An Expedient Synthesis of 2,4,6-Tris(trifluoromethyl)aniline

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Abstract: A simple two-step synthetic route leads to 2,4,6-tris(trifluoromethyl)aniline. It proceeds through deprotonation and iodination of 1,3,5-tris(trifluoromethyl)benzene, followed by copper-catalyzed amination.

Key words: fluorination, aniline, ligand precursor

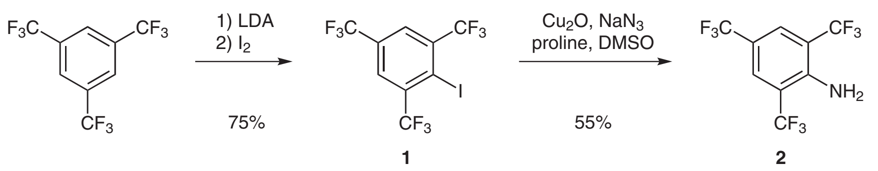
Fluorinated substituents have become a valuable tool in medicinal chemistry.[1] Strong and inert C–F bonds can also give robust supporting ligands for catalysis.[2] An easy method for the introduction of fluorinated substituents is through condensation with a fluorinated amine, particularly with formation of a Schiff base (imine). In this work, we target 2,4,6-tris(trifluoromethyl)aniline (**2**), a hindered aniline that shows great promise as a modular component for synthesis.

One previously reported synthesis of **2** starts with 1,2,3,5-benzenetetracarboxylic acid, which reacts with SF_4 to give 2,4,6-tris(trifluoromethyl)benzoyl fluoride. Addition of ammonia generates the corresponding amide, and a Hoffman rearrangement gives **2**.[3] While the overall reaction sequence provides a 56% total yield of **2**, specialized equipment is required for the reaction. Another literature route to compound **2** involves a five-step reaction sequence with an overall yield of 43%.[4] Another recently reported synthesis involved electrophilic trifluoromethylation of 2-(trifluoromethyl)aniline using CF_3I in the presence of an iron(II) catalyst, H_2O_2, and DMSO.[5] They reported a 55% yield for **2**, but 2,4-bis(trifluoromethyl)aniline was also formed in 28% yield, and experimental details were not provided. In order to provide an easier alternative, we have developed a synthesis leading to compound **2** from the commercially available 1,3,5-tris(trifluoromethyl)benzene (Scheme 1).

The addition of a strong base such as *n*-butyllithium to 1,3,5-tris(trifluoromethyl)benzene is known to give 2,4,6-tris(trifluoromethyl)phenyllithium, which can be handled in situ at 0 °C.[6] The addition of Cl_2 and Br_2 to the lithio derivative results in the formation of 1-chloro-2,4,6-tris(trifluoromethyl)benzene and 1-bromo-2,4,6-tris(trifluoromethyl)benzene, respectively, in low to moderate yields.[6a] Our initial experiments indicated that butyl groups from *n*-butyllithium had replaced fluorines on the substituents in the predominant by-products. In order to avoid this side reaction, we used the bulky base lithium diisopropylamide (LDA). We also used I_2 as the electrophile, due to the greater ease of handling.

Under optimized conditions of 2 equivalents of LDA and I_2, this method generates a 63–75% yield of the aryl iodide **1**. The superstoichiometric amounts of LDA and I_2 were necessary to achieve a high level of conversion to **1**, and ~15% of the starting material remains even under optimized conditions. The product **1** can be purified by sublimation. Singly sublimed **1** has an unidentified impurity peak at $\delta = 4.1$ in the ^1H NMR spectrum though it passed elemental analysis, and this material was sufficiently pure for continuing into the subsequent reaction below. Addition of a few drops of water and resublimation from CaO as a drying agent led to material with no detectable impurities by NMR spectroscopy, which was suitable for complete characterization. Compound **1** is a solid at room temperature (mp 34 °C), but is quite volatile and thus precautions must be taken to avoid loss during rotary evaporation.

