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An Efficient Synthetic Process for Scale-Up Production of 4,5-Diamino-2-(trifluoromethyl)benzonitrile and 5-Bromo-3-(trifluoromethyl)benzene-1,2-diamine

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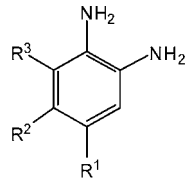
Abstract:

Starting from 4-amino-2-(trifluoromethyl)benzonitrile (6), an efficient and nonchromatographic process was developed for multihundred gram production of 4,5-diamino-2-(trifluoromethyl)-benzonitrile (1) in 73% yield and 98 HPLC area% purity over four synthetic steps. The same synthetic strategy was applied to 4-bromo-2-(trifluoromethyl)aniline (7) that afforded 5-bromo-3-(trifluoromethyl)benzene-1,2-diamine (5) in 81% overall yield and 99% HPLC area% purity.

Introduction

Substituted benzene-1,2-diamines are functional building blocks for the construction of biologically active heterocyclic molecules. For instance, compounds **1**−**4** (Figure 1) were used in the syntheses of 2,5,6-trisubstitued benzimidazole derivatives as selective androgen receptor modulators (SARMs),[1,2] and compound **5** was used to prepare 5,7-disubstitued 1,4-dihydroquinoxaline-2,3-dione analogues as glycine receptor antagonists.[3] Because 4,5-diamino-2-(trifluoromethyl)benzonitrile (**1**)

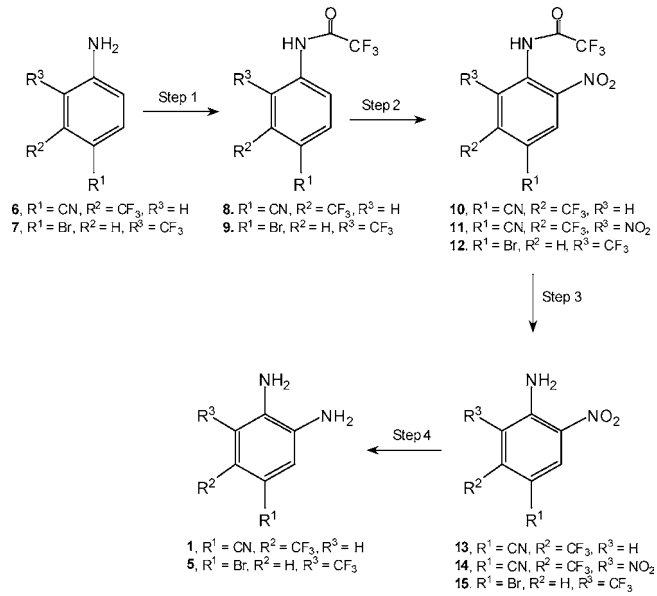


1. R^1 = CN, R^2 = CF_3, R^3 = H; **2**. R^1= R^2 = Cl, R^3 = H;
3. R^1 = Cl, R^2 = CF_3, R^3 = H; **4**. R^1 = Cl, R^2 = F, R^3 = H
5, R^1 = Br, R^2 = H, R^3 = CF_3

Figure 1

was commercially unavailable when a multihundred gram quantity of **1** was requested to support the advanced research activities, there was a need for developing a safe and scalable synthetic process for large-scale production of **1**. The Discovery route started with 4-amino-2-(trifluoromehthyl)benzonitrile (**6**) to afford compound **1** on a small scale (∼1.0 g) in 47% yield over four synthetic steps (Scheme 1). This route however,

Scheme 1[a]



[a] Reagents and conditions: Step 1. $(CF_3CO)_2O$, K_2CO_3, CH_2Cl_2, 20 °C, 2 h. **8** = 100%; **9** = 100%. Step 2. HNO_3, CF_3SO_3H, CH_2Cl_2, 20 °C, 20 h. **10** = 85%; **12** = 88%. Step 3. K_2CO_3, CH_3OH, H_2O, 20 °C, 4 h. **13** = 94%. HCl, EtOH, 76 °C, 120 h. **15** = 95%. Step 4. $SnCl_2 \cdot H_2O$, HCl, THF, 20 °C, 20 h. **1** = 91%; **5** = 97%.

