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Ortho-Selective Nucleophilic Aromatic Substitution Reactions of Polyhaloanilines with Potassium/Sodium *O*-Ethyl Xanthate: A Convenient Access to Halogenated 2(3*H*)-Benzothiazolethiones

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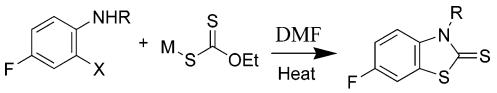
Abstract: Polyhaloanilines bearing an ortho halogen atom undergo smooth nucleophilic aromatic substitution reactions with anionic sulfur nucleophiles at relatively mild temperatures (95−120 °C). These reactions are very efficient and highly ortho-selective. With potassium/sodium *O*-ethyl xanthate as a nucleophile, subsequent cyclization follows to afford halogenated 2(3*H*)-benzothiazolethiones (2-mercaptobenzothiazoles) in high yields.

Simple halogenated anilines are considered poor substrates for aromatic nucleophilic halogen substitution reactions due to strong deactivating effects of the amino group.[1,2] Nonetheless, under certain conditions such as metal mediation, simple haloanilines have been shown to undergo halogen displacement reactions with alkyl and aryl thiolates.[3] In one instance, simply heating di- and trichloroanilines with potassium phenyl thiolate at high temperature (140−190 °C) is sufficient to effect such a substitution reaction to afford bis- and tris(phenylthio)-anilines in low to moderate yields.[4] While these reactions are useful in providing ready access to alkyl and arylthioanilines, the necessity of using heavy metal reagents or the unusually high reaction temperatures coupled with the lack of regioselectivity have prompted us to explore alternate reagents/conditions for halogen displacements in reactions with polyhaloanilines. We are primarily interested in regioselective halogen displacement in these reactions under relatively mild conditions.

Potassium/sodium *O*-ethyl xanthates have received little attention as anionic sulfur nucleophiles[5] in nucleophilic aromatic substitution reactions compared to the more widely studied thiolates. In one study, heating 4-alkyl- and alkoxy-2-bromo/chloroanilines with potassium *O*-ethyl xanthate in DMF at reflux (160 °C) afforded, respectively, 6-alkyl- and 6-alkoxy-2(3*H*)-benzothiazolethiones (6-substituted 2-mercaptobenzothiazoles).[6] While the potential mechanism for the benzothiazolethione formation was not discussed in the article, it is conceivable that the reaction proceeded via a nucleophilic halogen substitution reaction with the xanthate anion followed by a subsequent cyclization step (Scheme 1). We were intrigued by the possibility of an ortho-selective halogen displacement by the xanthate salt in polyhaloanilines, which would provide a ready access to halogentaed 2-mercaptobenzothiazoles. In this paper, we report that polyhaloanilines bearing an ortho halogen atom undergo smooth ortho-selective nucleophilic halogen substitution reactions with potassium/sodium *O*-ethyl xanthate at relatively mild temperatures (95−120 °C) to produce halogenated 2-mercaptobenzothiazoles in high yields.

We initially explored reactions of several 2-halo-4-fluoroanilines **1** with potassium/sodium *O*-ethyl xanthate in *N*,*N*-dimethylformamide (DMF) under various conditions. The results are summarized in Table 1. With 2,4-difluoroaniline **1a**, no reaction was observed after a period of 4 h at 80 °C, as the starting aniline was completely recovered (entry 1, Table 1). However, at 95 °C, after a similar period of time, near complete reaction was achieved, resulting in the isolation of the cyclized product benzothiazolethione **3a** in 91% yield, in analytically pure form (entry 2, Table 1). With potassium ethyl xanthate, 2-bromo-4-fluoroaniline afforded the same benzothiazole product **3a** in 99% isolated yield, although at a slightly higher temperature (105 °C) (entry 3, Table

TABLE 1. Reactions of 2-Halo-4-fluoroanilines with Potassium/Sodium *O*-Ethyl Xanthate

