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

Jason T. Manka1, Piotr Kaszynski*

Organic Materials Research Group, Department of Chemistry, Vanderbilt University, Box 1822 Station B, Nashville, TN 37235, USA

Received 10 June 2003; received in revised form 17 June 2003; accepted 23 June 2003

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 Me2SO were investigated.

© 2003 Elsevier B.V. All rights reserved.

Keywords: Halogenation; Deamination; Alkylthiolation

1. Introduction

While investigating the preparation of substituted halo-benzenes [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.

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 Br2 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 Br2 were used, significant quantities of several halogen-exchanged products were observed in addition to the desired 1a. However,
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 selec-
tivity of the bromination.

An analogous reaction of 3 with NCS in CHCl₃ gave only
the starting aniline after 1 day at ambient temperature. In the
presence of small amounts of CF₃COOH, 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-difluoro-
aniline (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 identi-
fied by ¹⁹F 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 ¹⁹F 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 optimiza-
tion 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 deami-
nation was difficult and inefficient. Therefore, the two
desired iodides 2a and 2b were prepared in an alternative
way. Taking advantage of regioselective lithiation of fluoro-
enbenzenes [3,14,15] and iodination of the resulting carba-
nions [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 Me₂SO or EtOH did
not give the expected substitution product 5. Instead the de-
iodination 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 inter-
mediates [16,17].

In contrast, the analogous thiolation of 1,3,5-tribromo-
2,4-difluorobenzene (2c) in Me₂SO gave the expected pro-
duct 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 mate-
rial was observed.

Propanethiolation of 1,3,5-tribromo-2,4-difluoroaniline (1c)
in Me₂SO appeared to be much slower than that of
2c. This is consistent with the generally deactivating proper-
ties of the amino group especially of the ortho and para
positions [18]. After 2 days, significant amounts of the corre-
sponding 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 chromato-
graphically in about 10% yield. This represents only about

Scheme 1.
iodination either in EtOH or Me₂SO solutions. The thiolation is a mild reaction and is suitable for the 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-trihalobenzenes.

LDA-thiolation of 1,3-difluoro-4,6-dihalobenzenes 4 followed by iodonation gives pentahalobenzenes 5 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 Me₂SO solutions. The thiolation of the bromo derivatives 1c and 1d 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. 1H NMR spectra were measured at either 300 or 400 MHz, and 13C NMR were measured at 75 or 100 MHz, respectively, in CDCl₃ and referenced to solvent. 19F NMR were obtained at 282 MHz in CDCl₃ and referenced to solvent. All reagents were used as received except as noted. Me₂SO was distilled from CaH₂ and stored over molecular sieves. Elemental analyses were obtained from Atlantic Microlabs. Acquired using an HP GC-MS instrument in EI mode. Samples were recorded in KBr. Mass spectrometry data was analyzed using a ThermoQuest Finnigan MAT 8230 mass spectrometer.

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 CHCl₃ (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:CH₂Cl₂, 2:1). The solvent was removed and the residue was purified on a silica gel column (hexanes:CH₂Cl₂, 3:1) to give 298 mg (72% yield) of white crystals: mp, 128–129 °C; 1H NMR δ 4.9 (br. s, NH); 13C NMR δ 54.23 (t, JCF = 32 Hz, C4), 90.0 (dd, JCF = 29 Hz, JCF = 3 Hz, C2), 144.1 (t, JCF = 5 Hz, C1), 158.0 (dd, JCF = 241 Hz, JCF = 8 Hz, C3); 19F NMR δ −84.5; IR (KBr) 3421 and 3310 (N–C) cm⁻¹, 19F NMR m/z 415, 413, 411 (M, 36:78:39), 127 (100). Analytically calculated for C₆H₂Br₂F₂IN: 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 CHCl₃ (4 ml) containing CF₃COOH (0.3 ml). The reaction was allowed to stir overnight at room temperature and then passed through a silica gel plug (hexanes:CH₂Cl₂, 2:1). The solvent was removed to give 220 mg of a solid residue: 19F 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-4-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; 1H NMR δ 4.8 (br. s, NH); 13C NMR δ 54.7 (t, JCF = 31 Hz, C4), 101.9 (dd, JCF = 24 Hz, JCF = 4 Hz, C2), 142.3 (t, JCF = 4 Hz, C1), 156.6 (dd, JCF = 243 Hz, JCF = 8 Hz, C3); 19F 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 C₆H₂Cl₂F₂IN: 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 Br₂ in AcOH gave 1c isolated as the sole white crystalline product: mp 118–119 °C; 1H NMR δ 4.87 (br. s, NH); 13C NMR δ 84.9 (t, JCF = 27 Hz, C4), 90.9 (dd, JCF = 27 Hz, JCF = 3 Hz, C2), 142.9 (C1), 155.8 (dd, JCF = 244 Hz, JCF = 6 Hz, C3); 19F 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 C₆H₂Br₃F₂N: 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 (Na₂SO₄), 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.

