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Synthesis and thiolation of 1,3-difluoro-2,4,6-trihaloanilines and benzenes

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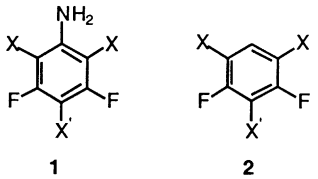
Abstract

Three pentahaloanilines were prepared by stepwise halogenation of 3,5-difluoroaniline and were deaminated to form pentahalobenzenes. Alternatively, two pentahalobenzenes were obtained by lithiation followed by iodination of 1,3-difluoro-4,6-dihalobenzenes. Alkylthiolation reactions of pentahaloanilines and benzenes in Me_2SO were investigated.

Keywords: Halogenation; Deamination; Alkylthiolation

1. Introduction

While investigating the preparation of substituted halobenzenes [1], we explored alkylthiolation of 3,5-difluoro-2,4,6-trihaloanilines **1** and the corresponding 1,3-difluoro-2,4,6-trihalobenzenes **2**, with an emphasis on achieving chemoselectivity. Such compounds with up to three types of halogens can undergo selective transformations, and are envisioned as building blocks for polyfunctionalized biphenyls [2] and pharmacological compounds [3]. In general, fluorine atoms can be displaced by nucleophiles [4], while other halogens, especially iodine and bromine, undergo metal-mediated substitution reactions [5]. This selectivity combined with the versatility of the amino group [6] offers a high degree of control in the functionalization process of the benzene ring when **1** is used.



1 **2**

a: X = Br, X' = I
b: X = Cl, X' = I
c: X = X' = Br
d: X = X' = Cl

It has been reported that thiolate anions selectively replace fluorine atoms on benzene rings when both bromine and fluorine atoms are present [7]. Some literature reports also show that replacement of fluorine atoms with certain nucleophiles can be accomplished in the presence of iodine [8–10]. Therefore, we envisioned the introduction of a propylthio group to benzene by chemoselective replacement of the fluorine atoms in **1** and **2**. Here we focused on the preparation of triheterohalogenated anilines **1a** and **1b** and the corresponding halobenzenes **2a** and **2b**. The tribromo derivative **1c** was isolated and the trichloro derivative **1d**, the only reported 3,5-difluoro-2,4,6-trihaloaniline to date [11], was observed as reaction side products. We also describe reactions of some of the anilines **1** and benzenes **2** with the 1-propanethiolate anion.

2. Results and discussion

The preparation of anilines **1a** and **1b** took advantage of the directing ability of the amino group in 3,5-difluoroaniline. Thus, iodination of 3,5-difluoroaniline under mild conditions [12] gave 3,5-difluoro-4-iodoaniline (**3**) in nearly quantitative yield (Scheme 1). The initial dibromination attempts of **3** to obtain pentahaloaniline **1a** with excess Br_2 in acetic acid resulted in displacement of the iodine and the formation of the 2,4,6-tribromo-3,5-difluoroaniline (**1c**). Even when stoichiometric amounts of Br_2 were used, significant quantities of several halogen-exchanged products were observed in addition to the desired **1a**. However,