contained a number of scale-up issues; for example, the protection of the amino group of **6** in step 1 was conducted in trifluoroacetic anhydride (13 equiv) as the solvent (Scheme 1), which caused the aqueous work up to be a highly exothermic process. An excess amount of fuming HNO_3 (3 equiv)/CF_3SO_3H (6 equiv) was used in step 2 for the nitration of compound **8**, which resulted in a moderate chromatographic isolated yield (67%) of the desired 2-nitro **10** together with more than 20% of the 2,6-dinitro byproduct **11**. A large excess of indium (24 equiv) was used in step 4 for the reduction of nitroamino intermediate **13** that required an additional column chromatographic purification of the final compound **1**. Herein, we report an improved nonchromatographic synthetic process that is suitable for large-scale production of **1**.

Results and Discussions

During scale-up of step 1, the large excess of $(CF_3CO)_2O$ (13 equiv) was reduced to an almost stoichiometric amount (1.05 equiv), and the reaction was performed in CH_2Cl_2 with the presence of a base (K_2CO_3, 1.13 equiv). This modified reaction provided a quantitative yield of trifluoroacetamide **8** in 99 HPLC area% purity.[4] With only a slight excess of

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$(CF_3CO)_2O$ in the reaction mixture, the aqueous work up was only mildly exothermic and was easily feed controlled by adjusting the addition rate of water.

The nitro intermediate **10** was prepared by nitration of compound **8** with nitronium trifluoromethylsulfonate salt ($NO_2^+CF_3SO_3^-$, a stable white crystalline solid when stored at 0 °C under nitrogen atmosphere), which was readily prepared in high yield following a published method.[5] In practice, the reaction selectivity was an additive result of the activating ortho/para-directing -$HNCOCF_3$ group to the deactivating meta-directing 4-CN group of compound **8**. After the amount of $NO_2^+CF_3SO_3^-$ salt was reduced from 3.0 to 1.35 equiv, compound **10** was obtained in an improved isolated yield (85%) as well as a better chemical purity (96% of **10** plus 3% of dinitro **11**; HPLC area%) without the need for chromatographic purification (step 2 of Scheme 1).

The trifluoroacetyl protecting group of **10** was cleaved using an aqueous solution of K_2CO_3 (1.06 equiv) in CH_3OH (step 3 of Scheme 1), and after workup, mononitroamine **13** was collected by simple filtration as a solid in a 94% isolated yield and 99 HPLC area% purity. Meantime, the undesired dinitroamine **14** was completely removed in the filtrate.[6]

The original reduction conditions for the last step (24 equiv of expensive indium) was replaced with $SnCl_2$ (3.2 equiv)/concentrated HCl (7.5 equiv) in THF.[8] Under these reaction conditions, **13** was reduced to benzene-1,2-diamine **1** in 91% isolated yield and 98.2 HPLC area% purity without the need for chromatographic purification. Residual tin was found at 34 ppm, the only time we measured the metal content in compound **1**. This was an acceptable level because **1** was an early intermediate used for the synthesis of target molecules.

Furthermore, the synthetic strategy described above was applied to 4-bromo-2-(trifluoromethyl)aniline (**7**) that afforded 81% overall yield of the corresponding **5**; of which a 38% yield was reported in the same number of synthetic steps under different reaction conditions.[3] As with the syntheses of **1**, the protection of the amino group of compound **7** was carried out using $(CF_3CO)_2O$ (1.05 equiv), which resulted in quantitative formation of trifluoroacetamide **9** on multihundred gram scale. Of interest, the nitronium (NO_2^+) preference for the electrophilic substitution on compound **9** was completely controlled by the additive effects of the ortho/para-directing -$HNCOCF_3$ group and meta-directed 2-CF_3 group, which produced the mononitro compound **12** as the only product.