For the transformation of **1** to the aniline **2**, a protocol developed by Helquist and co-workers[7] for the conversion of an aryl iodide into an arylamine was used. Compound **1** was combined with proline (1.3 equiv), NaN_3 (2 equiv),



Scheme 1

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and Cu_2O (1 equiv) in DMSO, and stirred at 80 °C for one hour. Again the major by-product was 1,3,5-tris(trifluoromethyl)benzene (~20% relative to **2**). An aqueous workup was used to remove ionic by-products, which should be handled with care (quenched with sodium nitrite and handled in a fume hood) due to the potentially explosive and toxic nature of any remaining azide salts. After extraction, the aniline was sublimed to give **2** as a white powder in 55% isolated yield. The ^1H NMR spectrum of **2** shows a singlet of the aromatic protons at $\delta = 7.86$ and a broad singlet at $\delta = 5.06$ corresponding to the NH protons. The $^{19}F\{^1H\}$ NMR spectrum consists of a singlet at $\delta = -64.5$ for the *o*-CF_3 groups, and a singlet at $\delta = -63.0$ for the *p*-CF_3 group.

Thus, a simple two-step procedure leads to 2,4,6-tris(trifluoromethyl)aniline on a gram scale. Detailed experimental details are given here, to facilitate the incorporation of this fragment into various useful molecules by other chemists.

Unless otherwise specified, all manipulations were performed under an inert atmosphere by standard Schlenk techniques or in an M. Braun Unilab N_2-filled glove box maintained at or below 1 ppm of O_2 and H_2O. Glassware was dried at 150 °C overnight. The 1,3,5-tris(trifluoromethyl)benzene (97% purity) was purchased from Oakwood Products, dried over molecular sieves, and degassed before use. NaN_3 and proline (99% purity) were purchased from Aldrich Chemical Co. and used without further purification. Cu_2O (97% purity) was purchased from Alfa Aesar and used without further purification. ^1H NMR, $^{19}F\{^1H\}$ NMR, and $^{13}C\{^1H\}$ NMR spectra were recorded on a Bruker Avance 400 spectrometer at r.t. (400 MHz for ^1H NMR, 376 MHz for ^{19}F NMR, and 100 MHz for ^{13}C NMR). All resonances in the ^1H NMR spectra were reported in ppm, relative to residual protiated solvent $CHCl_3$ ($\delta = 7.26$). All resonances in the ^{19}F NMR spectra were referenced to α,α,α-trifluorotoluene ($\delta = -63.72$) and were reported relative to $CFCl_3$ ($\delta = 0$). All resonances in the ^{13}C NMR spectra were referenced to $CDCl_3$ ($\delta = 77.0$). Pentane and Et_2O were purified by passage through activated alumina and 'deoxygenizer' columns from Glass Contour Co. (Laguna Beach, CA, USA). DMSO was degassed by applying vacuum for 4 min and refilling with N_2 for a total of three cycles. *i*-Pr_2NH was distilled under nitrogen and dried over 4 Å MS three times. IR spectra were recorded on a Shimadzu FT-IR Prestige 21 spectrometer equipped with a Pike diamond ATR. The CENTC Elemental Analysis Facility at the University of Rochester determined elemental analyses. Microanalysis samples were weighed with a PerkinElmer model AD-6 Autobalance, and their compositions were determined with a PerkinElmer 2400 Series II Analyzer. GC–MS was carried out on a Shimadzu GCMS-QP2010 instrument.

The numbering of carbon atoms used for ^{13}C NMR peak assignment is presented in Figure 1.

