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Mild persubstitution of di- and tetrabrominated arenes with arylthiolate nucleophiles

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ABSTRACT

A mild selective protocol was used to prepare tetrakis(2-chlorophenylthio)anthracene from tetrabromoanthracene and sodium 2-chlorobenzenethiolate avoiding the thiolate self-attack. The uncatalyzed nucleophilic substitution of a series of mono-, di-, and tetrabrominated arenes by arylthiolate ions was attempted in mild conditions to investigate the scope of the substitution reaction regarding the size of the aromatic system as well as the number of bromine atoms. Successful reactions afforded only the persubstituted products in good purity and yield after a simple workup and chemoselectivity of Br versus Cl substituents was achieved for the tetrabromide.

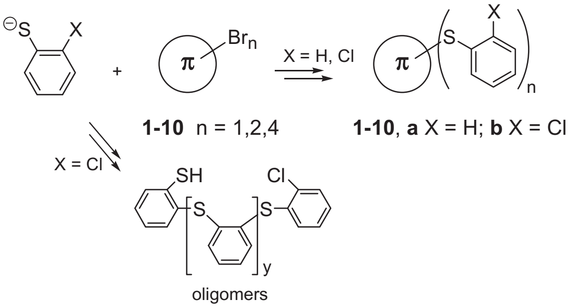
The substitution of bromine atoms by an alkyl or aryl thiolate anion is a highly effective synthetic tool in the making of organic materials ranging from polymers,[1] oligomers[2], and dendrimers[3] to molecular compounds, such as organic semiconductors[4] or pharmaceutical drugs.[5]

In particular, the substitution of bromine atoms by arene thiolates, followed by sulfide derivatization and intramolecular acid-induced cyclization, has been used as the initial step in the synthetic route to fused-ring semiconductors, such as dibenzothienobisbenzothiophene.[6] Likewise, diverse polycyclic aromatic or heteroaromatic systems including dibenzofurans,[7] dibenzopyrans and phenanthridines,[8] phenanthrenes,[9] benzofluoranthenes[10], and fluoranthenes[11] have been obtained by sequential or cascade[11] two-step ring-formation pathways involving several types of coupling reactions followed by intramolecular Heck-type dehydrohalogenations.[12]

In this context, we investigated the feasibility of using the simple uncatalyzed nucleophilic substitution of aryl bromides by phenylthiolate ions bearing a chloride atom as a key step in the route to sulfur-containing polycyclic aromatic semiconductors by Heck-type annulations. Thus, this communication reports a mild selective protocol for preparing polysubstituted arylthioethers from sodium arylthiolates and aryl bromides bearing no activating groups other than the bromine atoms themselves.

Although the presence of electron withdrawing groups is of importance for the outcome of aromatic nucleophilic substitution reactions, the halogen displacement reactions by alkyl and aryl thiolates can take place in inactivated or slightly activated mono- and polyhalogenoarylenes under a variety of reaction conditions. Thus, asymmetric thioethers have been obtained mainly by aromatic nucleophilic substitutions with alkyl thiolates at moderate temperatures[4a] or aryl thiolates at high temperatures,[13] microwave-assisted coupling,[14] photoirradiation[15], and transition metal catalyzed substitution of aryl halides by aryl thiolates using Pd[2c,16] or Cu[14,17] complexes.

However, most of the conditions employed by these reactions lack selectivity between chloride and bromine displacement or require the use of the more expensive and often unavailable polyiodide arenes to achieve chemoselectivity.[2c] Therefore, a careful selection of reaction conditions is needed to avoid the sodium 2-chlorophenythiolate self-attack. Hence, we carried out a series of blank reactions between 30 °C and 100 °C using a suspension



Scheme 1.