The same alkaline hydrolysis conditions that worked well for the preparation of compound **13** only produced a moderate isolated yield (43%) of nitroamine **15** due to the incomplete hydrolysis of compound **12**. Increasing the amount of K_2CO_3 to 4.4 equiv with extended reaction times (72−120 h) and elevated temperatures (60 °C) did not push the reaction to completion. In contrast to the alkaline conditions, treatment of **12** with a solution of HCl (10 equiv, 1.0 M in EtOH) at 76 °C for 5 days afforded a quantitatively isolated yield of **15** (as its HCl salt) in 95 HPLC area% purity, which could be used for the next step without further purification. The incomplete hydrolysis of compound **12** to **15** could be attributed to the steric hindrance of the 2-nitro and 6-trifluoromethyl substituents of compound **12**,[9] which are positioned adjacent to the -$HNCOCF_3$ group, resulting in OH^- anion attack at the carbonyl carbon of **12** being much more difficult than that for **10** (which lacks the 2,6-disubstitution). On the other hand, the $EtOH_2^+$ ion has an easier approach to the oxygen atom of the same carbonyl of **12** to initiate and further complete the hydrolysis reaction, although the long reaction time was a drawback of this acid-catalyzed ethanolysis of **12**. Finally, nitroamine **15** was reduced to benzene-1,2-diamine **5** in a quantitative isolated yield using the same $SnCl_2$/HCl conditions, which verified that $SnCl_2$/HCl reduction of substituted 2-nitroaniline to benzene-1,2-diamine is a robust alternative method for metal (Ni, Pt, or Pd)-catalyzed hydrogenation.[10] The above-described efficient process was successfully scaled up to 456 g of benzene-1,2-diamine **1** in our lab, and no further development is planned.

Conclusions

An efficient and nonchromatographic synthetic process was developed for safe scale-up production of 4,5-diamino-2-(trifluoromethyl)benzonitrile (**1**) in an improved overall yield (73% for four steps) with 98.2 HPLC area% purity. In addition, 5-bromo-3-(trifluoromethyl)benzene-1,2-diamine (**5**) was also prepared in 81% isolated yield and 99.0 HPLC area% purity using the same synthetic method without the need of chromatographic purification.

Experimental Section

Special cautions should be taken when handling substituted trifluoromethylaniline derivatives, due to the instability of 4-trifluoromethylaniline that has been reported.[11] All reactions were conducted in a four-neck, round-bottom flask (RBF) (1−22 L), equipped with a thermocouple controller, an overhead mechanical stirrer, a condenser, and a pressure-equalization addition funnel and nitrogen inlet/outlet whenever they were required. HPLC: Agilent Series 1100 system at 254 nm, using a Phenomenex Luna C_{18} (2) column (4.6 mm ID × 50 mm, 5.0 μm) at 35 °C with flow rate of 1.0 mL/min and run time of

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(6) 4-Amino-3,5-dinitro-2-(trifluoromethyl)benzonitrile (**14**) (2.4 g, 0.9% isolated yield, 94 HPLC area%) was isolated as a yellowish solid by filtration of the aqueous filtrate after sitting overnight. HPLC retention time = 3.52 min. The structure of **14** was confirmed by its ^{1}H NMR and LC−MS spectra. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.48 (brs, 2 H, NH_2), 8.91 (s, 1 H, H_6). LC−MS *m*/*z* 276 (M^+), 275 ($[M-H]^+$).

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10.0 min. Solvents: A - H_2O + 0.05% TFA, B - CH_3CN; Gradient: B 30%/0.0 min, B 40%/1.0 min, B 90%/4.0 min, B 90%/8.0 min, B 30%/10.0 min.