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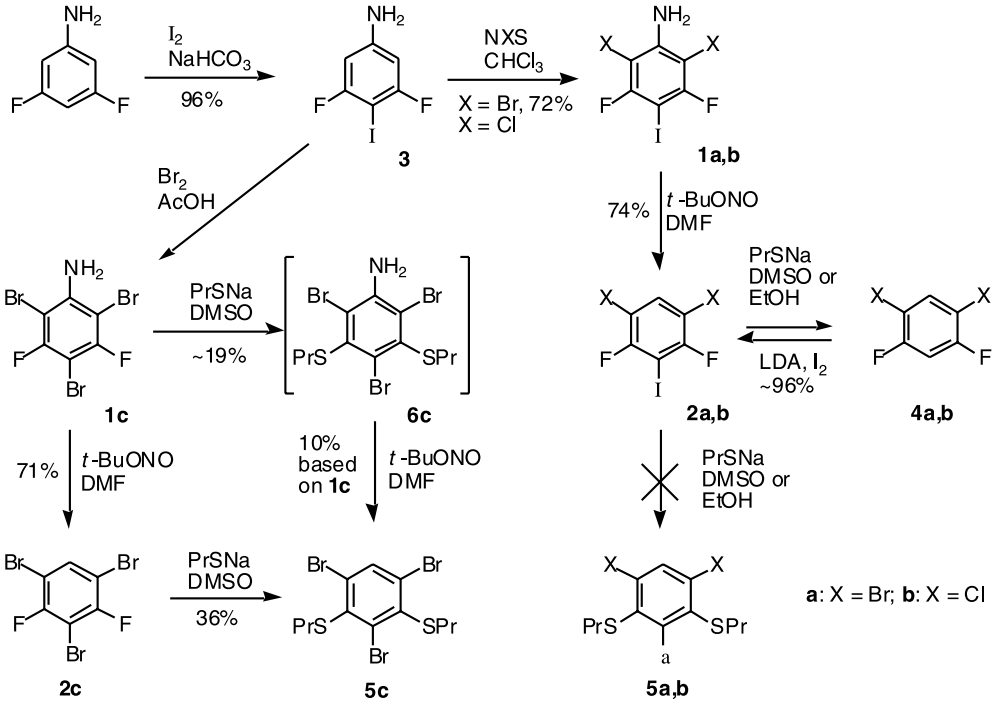

Scheme 1.

bromination of **3** with stoichiometric amounts of NBS gave the desired 2,6-dibromo-3,5-difluoro-4-iodoaniline (**1a**) in good yield. It was noticed that portionwise addition of NBS at ambient temperature is critical for achieving high selectivity of the bromination.

An analogous reaction of **3** with NCS in $CHCl_3$ gave only the starting aniline after 1 day at ambient temperature. In the presence of small amounts of CF_3COOH, chlorination of aniline **3** resulted in a mixture containing 2,6-dichloro-3,5-difluoro-4-iodoaniline (**1b**) and 2,4,6-trichloro-3,5-difluoroaniline (**1d**) as the major components. In addition, two other chlorinated materials including 2,4-dichloro-3,5-difluoro-6-iodoaniline, an isomer of **1b**, were identified by ^{19}F NMR and mass spectrometry. When stoichiometric amounts of NCS were used (2.0 equivalents) the ratio of **1b**:**1d**:others was about 5:1:1 based on ^{19}F NMR spectrum of the crude reaction mixture. A less complex mixture of products was obtained using only 1.8 equivalent of NCS. In this case, the ratio of **1b** to the monochloro derivative was about 4:1 with minimum amounts of the trichloro derivative **1d** and the starting aniline **3**. In either case, the separation of the mixture was difficult and only small quantities of pure **1b** were isolated by gradient sublimation. No further optimization of the reaction conditions was attempted.

The amino group in **1a** and **1c** was removed using Doyle's procedure [13] to give the corresponding pentahalobenzenes **2a** and **2c** in approximately 70% yield. Unfortunately, **1b** was not available in practical quantities for deamination, and the purification of halobenzenes obtained from the deamination was difficult and inefficient. Therefore, the two desired iodides **2a** and **2b** were prepared in an alternative way. Taking advantage of regioselective lithiation of fluorobenzenes [3,14,15] and iodination of the resulting carbanions [3], 1,3-difluoro-4,6-dihalobenzenes [1] **4a** and **4b** were conveniently converted to the corresponding iodides **2a** and **2b** in almost quantitative yields.

Attempts to thiolate **2a** or **2b** either in Me_2SO or EtOH did not give the expected substitution product **5**. Instead the deiodination product 1,3-difluoro-4,6-dihalobenzene (**4**) was formed as the sole product. The loss of iodine in the reaction with a thiolate anion is consistent with literature reports for other aryl halides and presumably involved radical intermediates [16,17].