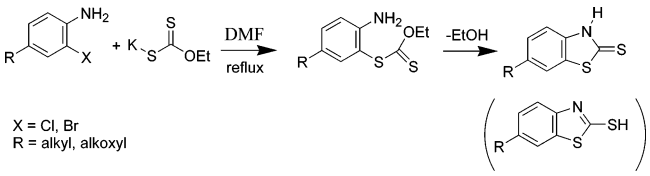


1 2 3

entry	aniline	X	R	M	temp (°C)	time (h)	yield (%)[a]
1	**1a**	F	H	K	80	4	NR[b]
2	**1a**	F	H	K	95	4	**3a**, 91
3	**1b**	Br	H	K	105	3	**3a**, 99
4	**1c**	Cl	H	K	100	3	NR[b]
5	**1c**	Cl	H	K	120	3	**3a**, 55[c]
6[d]	**1c**	Cl	H	K	100	3	**3a**, 94
7	**1c**	Cl	H	Na	100	4	**3a**, 96
8	**1d**	F	Me	K	100	3	**3d**, 15[c]
9	**1d**	F	Me	Na	100	3	**3d**, 70

[a] Isolated yield. [b] No reaction; starting aniline was recovered. [c] ^{1}H NMR yield, calculated on the basis of integration data of product and starting material peaks. [d] Also present was 2.2 equiv of 18-crown-6.

SCHEME 1



(1) For leading references on nucleophilic aromatic substitution reactions, see: (a) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; Chapter 13. (b) Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273−412.

(2) Berliner, E.; Monack, L. C. *J. Am. Chem. Soc.* **1952**, *74*, 1574−1579.

(3) (a) Adams, R.; Reifschneider, W.; Nair, M. D. *Croatica Chem. Acta* **1957**, *29*, 277. (b) Adams, R.; Ferretti, A. *J. Am. Chem. Soc.* **1959**, *81*, 4927.

(4) Caruso, A. J.; Colley, A. M.; Bryant, G. L. *J. Org. Chem.* **1991**, *56*, 862−865.

(5) (a) Scully, F. E., Jr.; Ortega, T. *J. Org. Chem.* **1989**, *54*, 2978−2980. (b) Creary, X. *Tetrahedron. Lett.* **1999**, *40*, 29−32.

(6) Chaudhuri, N. C. *Synth. Commun.* **1996**, *26*, 3783−3790.

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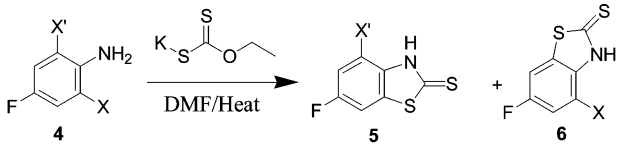
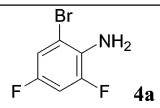
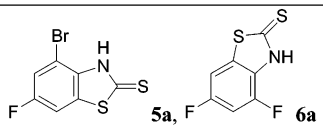
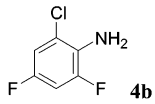
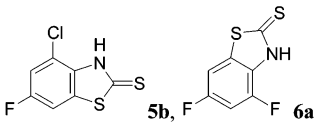
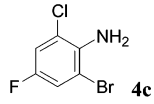
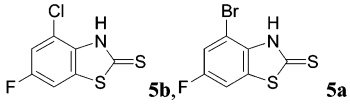
TABLE 2. Reactivity Order of F, Br, and Cl as Leaving Halogen Atoms



4 5 6

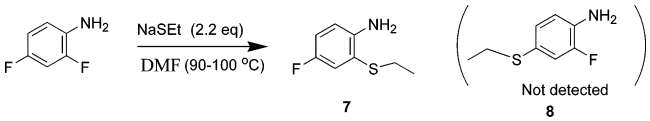
Entry	Aniline	Products	Product Ratio
1	 **4a**	 **5a**, **6a**	13:1
2	 **4b**	 **5b**, **6a**	100:0
3	 **4c**	 **5b**, **5a**	12:1

1). The 2-chloro analogue is less reactive than both the 2-fluoro and 2-bromo substrates. With potassium xanthate salt, after 3 h, no reaction at 100 °C and only ca. 50% reaction at 120 °C were observed (entries 4 and 5). However, the reaction was substantially faster (complete in 3 h at 100 °C) when 2.2 equiv of 18-crown-6 was present, reaching a level of reactivity comparable to that of the 2-fluoro analogue (entry 6, Table 1). This same level of reactivity, with the 2-chloro analogue, can also be achieved by replacing the potassium salt with the corresponding sodium salt (entry 7, Table 1).[7] Significantly, under the same reaction conditions, N-methylated 2,4-difluoroaniline afforded exclusively, in good yield, the N-methylated benzothiazolethione **3d** (entry 9, Table 1). This result is in sharp contrast to that of the conventional alkylation method of benzothiazolethione, which yields a mixture of N- and S-alkylation products, with the latter being the predominant product.[8] No 4-F displacement products were observed in any of the reactions in Table 1.