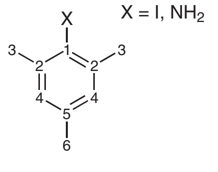

Figure 1 Atom-numbering used for ^{13}C NMR spectra

Lithium Diisopropylamide (LDA)

This synthesis and workup were performed in an inert-atmosphere glove box. To a solution of *i*-Pr_2NH (8.6 mL, 0.061 mol) in pentane (200 mL) at –78 °C was added a solution of *n*-BuLi (2.5 M in hexane, 24.4 mL, 0.0609 mol) slowly with stirring. The solution was stirred at –78 °C for 1 h, warmed to r.t., and stirred overnight. A white solid (4.03 g, 0.038 mol, 62%) was collected on a medium frit and washed with cold pentane (2 × 20 mL). The solid LDA was dried under vacuum and stored in a –40 °C glovebox freezer.

1-Iodo-2,4,6-tris(trifluoromethyl)benzene (1)

LDA (0.806 g, 7.52 mmol, 2.0 equiv) was dissolved in Et_2O (50 mL) in a 500 mL round-bottomed flask and cooled to 0 °C under N_2. 1,3,5-Tris(trifluoromethyl)benzene (1.06 g, 0.7 mL, 3.76 mmol) was dissolved in Et_2O (2 mL) and the resulting solution was slowly added to the LDA solution. The LDA turned dark as the addition proceeded. This mixture was stirred at 0 °C for 1.25 h. I_2 (1.91 g, 7.52 mmol, 2 equiv) was added all at once to the mixture and stirred at 0 °C for 5 min and then at r.t. for 15 min. The mixture was exposed to air, poured into a separatory funnel, and rinsed with Et_2O (2 × 20 mL). The mixture was washed with 10% aq $Na_2S_2O_3$ (4 × 100 mL) in order to remove excess I_2. A small amount of dark solid persists throughout the $Na_2S_2O_3$ washings. The organic layer was then washed with brine (2 × 75 mL). The combined aqueous layers were extracted with Et_2O (30 mL), which was combined with the other organic layers. The organic solution was then washed with 1 M aq HCl (3 × 75 mL) to remove *i*-Pr_2NH. The aqueous acid washes were extracted with Et_2O (65 mL). The Et_2O layer was passed through filter paper and combined with the other Et_2O layer. The combined Et_2O layers were dried ($MgSO_4$) and the orange solution was filtered through a pad of Celite. The majority of the solvent was removed with a rotary evaporator until a viscous oil remained (the product readily sublimed). The oil was transferred to a sublimator with a minimum amount of Et_2O and the solvent was evaporated with a stream of N_2. The resulting solid was sublimed at 20 °C under a static vacuum with dry ice/acetone in the cold finger to give **1** as an orange solid that is suitable for further reactions; yield: 1.1556 g (75%);[8] mp 34–35 °C.

IR (neat): 3102 (w), 1620 (m), 1584 (w), 1379 (w), 1269 (s), 1188 (s), 1043 (s), 1013 (s), 919 (s), 853 (m), 838 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.04$ (s, 2 H, H_{arom}).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta = 138.1$ (q, $J = 31$ Hz, C-2), 131.3 (q, $J = 35$ Hz, C-5), 127.2 (br s, C-4), 122.5 (q, $J = 273$ Hz, C-6), 122.0 (q, $J = 275$ Hz, C-3), 94.7 (s, C-1).

$^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): $\delta = -63.3$ (s, *o*-CF_3), –64.4 (s, *p*-CF_3).

MS (EI^+): *m/z* (%) = 408 (100), 281 (85), 212 (45) 162 (67), 143 (43).

Anal. Calcd for $C_9H_2F_9I$: C, 26.49; H, 0.49. Found: C, 26.32; H, 0.63.

2,4,6-Tris(trifluoromethyl)aniline (2)

Caution! Although no problems were encountered, the following procedure was carried out behind a shatter-resistant shield. The copper and azide starting materials should not be mixed before the other reagents, in order to avoid potential formation of explosive azide complexes.

