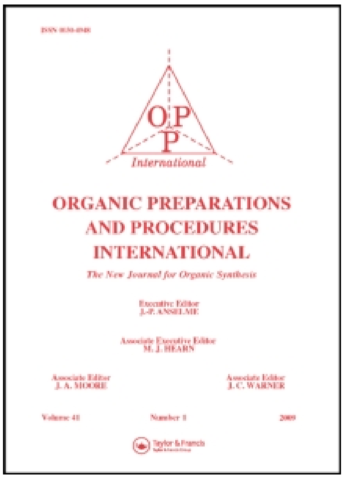

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ONE-STEP SYNTHESIS OF TRIFLUOROMETHYL- AND OF METHOXY-SUBSTITUTED BENZYNE PRECURSORS

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ONE-STEP SYNTHESIS OF TRIFLUOROMETHYL- AND OF METHOXY-SUBSTITUTED BENZYNE PRECURSORS

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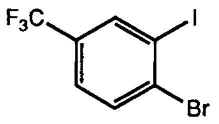
We have had a recurring need for trifluoromethyl- and methoxy- substituted benzyne precursors such as compounds **1-4**.[1,2,5] By application of the general conditions of Tanida *et al.*[3] to compounds **1-3**, benzyne formation and subsequent cycloaddition to a variety of dienes, such as cyclopentadiene,[1,2] furan[4] and 1,3-cyclohexadiene,[5] provided a number of benzobicyclic systems. We had prepared **1** by diazotization of commercially available 3-amino-4-bromobenzotrifluoride and treatment of the resulting diazonium salt with potassium iodide.



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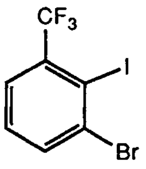

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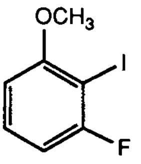

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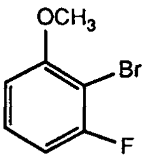

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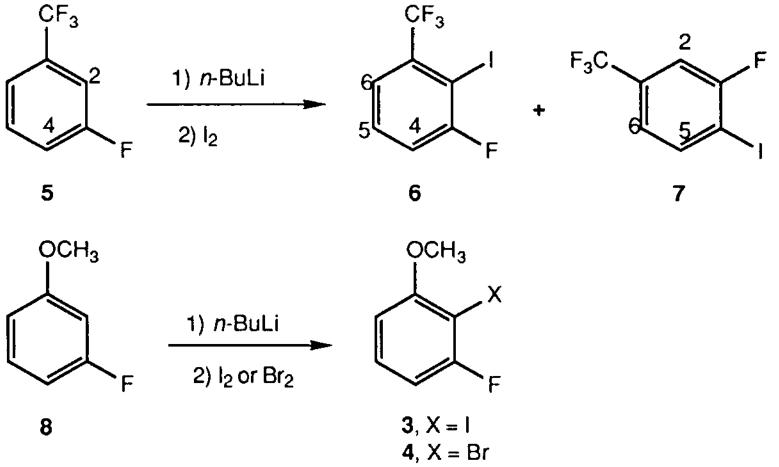
Because of the expense of the starting aniline and the moderate yields (ca. 50%), large scale preparation of **1** was impractical. Even more troublesome was the fact that the synthesis of regioisomer **2** started with 2-amino-5-nitrobenzotrifluoride and required six steps, with an overall yield of only 25%.[1] Similarly, the literature synthesis of **3** and **4** involved six steps from 3-fluorophenol.[6] We have devised a one-step procedure for the preparation of 3-fluoro-2-iodobenzotrifluoride (**6**), 3-fluoro-4-iodobenzotrifluoride (**7**), 2-bromo-3-fluoroanisole (**4**), and 3-fluoro-2-iodoanisole (**3**) *via* a lithiation of readily available starting materials as depicted below and have successfully utilized these compounds as precursors of the substituted benzynes.



