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A convenient synthesis of 4-alkoxy- and 4-hydroxy-2,6-difluoroanilines

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Abstract—Two independent synthetic pathways for the preparation of 4-methoxy, 4-benzyloxy and 4-hydroxy-2,6-difluoroanilines, versatile building blocks in medicinal chemistry, based on diazonium coupling or Curtius-type rearrangements are presented.

Fluorinated compounds play a major role in drug discovery, as the bioisosteric replacement of hydrogen by fluorine has an effect on electronic, lipophilic and steric parameters, which can critically influence the pharmacodynamic and pharmacokinetic properties of drugs.[1] Most importantly, fluoro derivatives are more resistant to metabolic degradation than their hydrogen counterparts. On the other hand, *ortho* substituents on aromatic rings have been recognized as conferring important properties on the molecules that contain them. In conformationally restricted systems, they are able to freeze the conformation, which leads to optimal target interaction. Moreover, it has been shown that reduced molecular flexibility is an important parameter to achieve good oral bioavailability.[2]

Within one of our drug discovery programs, we were confronted with the need to synthesize 4-hydroxy-2,6-difluoroaniline and several 4-alkoxy-2,6-difluoroanilines as building blocks (Fig. 1). Literature reported methods

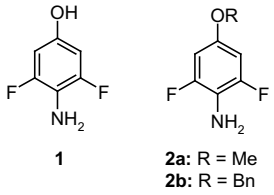
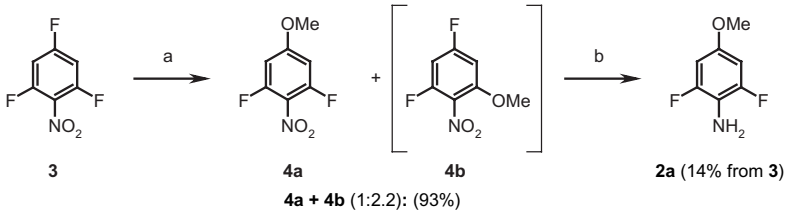


Figure 1.

for **2a** were not adequate for multigram synthesis,[3] while the synthesis of **1** and **2b** had not been previously described.[4] We herein describe convenient procedures for the synthesis of these compounds in multigram scale and with good overall yields.

The synthesis of **2a** described in the literature[3] (Scheme 1) relies on the nucleophilic attack of sodium methanoate on 2,4,6-trifluoronitrobenzene **3**. The drawback of this



Scheme 1. Reagents and conditions: (a) NaOMe/MeOH, rt, 24 h; (b) H_2 (1 atm), Pd/C (10%), MeOH, rt, 12 h.

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method is the lack of regioselectivity: an inseparable 1:2.2 mixture of the *para* and *ortho* substituted products **4a** and **4b** is obtained. Separation can only be achieved after selective demethylation of the *ortho* methoxy with boron tribromide. After reduction, the desired aniline **2a** is obtained in less than 20% overall yield.

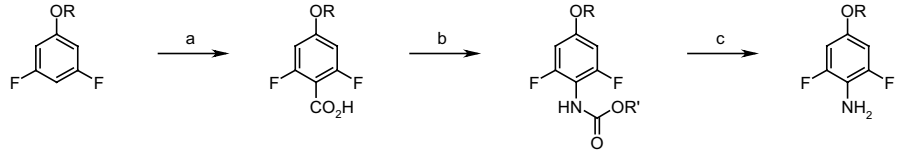
In our hands, all efforts to improve the regioselectivity by using different alcohols or bases failed. We found that after reduction of the difluoromethoxynitrobenzene regioisomeric mixture with hydrogen over palladium/carbon to the corresponding difluoromethoxyanilines, these could be separated into both regioisomers: the overall yield was 14% but the method was still limited by the large amount of undesired isomer isolated in the process (Scheme 1).