1/3 of the yield of 5c obtained by thiolation of 1,3,5-tribromo-2,4-difluorobenzene (1c).
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 I₂ (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 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; ¹H NMR δ 7.75 (t, ²JC₇F = 7.1 Hz, ArH); ¹³C NMR δ 72.3 (t, ²JC₂ = 32 Hz, C₃), 103.8 (dd, ²JC₂ = 26 Hz, ³JC₀ = 4 Hz, C₁), 136.0 (C₆), 158.0 (dd, ¹JC₃ = 247 Hz, ³JC₀ = 4 Hz, C₂); ¹⁹F NMR δ −83.6; EI-MS m/z 400, 398, 396 (M, 45:100:54). Analytically calculated for C₆HBr₂F₂I: C, 23.34; H, 0.37.

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: ¹H NMR δ 7.51 (t, ²JC₂ = 7.3 Hz, ArH); ¹³C NMR δ 72.7 (t, ²JC₀ = 30 Hz, C₃), 116.4–116.81 (m, C₁), 130.9 (C₆), 156.8 (dd, ¹JC₂ = 248 Hz, ³JC₀ = 5 Hz, C₂); ¹⁹F NMR δ −92.4; EI-MS m/z 312, 310, 308 (M, 13:63:100). Analytically calculated for C₆HCl₂F₂I: C, 23.34; H, 0.37.

4.6. 1,3,5-Tribromo-2,4-difluorobenzene (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; ¹H NMR δ 7.73 (t, ²JC₂ = 6.9 Hz, ArH); ¹³C NMR δ 99.9 (t, ²JC₂ = 26 Hz, C₃), 104.6–105.0 (m, C₁), 134.6 (C₆), 155.9 (dd, ¹JC₀ = 249 Hz, ³JC₀ = 3 Hz, C₂); ¹⁹F NMR δ −96.3; EI-MS m/z 354, 352, 350, 348 (M, 35:98:100:33). Analytically calculated for C₆HBr₃F₂: 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), NaHCO₃ (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 CH₂Cl₂. The extract was dried (Na₂SO₄) 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); ¹H NMR δ 3.96 (br, s, 2H, NH), 6.22–6.27 (m, 2H, ArH); ¹³C NMR δ 55.0 (t, ²JC₀ = 30 Hz, C₄), 98.3 (dd, ²JC₀ = 28 Hz, ³JC₀ = 2 Hz, C₂), 149.1 (t, ³JC₀ = 13 Hz, C₁), 163.1 (dd, ¹JC₀ = 243 Hz, ³JC₀ = 9 Hz, C₃); ¹⁹F 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 Me₂SO (8 ml) was added to a solution of 1-propanethiol (1.1 mmol) and NaH (1.15 mmol) in Me₂SO (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 short silica gel column (hexanes). The combined extracts were dried (Na₂SO₄) 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; ¹H NMR δ 7.75 (t, ²JC₂ = 7.1 Hz, ArH); ¹³C NMR δ 72.3 (t, ²JC₂ = 32 Hz, C₃), 103.8 (dd, ²JC₂ = 26 Hz, ³JC₀ = 4 Hz, C₁), 136.0 (C₆), 158.0 (dd, ¹JC₃ = 247 Hz, ³JC₀ = 4 Hz, C₂); ¹⁹F NMR δ −83.6; EI-MS m/z 400, 398, 396 (M, 45:100:54). Analytically calculated for C₆HBr₂F₂I: C, 20.54; H, 0.29. Found: C, 20.62; H, 0.31.

Acknowledgements

This project has been supported in part by the NSF Grants (CHE-9703002 and CHE-0096827).
References