Lithiation of commercially available 3-fluorobenzotrifluoride followed by treatment with iodine afforded a 94% yield of a mixture of **6** and **7** in a ratio of 3.5:1. The mixture was easily separated by medium pressure liquid chromatography over silica gel. Confirmation of the structures of regioisomers **6** and **7** was accomplished *via* spectroscopic analysis. It is well documented that the substitution pattern on the benzene ring gives rise to characteristic peaks in the IR spectrum in the region 2000-1667 cm^{-1}, irrespective of the nature of the functional groups present.[7-9] 1,2,3-Trisubstituted benzenes show three bands and 1,2,4-trisubstituted benzenes show two bands in this region. Although this band pattern was observable in the neat IR spectra of the benzyne precursors we synthesized, the intensity of the band was too weak to be of any diagnostic value. Therefore, the structure proof was obtained through proton NMR experiments. ^1H NMR studies of **6** showed two multiplets centered at 7.40 ppm and 7.21 ppm, in an integral ratio of 2:1, respectively. The COSY spectrum of **6** showed strong *ortho* coupling between the two multiplets. The ^1H NMR spectrum of **7** showed one multiplet centered at 7.86 ppm and two doublets centered at 7.27 ppm and 7.14 ppm, in an integral ratio of 1:1:1, respectively. The COSY spectrum of **7** showed strong coupling between the protons at 7.27 ppm (H5) and 7.14 ppm (H6) and moderate coupling between the protons at 7.86 ppm (H2) and 7.14 ppm (H6) and a weak coupling between the protons at 7.27 ppm (H5) and 7.86 ppm (H2), which corresponds to *ortho*, *meta* and *para* couplings, respectively. The ultimate confirmation of the assigned substitution patterns arose from the comparison of the cycloaddition products obtained from **6** and **7** with those previously obtained, respectively, from **2** and **1**.[1,4,5]

It was shown previously that the lithiation of 3-fluoroanisole followed by iodine addition resulted in exclusive formation of 3-fluoro-2-iodoanisole.[2] No other product was detectable by thin layer chromatography. This result is consistent with the report[10] by Ladd and Weinstock in which 3-fluoroanisole (**8**) was treated with *n*-BuLi followed by trimethyl borate and hydrogen peroxide to give 2-hydroxy-3-fluoroanisole as the sole product. Although lithiation can take place either at the 2- or 4-positions of 3-fluoroanisole, the 2-position is favored because of the combined *ortho* directing effects of the fluoro and methoxy groups. To rule out the presence of 3-fluoro-4-iodoanisole (**10**) in the lithiation-iodination of **8**, this compound was synthesized from 4-amino-3-fluoroanisole (**9**) by a slight modification of the literature method[6,12] (see Experimental Section). HPLC analysis on the crude product of our lithiation-iodination reaction showed that **10** was present in not more than 0.5 %. Similarly, lithiated 3-fluoroanisole (**8**) on treatment with bromine gave 2-bromo-3-fluoroanisole (**4**) as the only isolable product. The difference in behavior of 3-fluoroanisole (**8**) and 3-fluorobenzotrifluoride (**5**) towards lithiation can be explained by the relative potency of fluoro, methoxy and trifluoromethyl groups in directing the *ortho* lithiation. With the fluoro substituent being a much more powerful *ortho* director than the trifluoromethyl,[14] the lithiation of 3-fluorobenzotrifluoride (**5**) takes place at both *ortho* positions relative to the fluoro group. On the other hand, the methoxy and fluoro groups are comparable in their *ortho* directing properties[14] and therefore the lithiation of 3-fluoroanisole (**8**) takes place exclusively at the 2-position, which is *ortho* with respect to both the methoxy and fluoro groups.

In summary, our present method provides a short and efficient synthesis of various methoxy- and trifluoromethyl-substituted benzyne precursors, many of which were available till now only *via* multistep syntheses from expensive starting materials.