The relative reactivity order of the leaving halogen atoms was established with 2,4,6-trihaloanilines **4a**−**c** with both ortho positions occupied by different halogens (Table 2). The reactivity ratios (F/Br 13:1, F/Cl 100:0, and Br/Cl 12:1) were estimated by product ratios of **5a/6a**, **5b/6a**, and **5b/5a**, which were calculated on the basis of ^{1}H NMR integration.

The exclusive ortho selectivity of the nucleophilic aromatic substitution reactions of polyhaloanilines is not limited to xanthate salts as nucleophiles where subsequent cyclization ensues. Similarly, high ortho selectivity was also observed when sodium ethanethiolate (NaSEt) was used as a nucleophile (Scheme 2). Treatment of 2,4-

SCHEME 2



7 8

difluoroaniline with 2.2 equiv of sodium ethanethiolate in DMF at 90−100 °C afforded the corresponding 2-(ethylthio)-4-fluoroaniline **7** in 98% isolated yield. Its regioisomer **8** was not detected.[9] This experiment suggests that the cyclization step in the xanthate case played no role in bringing about the ortho selectivity.

To establish the scope of the aniline substrates, we investigated polyhaloanilines with and without an ortho halogen (**9b**−**j**). The reaction was carried out with potassium *O*-ethyl xanthate in DMF at 120 °C, and the results are summarized in Table 3. While polyfluoroanilines bearing an ortho halogen reacted efficiently and orthoselectively to produce the corresponding benzothiazolethiones **10** (entries 4, 7−11, Table 3), *aniline substrates lacking an ortho-halogen failed to react under the same conditions* (entries 1−3, Table 3). In sharp contrast to 2,4-difluoroaniline, which reacted smoothly with potassium *O*-ethyl xanthate at the ortho position (entry 2, Table 1), the 2,5-difluoro analogue reacted very sluggishly under similar conditions (entry 5, Table 3). 2,3-Dichloroaniline also reacted at a much slower rate, albeit cleanly at the ortho position (entry 10, Table 3).

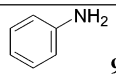
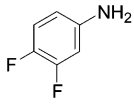
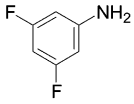
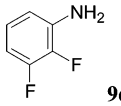
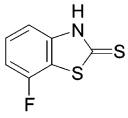
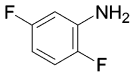
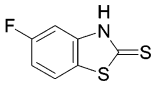
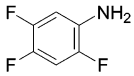
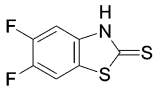
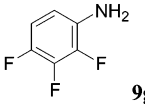
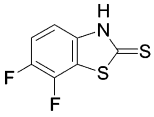
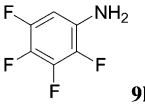
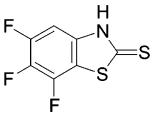
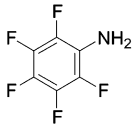
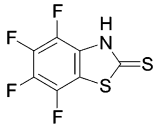
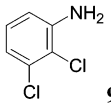
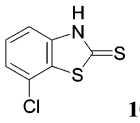
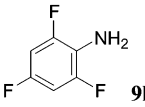
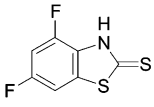
The origin of the regioselectivity is not entirely clear at this point. It is plausible that precoordination of the sulfur nucleophile to the amino group of the aniline via hydrogen bonding is responsible for delivering the nucleophile to the ortho position.[10] Hydrogen bonding between a sulfur anion and the N−H group has been extensively documented.[11] This explanation is reasonable, particularly as the experimental data have ruled out an

(7) The sodium salt is more reactive than the potassium salt in this case because Na^+ is a harder Lewis acid compared to K^+; thus, there is more mismatch between Na^+/S^- (a soft Lewis base) compared to K^+/S^-. As a result, the S^- is more exposed for nucleophilic attack, similar to the crown ether effect.

(8) Radha Rani, B.; Bhalerao, U. T.; Rahman, M. F. *Synth. Commun.* **1990**, *20*, 3045−3052.

(9) Small amount of the rearrangement product 2-mercapto-4-fluoro-*N*-ethylaniline was also present (<5% estimated by ^{1}H NMR).

