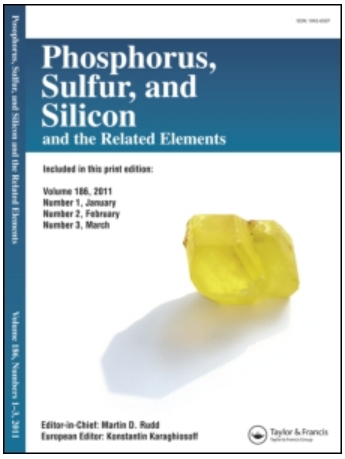

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SUBSTITUTION OF ARYL HALIDES BY THIOLATE ANIONS

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The reaction of 2,5-di- and 2,3,5,6-tetrachloroterephthalate esters with both alkyl and arylmercaptides in triglyme solvent at room temperature gave the corresponding di- and tetra-substituted alkylthio- and arylthio-substituted terephthalate esters. Similarly, the reaction of both 2,5-di- and 2,3,5,6-tetrachloroterephthalate thioesters with potassium *n*-octylmercaptide, **2a**, in triglyme gave the bis- and tetrakis(*n*-octylthio)terephthalate thioesters respectively. Both activated and unactivated aryl chlorides reacted with a suspension of a potassium alkylmercaptide in xylene using 18-crown-6 as a solid–liquid phase-transfer catalyst to give the corresponding alkylthio-substituted benzenes. The reaction of 1,2,4-trichlorobenzene with sodium *n*-dodecylmercaptide in tetraglyme solvent gave 1,2,4-tris(*n*-dodecylthio)benzene.

The substitution of aryl halides by thiolate anions continues to be an active area of interest from both a synthetic[1] and mechanistic[2] point of view. The use of hexamethylphosphoric triamide (HMPT) has been advocated as the solvent of choice for the substitution of both activated and unactivated aryl halides by thiolate anions at room temperature.[3] *N*,*N*-Dimethylacetamide (DMAC)[4] and *N*,*N*-dimethylformamide (DMF)[5] have been reported as suitable replacements for the potentially carcinogenic HMPT. Both DMAC and DMF, however, required temperatures in excess of 100°C, which is of concern when potentially sensitive functionalities are present in the molecule.

Quite recently we have reported the facile substitution of halogen by thiolate anions in polychloro-substituted phthalimides at room temperature in triethylene glycol dimethyl ether (triglyme).[6] In this paper we report an extension of this work to the substitution of halogen in polychloro-substituted phthalate esters and thioesters by thiolate anions. The first reported substitution of halogen in both activated and unactivated aryl halides by alkylmercaptides under solid–liquid phase-transfer conditions using a crown ether is also described. The previously unreported substitution of an unactivated aryl halide by thiolate anion in tetraethyleneglycol dimethyl ether (tetraglyme) is also noted.

DISCUSSION

Except for the pioneering work of Field *et al.*,[7] the substitution of halogen in aryl halides containing ester functionality by thiolate anions has received meager atten-

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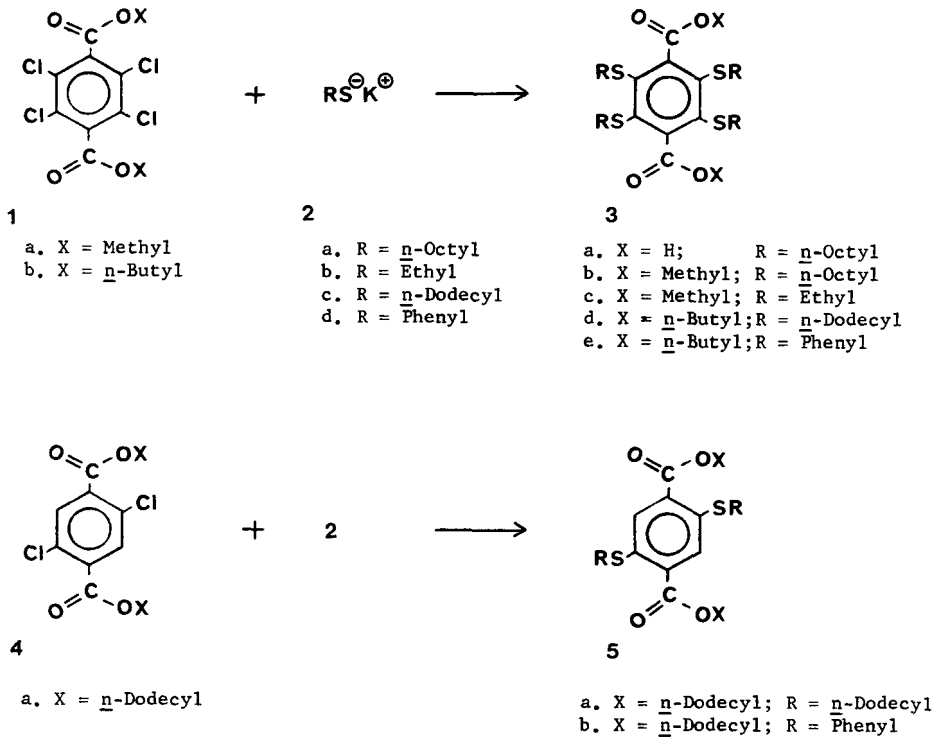