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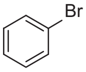
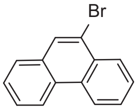
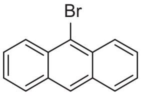
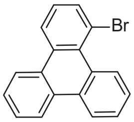
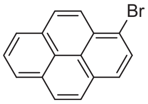
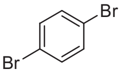
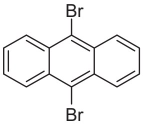
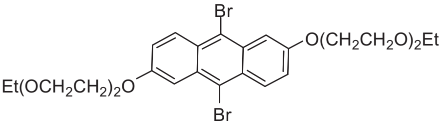
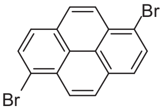
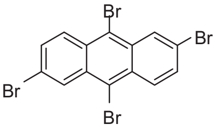
of sodium 2-chlorophenylthioate in 1,3-dimethyl-2-imidazolidinone (DMI) with all the reactants present except the aryl bromide which indicated that oligomerization of the nucleophile would occur as a competitive side reaction above 40 °C (see Scheme 1). DMI is the safe polar solvent of choice for polysulfuration of aromatic halides having replaced[18] HMPA, the recommended solvent for thiolate ionic aromatic nucleophilic substitutions used in early studies.[19]

Table 1
Nucleophilic substitution of aryl bromides by arylthiolate ions

Compound	Aryl bromide	X[a]	Yield %[b]	ΔH_r[c]
1		H	NR	−4.9
2		H	NR	−2.4
3		H	NR	−8.8
4		H	NR	−3.9
5		H	NR	−10.6
6		H	NR	−3.3
7		H Cl	86[d] NR	−19.3 −12.6
8		H Cl	99[d] NR	−16.7 −13.9
9		H Cl	72 NR	−15.3 −12.9
10		H	38[e]	−24.8[f]; −15.9[g]
		H Cl Cl	65 47[e] 78	−21.6[f]

[a] The reactions of phenylthiolate ion (X = H) or 2-chlorophenylthiolate ion (X = Cl) with **1**–**10** were carried out at 40 °C for a week, unless otherwise stated.

[b] Isolated yields. NR = No reaction. Products where characterized by ^{1}H and ^{13}CNMR and elemental analysis.

[c] Reaction heats, $\Delta H_r = \Delta H_f^M - (\Delta H_f^{AB} + \Delta H_f^{nucl})$, calculated for the first substitution reaction. In Kcal/mol. Phenylthiolate ion, $\Delta H_f^{nucl} = -1.665$ Kcal/mol and 2-chlorophenylthiolate ion, $\Delta H_f^{nucl} = -10.527$ Kcal/mol.

[d] The reaction was carried out for one day.

[e] The reaction was carried out for four days.

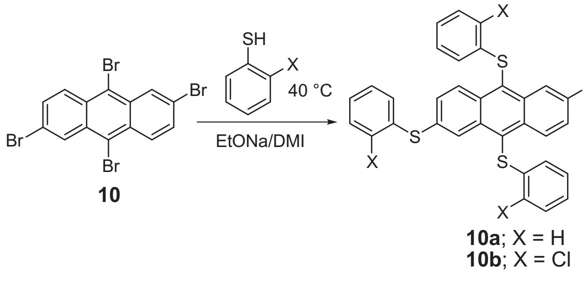
[f] Calculation done for the attack at the anthracene 9-position.

[g] Calculation done for the attack at the anthracene 2-position.

Subsequently, a series of screening reactions using an excess of the unsubstituted phenylthiolate anion (2 equiv) were performed to investigate the scope of the substitution reaction at 40 °C regarding the size of the aromatic system as well as the number of attached bromine atoms. The results are presented in Table 1. We found that monobromides **1**–**5** as well as the dibromide **6** do not react at such a moderate temperature. Reaction mixtures remained pale yellow for a week and from these most of the starting bromides were recovered unchanged (>70%). Moreover, no evidence of the formation of the aryl thioethers **1–6a** was obtained from these reaction mixtures.