EXPERIMENTAL SECTION

All reagents and solvents were reagent grade or were purified by standard methods before use. Infrared spectra (IR) were obtained on a Perkin-Elmer 1420 Infrared spectrophotometer. ^{1}H NMR spectra were determined at 300 MHz and ^{13}C NMR spectra were recorded at 75.4 MHz using a Varian XL-300 spectrometer, all in $CDCl_3$. All chemical shifts are reported in parts per million (δ) relative to Me_4Si. Electron-impact mass spectra (EIMS) were obtained on a Varian Atlas CH-5 mass spectrometer. Microanalyses were performed on a Hewlett-Packard Model 185B CHN analyzer at the University of Kansas by Mr. Nguyen. Medium-pressure liquid chromatography (MPLC), using an adaptation of the system of Meyers and coworkers,[13] was performed on silica gel 60 (230-400 mesh) at pressure of 20-95 psi. High Performance Liquid Chromatography (HPLC) was performed on a Shimadzu Liquid Chromatograph using a Chromega column (Chromegasphere SI-60, 25 cm x 4.6 mm, 5 μ/60 Å) supplied by ES Industries using hexanes as the eluent and UV spectrophotometric detection (λ_{max} 254 nm). Analytical thin-layer chromatography (TLC) was performed on silica gel with fluorescent indicator coated on 2.5 x 7.5 cm glass plates in 0.2 mm thickness.

3-Fluoro-2-iodobenzotrifluoride (6) and 3-Fluoro-4-iodo-benzotrifluoride (7).- A solution of 3-fluorobenzotrifluoride (25 g, 152 mmol) in 100 mL of THF was added slowly to a solution of *n*-BuLi (120 mL, 1.3 M in hexanes, 156 mmol) in 400 mL of THF at -70° After stirring for an additional 30 min, a solution of iodine (50 g, 210 mmol) in 50 mL of THF was added dropwise. The reaction was allowed to warm gradually and at -40°, 50 mL of water was added, followed by 200 mL of 10% aq $Na_2S_2O_3$. After warming to room temperature, the phases were separated and the organic phase was extracted with hexanes. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give a mixture of **6** and **7** as an oil. Separation of the regioisomers was achieved by MPLC over silica gel using hexanes as the eluent (TLC R_f values in the same solvent: **6**, 0.52; and **7**, 0.41).

3-Fluoro-2-iodobenzotrifluoride (6) was obtained (32.1 g, 73%) as a colorless oil, bp 86°/26 mm; IR (film): 3100, 1570, 1460, 1310, 1250, 1170, 1135, 1080, 1020, 895, 790 cm^{-1}; ^{1}H NMR: δ 7.40 (m, 2H), 7.21 (m, 1H); ^{13}C NMR: δ 168.62, 156.32, 130.01, 123.33, 119.15, 117.86, 80.02; EIMS, m/z (relative intensity) 290 (M$^+$, 100), 271 (7.7), 163 (58.8), 144 (21.5), 113 (17.6), 94 (15.6).

Anal. Calcd for $C_7H_3F_4I$: C, 28.99; H, 1.04. Found: C, 28.80; H, 1.43

3-Fluoro-4-iodobenzotrifluoride (7) was obtained (9.21 g, 73%) as a colorless oil, bp 72°/28 mm; IR (film): 3070, 1600, 1575, 1480, 1410, 1325, 1215, 1170, 1125, 1065, 1025, 900, 880 cm^{-1}; ^{1}H NMR: δ 7.86 (m, 1H), 7.27 (d, 1H, J = 7.5 Hz), 7.14 (d, 1H, J = 7.5

Hz); ^{13}C NMR: δ 168.01, 155.60, 140.42, 122.34, 113.51, 112.16, 86.36; EIMS, m/z (relative intensity) 290 (M^+,100), 271 (8.8), 163 (72.0), 143 (19.6), 113 (22.4), 94 (19.8).

Anal. Calcd for $C_7H_3F_4I$: C, 28.99; H, 1.04. Found: C, 28.69; H, 1.23

3-Fluoro-2-iodoanisole (3).[2]- The retention time for this compound was 12.2 min on Chromegasphere SI-60 column (25 cm x 4.6 mm, 5 μ/60 Å), using hexanes as the eluent, flow rate 1 mL/min.