FIGURE 1

tion in the literature.[1b] Field and coworkers noted several multi-step synthetic methods for the preparation of alkylthio-substituted phthalate esters.

In anticipation of preparing poly(alkylthio)phthalate esters directly from polychlorophthalate esters, the reaction of polychlorophthalate esters with potassium alkylmercaptides in DMAC was investigated. The reaction of the methyl ester **1a** with mercaptide **2a** in DMAC gave a complex reaction mixture from which a 22% yield of the diacid **3a** could be isolated. Several other reaction products were isolated whose spectral data and elemental analysis suggested that they were the result of incomplete substitution of halogen by **2a**. The cleavage of the methyl ester by thiolate anion is presumably competitive with the substitution of halogen under the reaction conditions (120°C). Indeed, Kornblum and Scott have reported the cleavage of esters by thiolate anions in DMF at -20°C.[8]

Since the substitution of halogen in polychlorophthalimides by thiolate anions has been shown to occur at room temperature in triglyme solvent,[6] the reaction of **1a** with **2a** was investigated under analogous conditions. Triglyme is known to solvate alkali metals,[9] which suggests that the potassium cation in **2a** would be strongly solvated in triglyme, thereby generating a highly-nucleophilic unsolvated thiolate anion. As anticipated, the reaction of **1a** with **2a** in triglyme at -5 to 5°C gave a 19% isolated yield of the desired product **3b**. The esters **3c–e** were prepared analogously from the corresponding tetrachlorophthalate esters **1a–b** and mercaptides **2a–d**. The IR, ^{1}H NMR, and elemental analysis of the reaction residues of

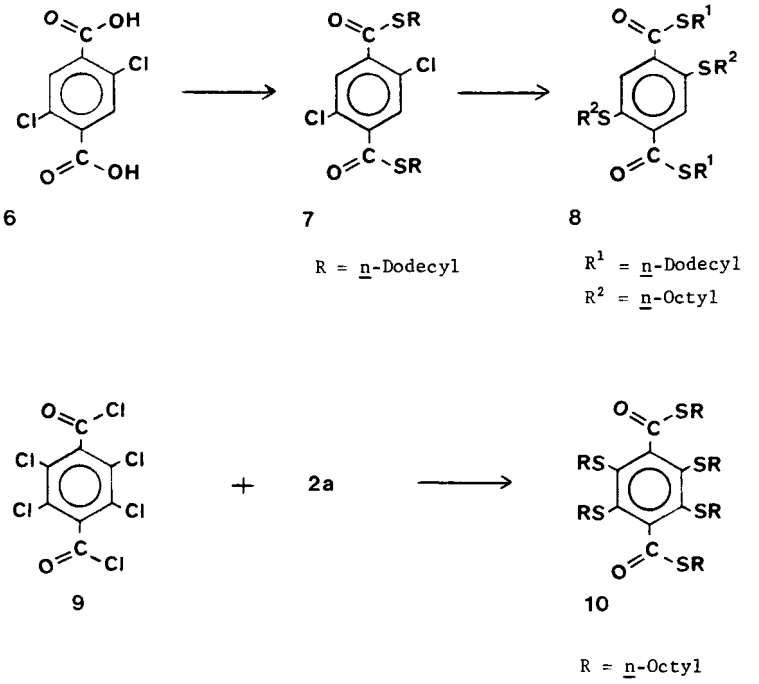
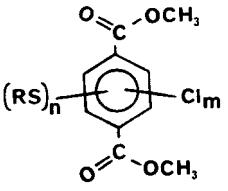