***N*-(4-Cyano-3-(trifluoromethyl)phenyl)-2,2,2-trifluoroacetamide (8).** 4-Amino-2-(trifluoromethyl)benzonitrile (**6**) (450.0 g, 2.418 mol) and CH_2Cl_2 (8.0 L) under nitrogen were treated with potassium carbonate (K_2CO_3, 377.6 g, 2.732 mol), and the suspension was cooled to 14 °C. Trifluoroacetic anhydride (TFAA, 358.5 mL, 2.538 mol) was added over 30 min. The mixture was stirred at 20 °C for 1 h; the progress of the reaction was determined by HPLC and ^{1}H NMR. After the reaction was cooled to 10 °C, it was quenched with H_2O (3.0 L) at ≤20 °C and stirred at 20 °C for 10 min. The off-pink solid was filtered, washed with H_2O (250 mL × 2), and dried by air-suction for 3 h. The filtrate was washed with brine (1.0 L × 2) and concentrated to give a pink solid (98.0 g), which was combined with the filtration cake. The solid was dried at ~ 260 mmHg at 60 °C for 18 h to afford 678.9 g (99.5% isolated yield, 99 HPLC area%) of trifluoroacetamide **8** as an off-white solid. HPLC retention time = 3.89 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (dd, J = 1.8, 8.6 Hz, 1 H, H_6), 8.18 (d, J = 8.6 Hz, 1 H, H_5) 8.28 (d, J = 1.8 Hz, 1 H, H_2), 11.9 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6, 100.61 MHz) δ 155.17 (q, $^2J_{CF}$ = 37.2 Hz), 141.10, 136.56, 131.65 (q, $^2J_{CF}$ = 31.9 Hz), 123.92, 122.14 (q, $^1J_{CF}$ = 276.5 Hz), 118.36 (q, $^3J_{CF}$ = 6.4 Hz), 115.21 (q, $^1J_{CF}$ = 287.1 Hz), 115.20, 104.25 (q, $^3J_{CF}$ = 6.4 Hz). LC−MS *m*/*z* 283 (MH^+), 282 (M^+), 281 $(M - 1)^+$.

***N*-(4-Bromo-2-(trifluoromethyl)phenyl)-2,2,2-trifluoroacetamide (9).** Prepared in the same manner as **8**. Starting from 4-bromo-2-(trifluoromethyl)aniline (**7**, 300.0 g, 1.24 mol), compound **9** (421.3 g) was obtained as an off-white solid in 100% crude yield with 98.8 HPLC area% purity (HPLC retention time = 4.07 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (dd, J = 1.7, 8.8 Hz, 1 H, H_5), 7.82 (d, J = 1.6 Hz, 1 H, H_3), 8.07 (d, J = 8.8 Hz, 1 H, H_6), 8.20 (br s, 1 H, NH). LC−MS *m*/*z*, 334 $(M - 2)^+$, 336 (M^+).

***N*-(4-Cyano-2-nitro-5-(trifluoromethyl)phenyl)-2,2,2-trifluoroacetamide (10).** Triflic acid (CF_3SO_3H, 336.4 mL, 3.829 mol) was cooled to 4 °C, and fuming HNO_3 (80.9 mL, 1.914 mol) was added over 20 min (*Caution: this was a high exothermic process; the internal reaction temperature was maintained below 24 °C by adjusting the addition rate of fuming HNO_3*!) and stirred at 10 °C for 20 min. Methylene chloride (CH_2Cl_2, 6.4 L) and trifluoroacetamide **8** (400.0 g, 1.418 mol) were sequentially added to this white nitronium salt, and the reaction was stirred at 20 °C for 20 h; the progress of the reaction was determined by HPLC and ^{1}H NMR. After the reaction was cooled to 0 °C, it was quenched with saturated $NaHCO_3$ solution (3.0 L), followed by the addition of solid Na_2CO_3 (180 g) in small portions over 20 min and stirred at 20 °C for another 20 min. After phase separation, the aqueous phase was extracted with CH_2Cl_2 (1.0 L × 2); the combined organic phases were washed with brine (2.0 L × 2); and concentrated at ~260 mmHg at 40 °C to afford 396.0 g of mononitroamide **10** (85% isolated yield; 96% of **3** plus <3% of dinitro byproduct **11**, HPLC area%) as an orange solid. HPLC retention time = 4.1 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (s, 1 H, H_6), 8.95 (s, 1 H, H_3), 12.3 (br s, 1 H, NH). ^{13}C NMR (DMSO-d_6, 100.61 MHz) δ 155.29 (q, $^2J_{CF}$ = 33.4 Hz), 147.65, 144.60, 134.80 (q, $^3J_{CF}$ = 5.6 Hz), 134.53 (q, $^2J_{CF}$ = 33.2 Hz), 132.83 (q, $^3J_{CF}$ = 5.6 Hz), 125.84, 121.29 (q, $^1J_{CF}$ = 273.0 Hz), 115.25 (q, $^1J_{CF}$ = 289.8 Hz), 113.59, 107.11 (q, $^3J_{CF}$ = 5.6 Hz). LC−-MS *m*/*z* 327 (M^+), 326 $(M - 1)^+$.