Under N_2, a 125 mL resealable flask with a stir bar was charged with proline (559 mg, 4.86 mmol, 1.3 equiv), NaN_3 (447 mg, 7.34 mmol, 2.0 equiv), Cu_2O (531 mg, 3.71 mmol, 1.0 equiv), the iodo compound **1** (1.49 g, 3.64 mmol, 1.0 equiv), and DMSO (10 mL). This mixture was heated at 80 °C for 1 h. An aliquot of the sample was removed under N_2, and $^{19}F\{^1H\}$ NMR spectroscopy (DMSO-d_6) indicated the complete consumption of the starting material [the product **2** and ~20% of 1,3,5-tris(trifluoromethyl)benzene were observed]. In a fume hood, the reaction mixture was cooled to r.t.

and quenched by the addition of sat. aq NH_4Cl (15 mL) and EtOAc (12 mL). This biphasic mixture was stirred at r.t. for 1 h. The resulting dark green solution was filtered through a pad of Celite that was subsequently washed with EtOAc (70 mL) and H_2O (20 mL) (the solid should be quenched with $NaNO_2$ and disposed with care because of the possible presence of metal-azide salts). The filtrate was transferred to a separatory funnel, the aqueous layer was removed, and the organic phase was washed with sat. aq $NaHCO_3$ (3 × 55 mL). The aqueous layer became less blue with each wash. After the third wash, the aqueous layer was still slightly blue, so the organic layer was washed with brine (2 × 55 mL), followed by a final washing with sat. aq $NaHCO_3$ (55 mL), which was now colorless. To remove DMSO, the organic phase was washed with deionized H_2O (4 × 100 mL). An emulsion formed after each wash but cleared up more rapidly after each wash.[9] The organic layer was washed a final time with brine (80 mL).[10] The combined organic layers were dried ($MgSO_4$) and the orange solution was filtered through filter paper into a 250 mL round-bottom flask. The majority of the solvent was removed with a rotary evaporator until a viscous oil remained (the aniline product readily sublimed). The oil was transferred to a sublimator with a minimum amount of Et_2O and the residual solvent was evaporated with a stream of N_2. The resulting solid was sublimed at 20 °C under a static vacuum with dry ice/acetone in the cold finger, to give **2** as a white solid; yield: 0.5958 g (55%); mp 54–55 °C (Lit.[4] mp 58–59 °C).

IR (neat): 3559 (w), 3465 (m), 1655 (m), 1507 (m), 1378 (m), 1254 (s), 1093 (s), 920 (s), 884 (m), 830 cm^{-1} (w).

^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.86$ (s, 2 H, H_{arom}), 5.06 (br s, 2 H, NH).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta = 148.1$ (s, C-1), 128.0 (br s, C-4), 123.5 (q, $J = 273$ Hz, C-3), 123.3 (q, $J = 271$ Hz, C-6), 118.6 (q, $J = 35$ Hz, C-5), 115.3 (q, $J = 31$ Hz, C-2).

$^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): $\delta = -63.0$ (s, p-CF_3), –64.5 (s, o-CF_3).

MS (EI^+): m/z (%) = 297 (100), 278 (55), 277 (63), 257 (56), 238 (45), 207 (41), 188 (54), 181 (23), 69 (19).

Anal. Calcd for $C_9H_4F_9N$: C, 36.38; H, 1.36; N, 4.71. Found: C, 36.14; H, 1.37; N, 4.58. Elemental analysis was also performed after the sample was resublimed over CaO. Found: C, 36.32; H, 1.32; N, 4.62.

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(8) This solid can be used in the synthesis of compound **2** directly, and passes elemental analysis. It can also be resublimed from CaO after adding a few drops of water, to give a white solid.

(9) If the emulsion after the first wash with water does not clear up, 20 mL of brine can be added to the separatory funnel and the mixture can be reshaken. It may take some time (~40 min) for the first emulsion to clear.

(10) When the aqueous layers and the brine layers were combined and extracted with Et_2O, no aniline **2** was observed in the organic extracts, indicating that the desired product was not water soluble.