FIGURE 2

these reactions suggested that competitive ester cleavage was responsible for the relatively low yields. The butyl esters **3d–e** were prepared in appreciably higher yields (40–54%), which is presumably partially the result of the lower rate of nucleophilic attack on a butyl group than on a methyl group.[10] The disubstituted esters **5a–b** were prepared from **4** and the appropriate mercaptide in a similar manner.

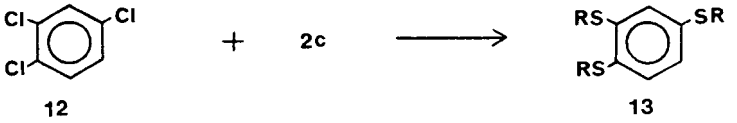
The substitution of halogen in chloro-substituted dithiophthalate esters by thiolate anions was investigated under analogous conditions. The thioester **7** was prepared from **6** in one step by *in situ* formation of the acid chloride with thionyl chloride catalyzed by DMF followed by the addition of *n*-dodecyl mercaptan using triethylamine as an acid acceptor. The reaction of **7** with **2a** in triglyme gave **8** in 44% isolated yield. Interestingly the tetrakis(octylthio)-substituted thioester **10** could be prepared in a single step from **9** by treatment with six equivalents of **2a**.

Recently Rolla *et al.* have reported S_NAr reactions of dichlorobenzenes with thiolate anions under liquid–liquid phase-transfer conditions.[1d] However, no reference was found in the literature for the use of solid–liquid phase-transfer conditions to effect these substitutions. The reaction of a solution of **1a** in xylene with a suspension of **2a** using 18-crown-6 as a phase-transfer catalyst gave **3b** upon flash chromatographic workup, albeit in a 5% isolated yield. Two other products were chromatographically isolated whose IR spectra and elemental analysis were generally consistent with the di- and tri-substituted esters **11a** and **11b** respectively. The IR spectrum of the crude reaction mixture prior to workup also showed broad absorp-



11

a. R = n-Octyl; n = m = 2
b. R = n-Octyl; n = 3; m = 1



12 13

R = n-Dodecyl

FIGURE 3

tions at both 3300–2500 cm^{-1} and 1700 cm^{-1} indicative of carboxylic acids resulting from ester cleavage. In a control experiment, the reaction of **1a** with **2a** in xylene *without* 18-crown-6 gave only ester cleavage reactions as indicated by the IR spectrum and TLC of the reaction mixture.

To further determine the synthetic utility of these crown esther catalyzed reactions, the substitution of an *unactivated* aryl halide by thiolate anion was investigated under solid–liquid phase-transfer conditions. The reaction of trichlorobenzene, **12**, with **2c** in xylene at reflux temperature[11] in the presence of 18-crown-6 gave **13** in 72% isolated yield. In a control experiment without 18-crown-6, the formation of **13** was not observed. The reaction of **12** with **2c** in DMAC gave **13** in 78% yield. The use of solid–liquid phase-transfer conditions gave **13** in comparable yield to the same reaction in DMAC.

The substitution of unactivated aryl halides by thiolate anions in a glyme solvent does not appear to have been previously reported. The reaction of **12** with sodium *n*-dodecylmercaptide in tetraglyme gave **13** in a 25% isolated yield. Further study is clearly needed to delineate the usefulness of glymes as solvents for aromatic substitution.

In summary, triglyme was found to be a suitable reaction medium to effect the substitution of halogen by thiolate anions at room temperature for both polychloro-substituted phthalate esters and thioesters. The use of crown-ether catalyzed solid–liquid phase-transfer conditions for the preparation of poly(alkylthio)benzenes from unactivated aryl halides and thiolate anions offers a convenient alternative to the often troublesome dipolar aprotic solvents.