N-(4-Bromo-2-nitro-6-(trifluoromethyl)phenyl)-2,2,2-trifluoroacetamide (12). Prepared in the same manner as **10**. Starting from N-(4-bromo-2-(trifluoromethyl)phenyl)-2,2,2-trifluoroacetamide (**9**, 40.0 g, 0.118 mol), compound **12** (39.8 g) was obtained in 88% isolated yield with 98.8 HPLC area% purity as a beige solid. HPLC retention time = 4.0 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (br s, 1 H, NH), 8.15 (d, J = 1.5 Hz, 1 H, H_5), 8.41 (d, J = 1.6 Hz, 1 H, H_3). LC−MS *m*/*z* 382 (MH^+), 381 (M^+), 379 $(M - 2)^+$.

4-Amino-5-nitro-2-(trifluoromethyl)benzonitrile (13). A solution of compound **10** (489.0 g, 1.495 mol) in CH_3OH (2.2 L) was treated with a solution of K_2CO_3 (218.8 g, 1.06 mol) in H_2O (2.2 L), and the reaction mixture was stirred at 20 °C for 4 h; the progress of the reaction was determined by HPLC and ^{1}H NMR. H_2O (12.0 L) was added with fast agitation, and the resulting solid was stirred for 20 min and then filtered. The filtration cake was washed with cold H_2O (500 mL × 2), dried by air-suction for 3 h and further dried at ~260 mmHg at 50 °C for 18 h to afford 323.8 g (93.7% isolated yield; 99.0 HPLC area%) of nitroaniline **13** as a yellow-light greenish solid. HPLC retention time = 3.26 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.54 (s, 1 H, H_3), 8.62 (s, 1 H, H_6), 8.44 (br s, 2 H, NH_2). ^{13}C NMR (DMSO-d_6, 100.61 MHz) δ 147.65, 134.77, 134.19 (q, $^2J_{CF}$ = 34.0 Hz), 130.62, 121.70 (q, $^1J_{CF}$ = 276.5 Hz), 118.99 (q, $^3J_{CF}$ = 4.8 Hz), 115.14, 91.70 (q, $^3J_{CF}$ = 4.8 Hz). LC−MS *m*/*z* 231 (M^+), 230 $(M - H)^+$, 254 $([M + Na]^+)$.

4-Bromo-2-nitro-6-(trifluoromethyl)aniline (15) Prepared under Alkaline Cleavage Conditions. Prepared in the same manner as **13**. Starting from **12** (30.0 g, 0.079 mol), compound **15** (9.6 g) was obtained in 43% isolated yield with 99.1 HPLC area% purity as a yellow-brownish solid (this reaction was conducted with an excess of K_2CO_3 (4.4 equiv) at 60 °C for 120 h). HPLC retention time = 4.32 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68 (br s, 2 H, NH_2), 7.83 (d, J = 1.6 Hz, 1 H, H_5), 8.50 (d, J = 1.6 Hz, 1 H, H_3). LC-MS *m*/*z* (no MH^+ = 286), 268 $(M - NH_2)^+$, 267 $([M - NH_2] - 1)^+$.