In contrast, the analogous thiolation of 1,3,5-tribromo-2,4-difluorobenzene (**2c**) in Me_2SO gave the expected product **5c** identical to that obtained from 2,4,6-tribromo-1,3-phenylenediamine [2]. A similar reaction of the tribromo derivative **2c** with sodium 1-propanethiolate in hot ethanol (75 °C) gave no reaction, and after 48 h only starting material was observed.

Propanethiolation of 1,3,5-tribromo-2,4-difluoroaniline (**1c**) in Me_2SO appeared to be much slower than that of **2c**. This is consistent with the generally deactivating properties of the amino group especially of the *ortho* and *para* positions [18]. After 2 days, significant amounts of the corresponding monothiolated product remained and the bispropylthio derivative **6c** was isolated in about 19% yield. The purification of **6c** was difficult due to similar polarity of the mixture components and no analytical sample could be isolated. Therefore, the crude mixture of the thiolated products was deaminated and **5c** was separated chromatographically in about 10% yield. This represents only about

1/3 of the yield of **5c** obtained by thiolation of 1,3,5-tribromo-2,4-difluorobenzene (**1c**).

3. Conclusions

2,6-Dihalogenation of 3,5-difluoro-4-iodoaniline (**3**) requires mild conditions to avoid halo de-iodination. Dibromination of **3** with NBS is highly chemoselective. In contrast, chlorination of **3** with NCS leads to a mixture of products and the method is impractical for preparation of **1b**. Anilines **1a** and **1b** are the first examples of triheterohalogenated anilines which, in principle, can undergo selective substitution reactions. By varying the order of the halogenation reactions, it should be possible to obtain other combinations of halogens in 2,5-difluoro-2,4,6-trihaloanilines.

LDA-lithiation of 1,3-difluoro-4,6-dihalobenzenes **4** followed by iodination gives pentahalobenzenes **2** in excellent yields (>95%). Deamination of anilines **1** is an alternative method for preparation of halobenzenes **2** but lower yields complicate the separation of pure products.

Alkylthiolation of iodides **2a** and **2b** results in a facile de-iodination either in EtOH or Me_2SO solutions. The thiolation of the bromo derivatives **1c** and **2c** gave the F-substituted products **6c** and **5c**, respectively. The low yields for the thiolation of the aniline **1c** reflect the deactivating effect of the amino group.

4. Experimental

Melting points were determined in open capillaries and are uncorrected. ^{1}H NMR spectra were measured at either 300 or 400 MHz, and ^{13}C NMR were measured at 75 or 100 MHz, respectively, in $CDCl_3$ and referenced to solvent. ^{19}F NMR were obtained at 282 MHz in $CDCl_3$ and referenced to $CFCl_3$. IR spectra of neat liquid or microcrystalline samples were recorded in KBr. Mass spectrometry data was acquired using an HP GC–MS instrument in EI mode. Elemental analyses were obtained from Atlantic Microlabs. All reagents were used as received except as noted. Me_2SO was distilled from CaH_2 and stored over molecular sieves.

^{19}F and ^{13}C NMR chemical shifts were assigned based on general trends and comparison with the results from ChemDraw 6.0 empirical calculations.