EXPERIMENTAL

All melting points were determined in open capillary tubes on a Thomas-Hoover melting-point apparatus and are uncorrected. ^{1}H NMR spectra were taken on a Varian model XL-100 or CFT-20 spectrometer and chemical shifts are reported in ppm relative to tetramethylsilane. IR spectra (1% solution in carbon tetrachloride–potassium bromide cells) were recorded on a Perkin-Elmer model 710 spectrometer. All solvents were dried prior to use when necessary. Reactions were carried out in flame-dried apparatus under a dry-nitrogen atmosphere. MERCK 9385 silica gel 60 (230–400 mesh) was used for flash chromatography. WOELM 04526 silica gel was used for dry-column chromatography. Reagents were purchased from Aldrich Chemical Company. Elemental analyses were performed by Analytical Research Services, CIBA-GEIGY Corporation. The syntheses of compounds **1b**, **3e**, **5a**, **7**, **10**, and **13** are illustrative of the methods employed for compound preparation. Analytical and spectral data are collected in Tables I and II.

Dibutyl 2,3,5,6-tetrachloroterephthalate (**1b**). To 5.64 g (117 mmol) of a 50% oil disperson of sodium hydride, which was washed with 200 mL of dry petroleum ether, was cautiously added 250 mL of *n*-butanol. The reaction mixture was slowly heated to 45°C during a period of one hour and then 40.0 g (117 mmol) of tetrachloroterephthaloyl chloride was added. The reaction mixture was heated at reflux for 12 hours and then it was cooled. The precipitate of sodium chloride was removed by filtration and the volatiles were removed *in vacuo*. The residue was dissolved in diethyl ether and the solution was sequentially washed twice with 6% aqueous potassium hydroxide and water. The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo*. The residue was recrystallized from methanol to give 25.0 g (51%) of a white solid, m.p. 58–60°C (lit.[12] 62–63°C).

Di-n-butyl 2,3,5,6-tetrakis(phenylthio)terephthalate (**3e**). A mixture of 14.3 g (130 mmol) of thiophenol, 8.3 g (130 mmol) of 87.3% aqueous potassium hydroxide, and 100 mL of toluene was heated at reflux until no more water was collected in a Dean-Stark trap. The toluene was removed by distillation and to the resultant **2d** was added 100 mL of triglyme. To the reaction mixture at 0 to −3°C was added dropwise a solution of 13.3 g (32 mmol) of **1b** in 50 mL of triglyme and then the reaction mixture was stirred at room temperature for 48 hours. The reaction mixture was poured into 700 mL of water and the resultant mixture was extracted with toluene. The toluene extract was washed with aqueous sodium chloride solution and it was dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and

TABLE I

Analytical results

Compound	m.p. (°C)	Recrystallization solvent	Percent[a] yield	Calcd. C	Calcd. H	Calcd. S	Found C	Found H	Found S
1b	58–60	Methanol	51	46.2	4.4	—	46.3	4.3	—
3a	125–127	Acetonitrile	22	64.7	9.5	17.3	65.0	9.3	16.9
3b	liquid	[b]	19	65.4	9.7	16.6	65.7	9.7	16.3
3c	112–113	Ethanol	14	49.7	6.0	29.5	49.8	5.7	29.2
3d	liquid	[c]	40	71.2	11.0	11.9	71.4	11.0	11.9
3e	123–124.5	Acetonitrile/ Heptane	54	67.6	5.4	18.0	67.6	5.2	17.7
4	67–68.5	Methanol	88	67.2	9.2	[f]	67.1	9.2	—
5a	82–83	Ethyl Acetate	58	74.4	11.4	7.1	74.5	11.1	7.1
5b	104–105.5	Ethyl Acetate	74	73.5	8.7	8.9	73.4	8.7	8.9
7[d]	44.5–46	2-Propanol	73	63.6	8.7	10.6	63.9	8.7	10.6
8	66–68	Ethyl Acetate	44	70.0	10.5	15.6	70.4	10.8	15.3
10	37–38.5	[e]	41	67.3	10.3	19.2	67.1	10.5	19.3
13	57–59	2-Propanol	72	74.3	11.6	14.2	74.4	11.3	14.1

[a]Analytically-pure isolated yields.
[b]Flash chromatography; 40 : 60 toluene : heptane eluent.
[c]Dry column chromatography; 25 : 75 toluene : heptane eluent.
[d]% Cl Calcd.: 11.7. Found: 11.3.
[e]Flash chromatography; 25 : 75 toluene : heptane eluent.
[f] % Cl Calcd.: 12.4. Found: 12.2.