2-Bromo-3-fluoroanisole (4).- A solution of *n*-BuLi in hexanes (42 mL, 2.26 M in hexanes, 95 mmol) was added dropwise to 250 mL of THF below -70° under argon. After addition had been completed, a solution of 3-fluoroanisole (12 g, 95 mmol) in 25 mL of THF was added slowly maintaining the internal temperature below -70°. The reaction mixture was stirred for an additional 10 min and then bromine (15.2 g, 95 mmol) was added dropwise keeping the internal temperature below -65°. The reaction mixture was allowed to come to room temperature overnight and 10% aq $NaHSO_3$ was added. The organic layer was separated from the aqueous layer and the latter was extracted with ether. The organic layers were combined and washed with water followed by brine and the solvent was evaporated in vacuo after drying over $MgSO_4$. The light brown oil was distilled under vacuum to give 16.2 g (83%) of **4** as a colorless oil, bp 75°/3.5 mm, lit.[6] bp 220°/755 mm; IR (film): 3080, 3010, 2940, 2830, 1590, 1580 cm^{-1}; ^{1}H NMR: δ 7.17-7.30 (dd, 1H, J_1 = 7.6 Hz, J_2 = 15 Hz, Ar H), 6.65-6.82 (m, 2H, Ar H), 3.90 (s, 3H, OCH_3); ^{13}C NMR: δ 160.20 (d, J_{CF} = 245 Hz), 157.50 (d, J_{CCCF} = 4.1 Hz), 128.60 (d, J_{CCCF} = 9.6 Hz), 108.70 (d, J_{CCF} = 22.8 Hz), 107.20 (d, J_{CCCCF} = 2.9 Hz), 99.30 (d, J_{CCF} = 22.3 Hz), 56.6.

Anal. Calcd for C_7H_6BrFO : C, 40.97; H, 2.92. Found : C, 41.19; H, 3.15

3-Fluoro-4-iodoanisole (10).- An ice cold solution of sodium nitrite (77 mg, 1.13 mmol) in 1 mL of water was added dropwise to a stirred solution of 2-fluoro-4-methoxyaniline hydrochloride[11] (200 mg, 1.13 mmol) in 1 mL of water containing 0.12 mL of concentrated HCl at ice bath temperature. After the addition was complete the diazotized solution was stirred for 5 min and then a precooled solution of pyrrolidine (87 mg, 1.22 mmol) in 0.1 mL of 1.1 M KOH was added dropwise. A heavy precipitate of triazene formed. The stirring was continued for an additional 10 min. At this stage the pH of the slurry was adjusted to 7 by addition of 1.1 M KOH, and the yellow precipitate was filtered, washed with water, and air dried on a Buchner funnel. The crude triazene was suspended in a cold solution of KI (187 mg, 1.13 mmol) in 1.5 mL of water and 0.25 mL of concentrated HCl was added. The reaction mixture was held at ice bath temperature for 30 min and then brought to room temperature. After neutralizing to pH 7, the reaction mixture was extracted with ether. The ether layer was washed with 10% aq $Na_2S_2O_3$ followed by water and brine. After drying over $MgSO_4$ the ether was removed *in vacuo*, leaving a dark red oil which was purified by chromatography on silica gel (eluted with 99:1 hexanes-ethyl acetate) to give 90 mg (32%) of **10**. The analytical sample was prepared by bulb to bulb distillation (bath temp 50°/0.7 mm). The retention time was 9.7 min on a Chromegasphere SI-60 column (25 cm x 4.6 mm, 5 μ/60 Å), using hexanes as the eluent, flow rate 1 mL/min. IR (film): 3000, 2960, 2940, 2900, 2830, 1595, 1575 cm^{-1}; ^1H NMR: δ 7.55-7.65 (dd, 1H, $J_1 = 7.5$ Hz, $J_2 = 8.5$ Hz, Ar H), 6.65-6.70 (dd, 1H, $J_1 = 2.8$ Hz, $J_2 = 10.0$ Hz, Ar H), 6.50-6.60 (dd, 1H, $J_1 = 2.8$ Hz, $J_2 = 8.5$ Hz, Ar H), 3.80 (s, 1H, OCH_3); ^{13}C NMR: δ 162.50 (d, $J_{CF} = 244$ Hz), 161.40 (d, $J_{CCCF} = 9.4$ Hz), 139.00 (d, $J_{CCCF} = 3.7$ Hz), 112.20 (d, $J_{CCCCF} = 2.9$ Hz), 102.30 (d, $J_{CCF} = 27.5$ Hz), 69.40 (d, $J_{CCF} = 27.5$ Hz), 55.70.

Anal. Calcd for C_7H_6FIO : C, 33.33; H, 2.38; Found : C, 33.24; H, 2.40

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