4.1. 2,6-Dibromo-3,5-difluoro-4-iodoaniline (*1a*)

3,5-Difluoro-4-iodoaniline (**3**, 255 mg, 1.0 mmol) was dissolved in $CHCl_3$ (4 ml) and NBS (356 mg, 2.0 mmol) was added in portions over a 1.5 h period. The reaction was allowed to stir for 3 h at room temperature and then passed through a silica gel plug (hexanes:CH_2Cl_2, 2:1). The solvent was removed and the residue was purified on a silica gel column (hexanes:CH_2Cl_2, 3:1) to give 298 mg (72% yield) of white crystals: mp, 128–129 °C; ^{1}H NMR δ 4.9 (br. s, NH); ^{13}C NMR δ 54.23 (t, $^2J_{CF} = 32$ Hz, C4), 90.0 (dd, $^2J_{CF} = 29$ Hz, $^4J_{CF} = 3$ Hz, C2), 144.1 (t, $^3J_{CF} = 5$ Hz, C1), 158.0 (dd, $^1J_{CF} = 241$ Hz, $^3J_{CF} = 8$ Hz, C3); ^{19}F NMR δ −84.5; IR (KBr) 3421 and 3310 (N–H), 1609 (C=C) cm^{-1}; EI-MS *m/z* 415, 413, 411 (*M*, 36:78:39), 127 (100). Analytically calculated for $C_6H_2Br_2F_2IN$: C, 17.46; H, 0.49; N, 3.39. Found: C, 17.63; H, 0.45; N, 3.39.

4.2. 2,6-Dichloro-3,5-difluoro-4-iodoaniline (*1b*)

NCS (209 mg, 1.56 mmol) was added in portions over a 1.5 h period to a solution of aniline **3** (200 mg, 0.78 mmol) in $CHCl_3$ (4 ml) containing CF_3COOH (0.3 ml). The reaction was allowed to stir overnight at room temperature and then passed through a silica gel plug (hexanes:CH_2Cl_2, 2:1). The solvent was removed to give 220 mg of a solid residue: ^{19}F NMR δ (intensity) −70.8 (1.0), −91.1 (0.4), −92.2 (1.0), −94.3 (12.0, **1b**), −112.4 (0.5), −114.8 (2.3, **1d**). The two pairs of unassigned signals were attributed to 2-chloro-3,5-difluoro-4-iodoaniline (δ, −70.8 and −92.2 ppm) and 2,4-dichloro-3,5-difluoro-6-iodoaniline (δ, −91.1 and −112.4 ppm).

Fractional sublimation of the mixture (0.8 Torr) gave white crystals of **1b** as the last fraction: mp 77–78 °C; ^{1}H NMR δ 4.8 (br. s, NH); ^{13}C NMR δ 54.7 (t, $^2J_{CF} = 31$ Hz, C4), 101.9 (dd, $^2J_{CF} = 24$ Hz, $^4J_{CF} = 4$ Hz, C2), 142.3 (t, $^3J_{CF} = 4$ Hz, C1), 156.6 (dd, $^1J_{CF} = 243$ Hz, $^3J_{CF} = 8$ Hz, C3); ^{19}F NMR δ −94.3; IR (KBr) 3427 and 3304 (N–H), 1610 (C=C) cm^{-1}; EI-MS *m/z* 327, 325, 323 (*M*, 8:61:100). Analytically calculated for $C_6H_2Cl_2F_2IN$: C, 22.25; H, 0.62; N, 4.32. Found: C, 22.41; H, 0.60; N, 4.29.

4.3. 2,4,6-Tribromo-3,5-difluoroaniline (*1c*)

Treatment of aniline **3** with an excess of Br_2 in AcOH gave **1c** isolated as the sole white crystalline product: mp 118–119 °C; ^{1}H NMR δ 4.87 (br. s, NH); ^{13}C NMR δ 84.9 (t, $^2J_{CF} = 27$ Hz, C4), 90.9 (dd, $^2J_{CF} = 27$ Hz, $^4J_{CF} = 3$ Hz, C2), 142.9 (C1), 155.8 (dd, $^1J_{CF} = 244$ Hz, $^3J_{CF} = 6$ Hz, C3); ^{19}F NMR δ −97.1; IR (KBr) 3422 and 3311 (N–H), 1612 (C=C) cm^{-1}; EI-MS *m/z* 369, 367, 365, 363 (*M*, 33:98:100:34). Analytically calculated for $C_6H_2Br_3F_2N$: C, 19.70; H, 0.55; N, 3.83. Found: C, 19.55; H, 0.50; N, 3.83.