On the contrary, the anthracene and pyrene dibromides, **7,** and **9** underwent smooth reactions with the phenylthiolate anion. Thus, the reaction mixtures turn orange or dark orange after 2 h. An additional reaction time of 22 hours and a simple workup were needed to obtain the corresponding di(arylthio)arenes **7a** and **9a** in very good yields and purity. Neither the dibromides nor the monosubstituted bromides were detected in the crude products by GC-MS. We also verified that the solvents DMSO and DMAc are not as convenient as DMI. Reaction times of one week were needed in DMSO and DMAc to match the yield of **7a** achieved after one day in DMI. In addition, we detected 1% of **7** in the crude product obtained using DMSO while 2–3% of **7** and 1% of the monosubstituted bromide where found in the case of DMAc. Unfortunately, the reactions of the dibromides **7** and **9** with the less nucleophilic 2-chlorobenzenethiolate anion were unsuccessful even after a week. We noted that the successful reactions took place in heterogeneous conditions; as the sodium thiolate, the dibromides **7** and **9** and their related 9,10-diphenylthioanthracene, **7a**, and 2,6-diphenylthiopyrene, **9a**, were not appreciably soluble in DMI. So in an effort to counterbalance the reduced nucleophilicity of the Cl-substituted thiolate with an increased solubility of the substrate, the dibromoanthracene **8** bearing two polar side chains was treated with the thiolate anion and the 2-chlorothiolate anion. However, **8** and its chainless counterpart **7** showed the same reaction patterns, suggesting that their reactivity depends mainly on intrinsic structural factors.

The treatment of 2,6,9,10-tetrabromoanthracene, **10**, (see Scheme 2) with 2 equiv of either the phenylthiolate or the 2-chlorobenzenethiolate anion for a week then afforded the persubstituted tetrakis(phenylthio)- anthracenes **10a** (65%) and **10b** (78%) in good yields although at a slower pace than the dibrominated anthracenes **7** and **8**, which could possibly be due to a lower reactivity of the bromine in the positions 2 and 6 coupled with the very low solubility of **10** in DMI. Shortening the reaction times to four days results in lower yields, for example, **10** yielded 38% (X = H) and 47% (X = Cl) of its perthioethers. The higher yield of **10b** compared to **10a** probably results from a better recovery due to its lower solubility. Thus, the solubility of **10a** in DMI at 40 °C is 0.8% w/v while that of **10b** is <0.2 % w/v. Again, no significant amounts of unreacted or partially substituted bromides were detected in the crude products **10a** and **10b** that were isolated by filtration after either four or seven days.



10

10a; X = H
10b; X = Cl

Scheme 2.

Similarly, only **10a** was obtained after the week-long treatment of **10** with the phenylthiolate anion (2 equiv) when the workup protocol was modified to recover all anthracene derivatives, that is, the reaction mixture was thoroughly extracted with chloroform. However, when less phenylthiolate anion (1 equiv) was used, the chloroformic extract of the reaction mixture contained a significant quantity of 2,6-dibromo-9,10-diphenylthioanthracene **11** (85%) along with a little **10a** (8%), a bromotriphenylthioanthracene (7%), and traces of the tetrabromide (1%). The dibromide **11** was isolated for characterization from a mixture of starting tetrabromide **10** (64%) and **11** (36%), which were the only products obtained when a deficit of the phenylthiolate anion (0.5 equiv) was used. These results show that the 9- and 10-positions of **10** are more reactive than the 2- and 6-positions and that an excess of the phenylthiolate anions is needed to achieve persubstitution.

In summary, the procedure is very convenient when an excess of phenylthiolate anions is used since each successful reaction afforded only the persubstituted products in good purity and yield after a simple workup and chemoselectivity of Br versus Cl substituents was achieved for the tetrabromide **10**.

We also tested the use of molecular modeling as a practical predictive tool for selecting synthetic targets within this substitution reaction framework. We assumed that the nucleophilic substitution reaction operates through an ionic mechanism. Thus, the reaction heats, ΔH_r, were calculated at the AM1 level from the heats of formation of the aryl bromides, ΔH_f^{AB}, and the corresponding Meisenheimer complex, ΔH_f^{M}, formed in the first attack of the thiolate to the mono-, di-, or tetrabromide. The analysis of the last column of Table 1 indicates that all successful reactions have $\Delta H_r < -15$ Kcal/mol. It also shows that the substitution would occur with preference at the 9-position of **10**. Indeed, the calculated ΔH_r for the second attack to give **11** is −30.0 Kcal/mol and the values obtained for the two subsequent attacks to the 2- and 6-positions are −17.0 and −17.7 Kcal/mol, indicating that **11** accumulates to gradually give **10a**. Moreover, we calculated a ΔH_r value of −22.5 Kcal/mol for the reported[20] persubstitution of tetrabromopyrene by sodium phenylthiolate, that is, in agreement with this thermodynamic criteria. Though they have to be handed with great care, molecular modeling results suggest that, for example, selective substitution of bromide could hardly be achieved with 2,3,6,7-tetrabromo anthracene ($\Delta H_r = -12.2$ Kcal/mol) while it is very likely that the isomeric 2,3,9,10-tetrabromoanthracene ($\Delta H_r = -24.3$ Kcal/mol) or the 2,3,6,7,10,11-hexabromotriphenylene ($\Delta H_r = -15.9$) could render their corresponding perthioethers, making these bromides interesting synthetic targets. Further experimental work is in progress regarding the last two above mentioned bromides.