TABLE 3. Reactions of Polyhaloanilines with Potassium *O*-Ethyl Xanthate in DMF

Entry	Aniline (**9**)	Time (h)	Product (**10**)	Yield (%) [a]
1	 **9a**	4	NR[b]	
2	 **9b**	4	NR[b]	
3	 **9c**	6	NR[b]	
4	 **9d**	2	 **10d**	100 (96)
5[c]	 **9e**	18 2.5	 **10e**	76 (33) 18
6	 **9f**	2	 **10f**	100 (88)
7	 **9g**	1	 **10g**	100 (89)
8	 **9h**	3	 **10h**	(86)
9	 **9i**	2	 **10i**	(84)
10	 **9j**	18	 **10j**	96 (88)
11	 **9k**	1	 **6a**	(97)

[a] ^{1}H NMR yields, calculated on the basis of integration data of product and starting material peaks. Isolated yields are in parentheses. The isolation procedure was not optimized. [b] No reaction; starting aniline was recovered. [c] Run at 110 °C with sodium *O*-ethyl xanthate.

initial reaction of the xanthate with the amino group followed by a cyclization onto the ortho position.[12]

(10) Precoordination of reactants via noncovalent forces can have dramatic effects on reactivity by bringing the reactive sites in close proximity. For a recent example, see: Gatti, F, G.; Leigh, D. A.; Nepogodiev, S. A.; Slawin, A. M. Z.; Teat, S. J.; Wong, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 5983−5989.

In summary, we have demonstrated that polyhalogenated anilines bearing an ortho halogen can be good substrates for nucleophilic aromatic substitution reactions with excellent regioselectivity and efficiency. With appropriate nucleophiles (e.g., xanthate salts), intramolecular cyclization with the amino group can ensue to form important heterocycles in high yields.

Experimental Section

Typical Procedure for Benzothiazole-2(3*H*)-thione Formation as Illustrated by the Preparation of 6-Fluoro-1,3-benzothiazole-2(3*H*)-thione (3a). 2,4-Difluoroaniline (15.0 g, 116.2 mmol, 1.0 equiv) and potassium *O*-ethyl xanthate (41.0 g, 255.6 mmol, 2.2 equiv) were heated in anhydrous DMF (75 mL) at 95 °C (internal temperature) for 4 h under nitrogen. The reaction mixture was then cooled to room temperature, diluted with water (150 mL), and acidified to pH 3−4 by adding 1 N HCl solution (200 mL). The suspension formed on acidification was stirred for 30 min and filtered under vacuum. The wet cake was rinsed with water twice and dried to obtain 6-fluoro-1,3-benzothiazole-2(3*H*)-thione (**3a**) as an off-white solid (19.5 g, 91%): ^{1}H NMR (DMSO-d_6) δ 13.80 (s, 1H), 7.65 (d, J = 8.0, 1H), 7.28 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 188.78, 158.21 (d, J_{C-F} = 238), 137.28, 129.58 (d, J = 10.9), 114.18 (d, J = 24.2), 112.86, 108.40 (d, J = 27.3); ^{19}F NMR (DMSO-d_6) δ −118.50 (m). ESI-MS m/z (MH^+) 186. Anal. Calcd for $C_7H_4FNS_2$: C, 45.39; H, 2.18; N, 7.56. Found: C, 45.40; H, 2.25, N, 7.54.

(11) (a) Letcher, T. M.; Bricknell, B. C. *J. Chem. Eng. Data* **1996**, *41*, 166−169. (b) Krepps, M. K.; Parkin, S.; Atwood, D. A. *Cryst. Growth Des.* **2001**, *4*, 291−297, and references cited therein.

(12) Formation of the benzothiazole heterocycle could also be expected if the NH_2 group somehow reacted first with the xanthate to form a dithiocarbamate intermediate that then cyclized onto the ortho position. To rule out this possibility, aniline and sodium *O*-ethyl xanthate was heated in DMF-d_7 at 120 °C in an NMR tube and monitored by ^{1}H NMR. No reaction between the aniline and the xanthate was observed after 6 h (in the absence of a reaction with aniline, sodium *O*-ethyl xanthate undergoes slow decomposition under these conditions). This observation is consistent with the fact that aniline substrates lacking an ortho halogen were recovered under the reaction conditions (entries 1−3, Table 3).

Acknowledgment. We thank Laszlo Musza and Jeff Chin for assistance in NMR analysis and Miao Dai for providing some experimental help.

Supporting Information Available: General experimental information and complete characterization data for compounds **3d**, **5a**,**b**, **6a**, **7**, and **10d**−**j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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