4 H). The product was oxidized to the sulfone (25% peracetic/acetic acid in CH_2Cl_2; 95% yield). Recrystallization from hexane gave mp 31–32 °C; NMR δ 0.92 (t, 3 H), 1.2–1.9 (m, 12 H), 3.13 (t, J = 8 Hz, 2 H), 7.45–8.0 (m, 4 H); high-resolution MS calcd for $C_{14}H_{21}ClO_2S$, 288.0951; found, 288.0963.

Octyl 3-chlorophenyl sulfide: product was an oil; NMR δ 0.9 (t, 3 H), 1.2–1.9 (m, 12 H), 2.91 (t, J = 7 Hz, 2 H), 7.1–7.35 (m, 4 H). Oxidation to the sulfone with peracetic acid afforded the sulfone in 87% yield: NMR δ 0.89 (t, 3 H), 1.2–1.9 (m, 12 H), 3.43 (t, J = 8 Hz, 2 H), 7.3–7.55 (m, 3 H), 8.1–8.25 (m, 1 H); high-resolution MS calcd for $C_{14}H_{21}ClO_2S$, 288.0951; found, 288.0972.

Acknowledgment. I thank Steven B. Dorn for providing high-resolution mass spectral data.

Registry No. **1a**, 89165-35-5; **1b**, 89165-36-6; **2**, 89165-37-7; **3**, 89165-38-8; **4**, 17733-23-2; **5**, 65662-89-7; **6**, 89165-39-9; **7**, 89165-40-2; 18-crown-6, 17455-13-9; PEG 300, 25322-68-3; Cy_3PC_{12}, 57441-08-4; 1,2,4,5-Cl_4Ph, 95-94-3; 1,2,4-Cl_3Ph, 120-82-1; 1,3,5-Cl_3Ph, 108-70-3; 1,2,3,5-Cl_4Ph, 634-90-2; m-Cl_2Ph, 541-73-1; n-$C_{12}H_{25}SH$, 112-55-0; n-$C_7H_{15}SH$, 1639-09-4; n-$C_8H_{17}SH$, 111-88-6; Bu_4PBr, 3115-68-2; m-bromophenyl octyl sulfide, 89165-41-3; 1,2,3-trichlorobenzene, 87-61-6; 2,4,5-trichlorobiphenyl, 15862-07-4; 2,3,4,5,6-pentachlorobiphenyl, 18259-05-7; m-dibromobenzene, 108-36-1; m-bromochlorobenzene, 108-37-2; heptyl 2,4,5-trichlorophenyl sulfide, 89165-42-4; octyl 2-chlorophenyl sulfide, 89165-43-5; octyl 3-chlorophenyl sulfide, 89165-44-6.

A Mild and Convenient Procedure for the N-Formylation of Secondary Amines Using Organosilicon Chemistry

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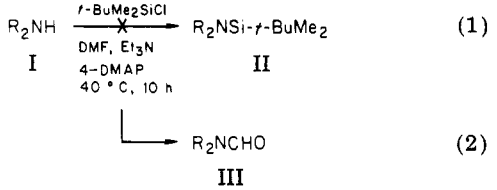
Received July 21, 1983

At the onset of our program to explore the utility of aminosilanes[1] as reactive aminating agents in heterocyclic synthesis, we attempted to prepare the requisite aminosilanes as shown in eq 1.[2]

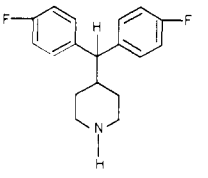
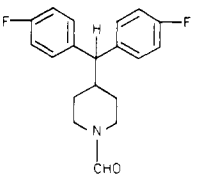
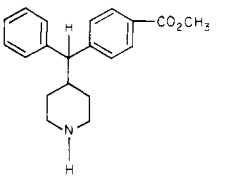
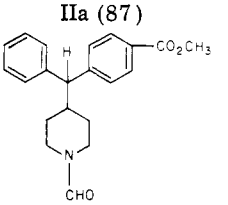
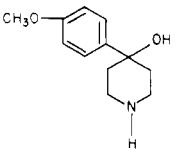
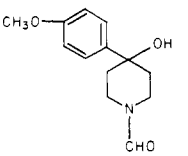
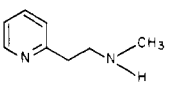
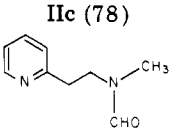
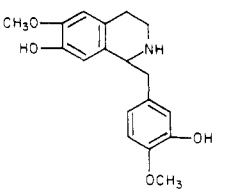
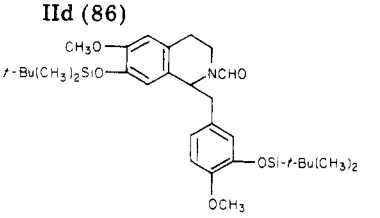
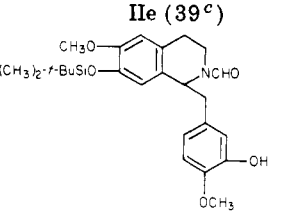
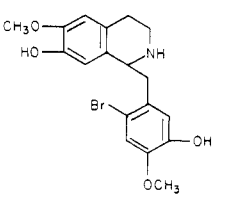
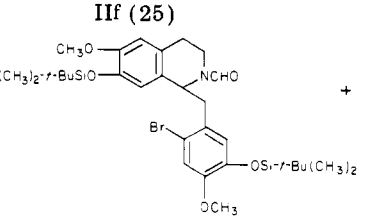
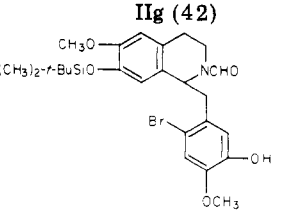


(1)

(2)

We were surprised to find that no aminosilane (II) could be isolated from the reaction mixture. However, the N-formyl derivative III could be isolated in good yield. This reaction proved to be general for a variety of secondary amines (Table I).

Table I

amine	temp, °C	product[b] (yield,[a] %)
 Ia	40	 IIa (87)
 Ib	45	 IIb (80)
 Ic	45	 IIc (78)
 Id	40	 IId (86)
 Ie	60	 IIe (39[c])
		 IIf (25)
 Ig	60	 IIg (42)
		 IIh (25)

[a] Yields are based on recovered starting material where appropriate. [b] All N-formyl derivatives gave satisfactory spectral data and, where possible, elemental analysis. [c] The N-formyl derivatives exist as discrete rotamers, as seen by ^{1}H NMR spectroscopy.[3]

(1) For a recent synthetic application of aminosilanes, see: Ando, W.; Tsumaki, H. *Chem. Lett.* **1981**, 693.

(2) Aminosilanes can be prepared by several procedures. See: Magnus, P. D.; Sarkar, T.; Djurić, S. "Comprehensive Organic Chemistry"; Pergamon Press: 1982; Chapter 48, p 586. See also: Mawhinney, T. P.; Madson, M. A. *J. Org. Chem.* **1982**, *44*, 3336.

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