4.4. 1,5-Dibromo-2,4-difluoro-3-iodobenzene (*2a*)

4.4.1. Method A

A solution of amine **1a** (413 mg, 1 mmol) in DMF (5 ml) was added dropwise to a solution of *t*-BuONO (129 mg, 1.25 mmol) in DMF (5 ml) at 60 °C. After stirring for 0.5 h, the reaction mixture was poured into 6M HCl (150 ml) and products extracted with hexanes. The combined extracts were dried (Na_2SO_4), the solvent removed, and the crude product passed through a silica gel plug (hexanes). The solvent was removed to give 296 mg (74% yield) of a light brown solid which was sublimed under reduced pressure.

4.4.2. Method B

A 2.4 M solution of *n*-BuLi (1.8 ml, 4.4 mmol) was added dropwise to a cooled (−5 °C) solution of diisopropylamine (464 mg, 4.6 mmol) in dry THF (15 ml). After 30 min, the resulting solution of LDA was added dropwise to a solution of 1,3-dibromo-4,6-difluorobenzene [1] (**4a**, 1.00 g, 3.7 mmol) in THF (15 ml) at −78 °C and stirred for 45 min. A solution of I_2 (2.05 g, 8.1 mmol) in THF (15 ml) was added at once, and the reaction was allowed to warm to room temperature. 6 M HCl (5 ml) was added, and most of the THF was removed under reduced pressure. The concentrate was poured into water (100 ml) and products extracted with hexanes. The combined extracts were dried (Na_2SO_4) and passed through a short silica gel column (hexanes). The solvent was removed to give 1.41 g (96% yield) of a light brown solid. An analytical sample was obtained by vacuum sublimation (∼60 °C/0.8 Torr) onto a cold finger to give white crystals: mp 75–76 °C; ^{1}H NMR δ 7.75 (t, $^4J_{CF} = 7.1$ Hz, ArH); ^{13}C NMR δ 72.3 (t, $^2J_{CF} = 32$ Hz, C3), 103.8 (dd, $^2J_{CF} = 26$ Hz, $^4J_{CF} = 4$ Hz, C1), 136.0 (C6), 158.0 (dd, $^1J_{CF} = 247$ Hz, $^3J_{CF} = 4$ Hz, C2); ^{19}F NMR δ −83.6; EI-MS *m/z* 400, 398, 396 (*M*, 45:100:54). Analytically calculated for $C_6HBr_2F_2I$: C, 18.12; H, 0.25. Found: C, 18.32; H, 0.28.

4.5. 1,5-Dichloro-2,4-difluoro-3-iodobenzene (*2b*)

Aniline **1b** (300 mg, 0.93 mmol) was deaminated as described in Method A for the preparation of **2a** to give 205 mg (72% yield) of a pale yellow low melting solid. Using Method B the iodide was obtained in 97% yield from 1,3-dichloro-4,6-difluorobenzene [1] (**4b**). An analytical sample was obtained by sublimation (45 °C/0.8 Torr) onto a cold finger: ^{1}H NMR δ 7.51 (t, $^4J_{CF} = 7.3$ Hz, ArH); ^{13}C NMR δ 72.7 (t, $^2J_{CF} = 30$ Hz, C3), 116.54–116.81 (m, C1), 130.9 (C6), 156.8 (dd, $^1J_{CF} = 248$ Hz, $^3J_{CF} = 5$ Hz, C2); ^{19}F NMR δ −92.4; EI-MS, *m/z* 312, 310, 308 (*M*, 13:63:100). Analytically calculated for $C_6HCl_2F_2I$: C, 23.33; H, 0.33. Found: C, 23.34; H, 0.37.