TABLE II

IR and NMR spectral data

Compound	IR (cm^{-1})	^1H NMR (deuteriochloroform)
1b	1740 (ester)	δ 0.96 (t, CH_3, 6 H), 1.20–1.85 (m, CH_2, 8 H), 4.40 (t, OCH_2, 4H)
3a	3350–2450 (OH), 1710 (C=O), 920 (OH out-of-plane bend)	δ 0.83 (t, CH_3, 12 H), 1.08–2.15 (m, CH_2, 48 H), 3.05 (t, SCH_2, 8 H), 10.96 (exchangeable s, CO_2H, 2 H)
3b	1735 (ester)	δ 0.85 (t, CH_3, 12 H), 1.25 (m, CH_2, 48 H), 29.4 (t, SCH_2, $^3J_{HCCH}$ = 6 Hz, 8 H), 3.94 (s, OCH_3, 6 H).
3c	1740 (ester)	δ 1.20 (t, CH_3, $^3J_{HCCH}$ = 8 Hz, 12 H), 2.98 (q, SCH_2, $^3J_{HCCH}$ = 8 Hz, 8 H), 3.96 (s, OCH_3, 6 H)
3d	1730 (ester)	δ 0.95 (overlapping t, CH_3, 18 H), 1.30 (m, CH_3, 88 H), 2.94 (t, SCH_2, 8 H), 4.32 (t, OCH_2, 4 H)
3e	1730 (ester)	δ 0.70 (t, CH_3, 6 H), 1.18 (m, CH_2, 8 H), 3.96 (t, OCH_2, 4 H), 7.11 (m, ArH, 20 H)
5a	1720 (ester)	δ 0.88 (t, CH_3, 12 H), 1.30–1.72 (m, CH_2, 80 H), 2.91 (t, SCH_2, 4 H), 4.32 (t, OCH_2, 4 H), 7.80 (s, ArH, 2 H)
5b	1720 (ester)	δ 0.85 (t, CH_3, 6 H), 1.25 (m, CH_2, 40 H), 4.16 (t, OCH_2, 4 H), 7.30–7.60 (m, ArH, 12 H)
7	1675 (thioester)	δ 0.88 (t, CH_3, 6 H), 1.30–1.69 (m, CH_2, 20 H), 3.07 (t, SCH_2, 4 H), 7.61 (s, ArH, 2 H)
8	1660 (thioester)	δ 0.85 (overlapping t, CH_3, 12 H), 1.25 (m, CH_2, 64 H), 2.92 (t, SCH_2, 4 H), 3.08 (t, SCH_2, 4 H), 7.62 (s, ArH, 2 H)
10	1680 (thioester)	δ 0.95 (overlapping t, CH_3, 18 H), 1.25 (m, CH_2, 72 H), 2.96 (t, $ArSCH_2$, 8 H), 3.12 (t, SCH_2, 4 H)
13	—	δ 0.90 (t, CH_3, 9 H), 1.15–1.83 (m, CH_2, 60 H), 2.90 (t, SCH_2, 6 H), 7.15 (m, ArH, 3 H)

the residue was recrystallized from both acetonitrile and a 3 : 1 acetonitrile : heptane mixture to give 13.4 g (54%) of a white solid.

Di-n-dodecyl 2,5-bis(n-dodecylthio)terephthalate (**5a**). By the procedure used to prepare **3e**, compound **5a** was prepared from 13.3 g (66 mmol) of *n*-dodecyl mercaptan, 4.17 g (65 mmol) of 87.3% aqueous potassium hydroxide, and 17.5 g (30 mmol) of **4**.[13] The residue was recrystallized from ethyl acetate to give 15.7 g (58%) of a light yellow solid.