4-Bromo-2-nitro-6-(trifluoromethyl)aniline (15) Prepared under Acidic Cleavage Conditions. Compound **12** (10.0 g, 26.2 mmol) was treated with a solution of HCl (262.4 mL, 262.4 mmol) in EtOH. The reaction mixture was refluxed at 76 °C for 120 h; the progress of the reaction was monitored by HPLC and LC/MS. After the reaction was cooled to 20 °C, the solvent was concentrated at ~20 mmHg that afforded 8.7 g (100% isolated yield, 95.0 HPLC area%) of nitroaniline **15** HCl salt as a bright yellow-greenish solid. The ^{1}H NMR and HPLC data of compound **15** prepared under this acidic condition were identical to that was prepared from alkaline hydrolysis.

4,5-Diamino-2-(trifluoromethyl)benzonitrile (1). A solution of compound **13** (578.0 g, 2.50 mol) in THF (3.0 L) was cooled to 0 °C under nitrogen with stirring. A solution of $SnCl_2 \cdot 2H_2O$ (1805.6 g, 8.0 mol) in conc. HCl (37.5%, 1.85 L) was added dropwise over a 3-h period (*Caution: this was an exothermic process; the internal reaction temperature was*

maintained below 13 °C by adjusting the addition rate!). After the addition, the reaction was stirred at 20 °C for 20 h; the progress of the reaction was determined by HPLC and ^{1}H NMR. The reaction mixture was diluted with THF (4.0 L) and H_2O (4.0 L) and then cooled to 0 °C. The pH of the mixture was adjusted with 5 N NaOH solution (~7.6 L) to pH = 9−10. After phase separation, the aqueous phase was extracted with EtOAc (3.0 L × 1; 2.0 L × 2), and the combined organic phases were washed with brine (2.0 L × 2). The solvent was concentrated at ~260 mmHg at 60 °C to afford 456.0 g of compound **1** (91% isolated yield; 98.2 HPLC area%) as a light-rose solid. HPLC retention time = 2.26 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.53 (br s, 2 H, NH_2), 5.88 (br s, 2 H, NH_2), 6.92 (s, 1 H, H_3), 6.93 (s, 1 H, H_6) ^{13}C NMR (DMSO-d_6, 100.61 MHz) δ 138.87, 137.36, 123.69 (q, $^1J_{CF}$ = 273.7 Hz), 119.99 (q, $^2J_{CF}$ = 31.7 Hz), 117.66, 116.90, 110.09 (q, $^3J_{CF}$ = 4.0 Hz), 94.13 (d, $^3J_{CF}$ = 4.0 Hz). LC−MS *m*/*z* 202 (MH^+), 224 ([M + Na]$^+$). Calcd for $C_8H_6F_3N_3$: C, 44.77; H, 3.01; N, 20.89; F, 28.33. Found: C, 44.53; H, 2.96; N, 20.63; F, 28.12. Sn = 34 ppm.

5-Bromo-3-(trifluoromethyl)benzene-1,2-diamine (5). Prepared in the same manner as for **1.** Starting from 4-bromo-2-nitro-6-(trifluoromethyl)aniline (**15**, 10.0 g, 3.44 mmol), compound **5** (7.95 g) was obtained in 97% isolated yield with 99.0 HPLC area% purity as an orange solid. HPLC retention time = 4.75 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.51 (br s, 2 H, NH_2), 3.92 (br s, 2 H, NH_2), 6.98 (d, J = 1.8 Hz, 1 H, H_6), 7.14 (d, J = 1.8 Hz, 1 H, H_4). LC−MS *m*/*z* 255 (M^+), 257 ($M + 2)^+$. Calcd for $C_7H_6BrF_3N_2$: C, 32.97; H, 2.37; Br, 31.33; F, 22.35; N, 10.98. Found: C, 32.61; H, 2.11; Br, 31.46; F, 22.0; N, 10.73.

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