We were interested in an alternative approach leading to this versatile reagent. It should be highly effective and applicable to large-scale synthesis forming the desired regioisomer exclusively. It is well known that fluoroarenes undergo smooth *ortho* metallation when they are treated with organolithium reagents. A second electronegative substituent accelerates the deprotonation considerably, and in the case of 1,3-difluorobenzene the substrate is acidic enough to react smoothly with *n*-butyllithium forming solely the 2-lithiated derivative.[5] The resulting organolithium compounds are multipurpose reagents, and for example the almost quantitative conversion of 3,5-difluoroanisole into 2,6-difluoro-4-methoxybenzoic acid after successive treatment with *n*-butyllithium and carbon dioxide has been described.[6] Since the degradation of 2,6-difluorobenzoic acid and analogues into the corresponding anilines using the *Schmidt* or *Curtius* rearrangement has been reported, we intended to apply this pathway to synthesize the desired 2,6-difluoro-4-alkoxyaniline.

Starting from 3,5-difluoroanisole,[7] lithiation with *n*-butyllithium in THF at −78 °C and treatment with solid or gaseous carbon dioxide smoothly gave the desired product **6a** in 81% yield and with complete regioselectivity (Scheme 2).[8]

The degradation reaction of a carboxylic acid to the corresponding amine with one less carbon unit is linked with the names of *Hofmann*, *Curtius*, *Schmidt* and *Lossen*, respectively, depending on the nature of the intermediate species.[9] The direct conversion of the carboxylic acid into the amine, the so-called *Schmidt* reaction,[10] has been reported for 2,6-difluorobenzoic acid using sodium azide in sulfuric acid.[11] Applying this methodology we obtained the desired aniline in low yield accompanied by the 1,4-diamino compound. Using the same reagents diluted in chloroform[12] the reaction resulted in decomposition of the components. In cases where the acyl azide is isolated prior to its thermal rearrangement to yield an isocyanate the reaction is known as the *Curtius* rearrangement.[13] After generation of the acyl chloride with thionyl chloride, reaction with sodium azide, thermal rearrangement and treatment with water, we obtained the desired aniline in about 39% yield.[14] Using trimethylsilyl azide as azide source did not show a positive effect. A further opportunity was the facile generation of the intermediate acyl azide directly from the acid by using diphenyl phosphorylazide (DPPA).[15] However, using this convenient method the yield was also low, probably due to problems during the purification of the polar and oxidizable product. On the other hand, when treated with alcohols instead of water, the intermediate isocyanates of the *Claisen*- or *Schmidt*-rearrangements form carbamates, which can be purified more easily than the unprotected *p*-alkoxyaniline. Therefore we generated the *t*-butyl carbamate[16] **7a** with *t*-butanol and—more rapidly—the ethyl-carbamate **7b** with ethanol in 47% and 68% yields starting from the acid (Scheme 2).[17] From the carbamates, which can be stored without decomposition at room temperature in air, the aniline can be liberated almost quantitatively by treatment with a base.

In the course of our investigations we were also interested in analogues bearing a protecting group on the oxygen, which can be removed under milder conditions than the methyl ether in **2a**, as for example the benzyloxy ether **2b**. Starting from 3,5-difluorophenol we generated the benzyl ether **5b** in 89% yield.[18] The lithiation/carboxylation sequence gave access to the desired carboxylic acid **6b** (42% yield),[19] which was converted into the ethyl carbamate **7c** using DPPA in almost quantitative yield.[20] From this compound the aniline **2b** could be obtained under basic conditions (86%).[21] Additionally we were interested in a carbamate that liberates the aniline in an acidic environment. Consequently we used



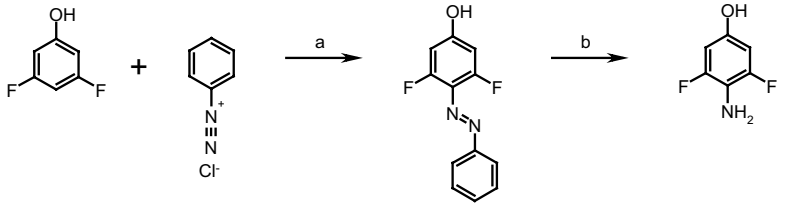
5a: R = Me
5b: R = Bn

6a: R = Me (81%)
6b: R = Bn (42%)

7a: R = Me, R' = tBu (47%)
7b: R = Me, R' = Et (68%)
7c: R = Bn, R' = Et (95%)
7d: R = Bn, R' = TMSE (75%)

2a: R = Me (39% from **6a**)
2b: R = Bn (86%)

Scheme 2. Reagents and conditions: (a) 1. *n*BuLi, THF, −78 °C, 2. CO_2, −78 °C to rt; (b) 1. DPPA, NEt_3, dioxane, 2. alcohol; (c) KOH, ethanol, reflux.