S,S-Di-n-dodecyl 2,5-dichloro-dithioterephthalate (**7**). A mixture of 23.5 g (0.10 mol) of **6**, 48.9 g (0.41 mol) of thionyl chloride, and 0.5 mL of DMF was stirred at rt until gas evolution (removal was facilitated by a nitrogen sweep of the reaction vessel) slowed. The reaction mixture was then heated slowly to 85°C over a six hour period. After cooling, the volatiles were removed *in vacuo* and 150 mL of toluene was added to dissolve the solid residue. To the resultant solution at 0 to 5°C was added dropwise a solution of 50.7 g (0.25 mol) of *n*-dodecyl mercaptan and 21.8 g (0.22 mol) of triethylamine in 60 mL of toluene. The reaction mixture was stirred one hour at rt and the precipitate of triethylamine hydrochloride was removed by filtration. The filtrate was washed sequentially with dilute hydrochloric acid and water, and it was dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* and the residue was recrystallized from 2-propanol to give 43.8 g (73%) of a white solid.

S,S-Di-n-octyl 2,3,5,6-tetrakis(n-octylthio)dithioterephthalate (**10**). By the method used to prepare **2d** (see preparation of compound **3e**), mercaptide **2a** was prepared from 24.1 g (165 mmol) of *n*-octyl mercaptan and 10.6 g (165 mmol) of 87.3% aqueous potassium hydroxide. To the **2a** in 100 mL of triglyme at −10°C was added dropwise a solution of 8.52 g (25 mmol) of **9**[14] in 125 mL of triglyme (warmed to effect solution). The reaction mixture was stirred at rt overnight and then it was poured into

one liter of water. The resultant mixture was extracted with toluene. The toluene extract was washed with water and it was dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue was purified by flash chromatography to give 10.1 g (41%) of a light yellow solid.

1,2,4-Tris(n-deodecylthio)benzene (**13**)

Method A DMAC Solvent. By the method used to prepare **2d** (see preparation of compound **3e**), mercaptide **2c** was prepared from 33.4 g (165 mmol) of *n*-dodecyl mercaptan and 10.8 (165 mmol) of 85.8% aqueous potassium hydroxide. To the **2c** in 90 mL of DMAC was added 9.1 g (50 mmol) of **12** and the reaction mixture was heated at 120°C for three hours. The cooled reaction mixture was diluted with 200 mL of toluene and it was extracted three times with water. The organic phase was dried over anhydrous sodium sulfate. The volatiles were removed *in vacuo* and the residue was recrystallized from 2-propanol to give 26.5 g (78%) of white solid, m.p. 57–59°C.

Method B Solid–Liquid Phase-Transfer Catalysis. A mixture of 33.4 g (165 mmol) of *n*-dodecyl mercaptan, 10.8 g (165 mmol) of 85.8% aqueous potassium hydroxide, and 120 mL of xylene[11] was heated at reflux until no more water was collected in a Dean-Stark trap (approximately 5 hours). To the reaction mixture was added 0.7 g (3 mmol) of 18-crown-6 and 9.1 g (50 mmol) of **12** and it was heated at reflux for 17 hours. To the cooled reaction mixture was added 3 mL of glacial acetic acid and then it was extracted three times with water. The xylene phase was dried over anhydrous sodium sulfate. The volatiles were removed *in vacuo* and the residue was recrystallized from acetone to give 24.5 g (72%) of white solid, m.p. 57–59°C.

Method C Tetraglyme Solvent. To a suspension of 1.44 g (60 mmol) of sodium hydride in 150 mL of tetraethyleneglycol dimethyl ether was added carefully (*frothing*) a solution of 12.14 g (60 mmol) of *n*-dodecyl mercaptan. The reaction mixture was stirred until gas evolution was complete and 3.20 g (18 mmol) of **12** was added. The reaction mixture was heated at 140°C for 22 hours. To the cooled reaction mixture was added 500 mL of diethyl ether and it was extracted sequentially with dilute acetic acid and water. The ether phase was dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The residue was recrystallized from acetone to give 3.11 g (25%) of a white solid, m.p. 57–59°C.

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