4.6. 1,3,5-Tribromo-2,4-difluorobezene (*2c*)

Aniline **1c** (206 mg, 0.6 mmol) was deaminated using Method A described for the preparation of **2a** to give 140 mg (71% yield) of a white solid: mp 60–61 °C; ^{1}H NMR δ 7.73 (t, $^4J_{CF} = 6.9$ Hz, ArH); ^{13}C NMR δ 99.9 (t, $^2J_{CF} = 26$ Hz, C3), 104.6–105.0 (m, C1), 134.6 (C6), 155.9 (dd, $^1J_{CF} = 249$ Hz, $^3J_{CF} = 3$ Hz, C2); ^{19}F NMR δ −96.3; EI-MS *m/z* 354, 352, 350, 348 (*M*, 35:98:100:33). Analytically calculated for $C_6HBr_3F_2$: C, 20.54; H, 0.29. Found: C, 20.62; H, 0.31.

4.7. 3,5-Difluoro-4-iodoaniline (*3*) [19]

Ice (20 g) followed by iodine (11.3 g, 45 mmol) were added to a stirred mixture of powdered 3,5-difluoroaniline (4.8 g, 37 mmol), $NaHCO_3$ (4.7 g, 56 mmol) and water (250 ml), and the mixture was stirred overnight. A 10% solution of sodium meta-bisulfite in water was added until the disappearance of color and the product was extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and solvent removed to give 9.1 g (96% yield) of a light brown crystals: mp 111–112 °C (lit. [19] mp 112–114 °C); ^{1}H NMR δ 3.96 (br. s, 2H, NH), 6.22–6.27 (m, 2H, ArH); ^{13}C NMR δ 55.0 (t, $^2J_{CF} = 30$ Hz, C4), 98.3 (dd, $^2J_{CF} = 28$ Hz, $^4J_{CF} = 2$ Hz, C2), 149.1 (t, $^3J_{CF} = 13$ Hz, C1), 163.1 (dd, $^1J_{CF} = 243$ Hz, $^3J_{CF} = 9$ Hz, C3); ^{19}F NMR δ −94.2; EI-MS *m/z* 255 (*M*, 100).

4.8. Reaction of haloarenes with 1-propanethiolate: general procedure

4.8.1. Method A

A solution of haloarene (0.5 mmol) in Me_2SO (8 ml) was added to a solution of 1-propanethiol (1.1 mmol) and NaH (1.15 mmol) in Me_2SO (5 ml), and the reaction mixture was stirred at 90 °C for 48 h. Most of the solvent was removed under reduced pressure, and the residue was purified on a silica gel column (CH_2Cl_2:hexanes, 1:2).

4.8.2. Method B

A solution of haloarene (0.5 mmol), 1-propanethiol (1.1 mmol) and NaOH (1.15 mmol) in 95% EtOH (15 ml) was stirred overnight at 80 °C. Most of the EtOH was removed and 6 M HCl (5 ml) was added. The mixture was poured into water (100 ml) and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and purified on a silica gel column (CH_2Cl_2:hexanes, 1:2).

4.9. 2,4,6-Tribromo-3,5-bis(propylthio)benzene (*5c*) [2]

4.9.1. Method A

1,3,5-Tribromo-2,4-difluorobezene (**2c**) was reacted with sodium 1-propanethiolate in Me_2SO as described above. The product was isolated by column chromatography in 36% yield as a pale oil.

4.9.2. Method B

Aniline **1c** was reacted with sodium 1-propanethiolate in Me_2SO as described in the general procedure. The crude product was purified chromatographically to give **6c** in 19% yield. The aniline **6c** was deaminated with *t*-BuONO as described for the preparation of **2a** to give the bispropylthio derivative **5c** in about 10% overall yield. Similar overall yield of **5c** was obtained when a crude mixture of the thiolated aniline **1c** was deaminated prior to chromatographic separation. Physical and spectroscopic properties are identical to those reported for **5c** elsewhere [2].

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