The typical synthetic procedure is exemplified by the synthesis of tetrakis(2-chlorophenylthio)anthracene. First, 2,6,9,10-tetrabromoanthracene, **10**, was synthesized as follows: a solution of bromine (0.57 g, 3.59 mmol, 0.19 mL) in nitrobenzene (0.35 mL) was added to a solution of 9,10-dibromoanthracene (0.50 g, 1.5 mmol) in nitrobenzene (3.5 mL) at 100 °C. The solution was stirred at 160 °C for 6 h. and for 30 min. at 200 °C. The mixture was cooled at room temperature and stirred overnight. The resulting solid was filtered off and washed with hot CH_2Cl_2 (3 × 15.0 mL) to give a yellow solid. Yield: 0.30 g (40%). mp: 296 °C (lit.[21], mp 294 °C). ^1H NMR: (300 MHz, $CDCl_3$): $\delta = 8.33$ (d, $J = 1.75$ Hz, 1H), 8.05 (d, $J = 9.34$ Hz, 1H), 7.32 (dd, $J = 9.34$, 1.75 Hz, 1H). ^{13}C NMR: ($CDCl_3$) $\delta = 137.4$, 131.9, 131.8, 131.7, 130.4, 130.2, 129.1, GC–MS: m/e = 494 (100%), 492 (68%), 496 (64%), 490 (17%), 498 (15%).

Secondly, in a Schlenk tube, 2-chlorothiophenol (0.18 mL, 1.60 mmol) was added with stirring to a solution of sodium (0.04 g, 1.60 mmol) in ethanol (5.0 mL). The resulting sodium thiophenolate solution was evaporated to dryness *in vacuo* and the whitish residue was suspended in DMI (2.0 mL). Then, tetrabromide **10** (0.100 g, 0.202 mmol) was added to the reaction mixture and the suspension was stirred for 1 h. at room temperature and seven days at 40 °C. After the addition of MeOH (5 ml), the suspended greenish yellow solid was filtered off, washed with methanol and dried. Yield: 0.116 g (78%), mp: 230–232 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.75 (d, J = 9.12 Hz, 2H), 8.43 (d, J = 1.57 Hz, 2H), 7.40 (dd, J = 9.12 Hz, 1.57 Hz, 2H), 7,36 (m, J = 7.73 Hz, 1.42 Hz, 4H), 7.33 (dd, J = 7.64 Hz, 1.62 Hz, 2H), 7.25 (dt, J = 7.78 Hz, 1.62 Hz, 2H), 7.13 (dt, J = 7.64 Hz, 1.42 Hz, 2H), 7.01 (dt, J = 7.88 Hz, 1.48 Hz, 2H), 6.82 (dt, J = 7.92 Hz, 1.34 Hz, 2H), 6.06 (dd, J = 7.88 Hz, 1.40 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ = 136.8, 136.2, 136.1, 135.2, 134.6, 134.3, 133.8, 132.2, 131.7, 131.1, 130.8, 130.3, 129.6, 129.1, 128.9, 128.8, 128.0, 127.7, 127.4, 127.1, 127.0, 126.9, 126.1, 125.7, 125.6, 125.3. **10a** was recrystalized from THF–MeOH. Anal. Calcd for $C_{38}H_{22}Cl_4S_4$: C, 60.96; H, 2.96; Cl, 18.94; S, 17.13. Found: 60.79; H, 2.91; S, 16.97.

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Supplementary data

Supplementary data associated (the synthesis of the aryl bromides, characterization of **11**, ^{1}H NMR and ^{13}C NMR characterization of crude products and computational details) with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.069.

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