Scheme 3. Reagents and conditions: (a) 2N NaOH, 5–10 °C; (b) Pd/C (10%), H_2 (1 atm), ethanol, rt.

2-trimethylsilanyl ethanol as the alcohol component[22] and obtained the desired carbamate **7d** in 75% yield (Scheme 2).[23]

A different approach was chosen to synthesize 4-hydroxy-2,6-difluoroaniline **1** (Scheme 3). We envisaged 3,5-difluorophenol as a suitable aromatic substrate for the coupling with diazonium compounds, a reaction known to be *para*-selective with respect to the electron-donor substituent.[24] Indeed, coupling of 3,5-difluorophenol with freshly prepared phenyl diazonium salt (generated by diazotization of aniline with nitrous acid) under alkaline conditions regioselectively resulted in the azo compound **8**,[25] which could be cleaved to give **1** by hydrogenation in good yield (73%).[26] Aimed at 4-hydroxy-2,6-difluoroaniline **1**, this sequence in terms of length and yield is obviously superior to alternative approaches applying the methodologies shown in Schemes 1 and 2, respectively, as in these cases a final ether cleavage step should be incorporated. However, the coupling with diazonium ions demands substrates with strong electron-donor substituents and is therefore limited to phenols and is not applicable for anisoles or other alkoxy substituted aryls.

In conclusion, we have developed two independent synthetic pathways for the preparation of 4-methoxy, 4-benzyloxy and 4-hydroxy-2,6-difluoroanilines, which achieve the desired compounds in good overall yields and have proven to be adequate for multigram scale.

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7. 3,5-Difluoroanisole **5a**: To a solution of 25.0 g (192 mmol) 3,5-difluorophenol in 200 mL acetone were added 45.2 g (327 mmol) potassium carbonate and 20 mL (290 mmol) methyl iodide. The mixture was warmed to 40 °C for 5 h, then filtered and evaporated. Diethyl ether was added to the residue and the solution was washed twice with water. The organic phase was dried over sodium sulfate and the solvent removed to yield 27.7 g (100%) of the desired difluoroanisole. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 3.78$ (s, 3H), 6.36–6.46 (m, 3H).
8. 2,6-Difluoro-4-methoxybenzoic acid **6a**: 28.0 g (194 mmol) 3,5-difluoroanisole in 500 mL THF were cooled to −78 °C and 77.7 mL of a 2.5 M solution of *n*-butyllithium in hexane (194 mmol) was added. After 45 min dry ice was added. After 2 h the reaction was warmed to rt. The mixture was evaporated and the residue dissolved in water. After addition of 30 mL of a 2 M NaOH solution the aqueous phase was extracted twice with ether, then acidified with 100 mL 4 M HCl and extracted with diethyl ether (6×150 mL). The combined organic phases were dried over sodium sulfate and evaporated to yield 29.6 g (81%) of the desired benzoic acid. ^{1}H NMR (300 MHz, DMSO-d_6) $\delta = 3.83$ (s, 3H), 6.81 (m, 2H), 13.4 (br s, 1H); MS (DCI): m/z 206 $[M+NH_4]^+$.
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14. 2,6-Difluoro-4-methoxyphenylamine **2a**: 2.00 g (10.6 mmol) of **6a** was dissolved in 16 mL thionyl chloride, one drop of DMF was added and the mixture was heated to reflux for 2 h. The crude mixture was evaporated to dryness and the residue was dissolved in 5 mL acetone. A solution of 970 mg (14.9 mmol) sodium azide in 2 mL water was added dropwise at rt. After 30 min, water (10 mL) was added and the solution was extracted with toluene (50 mL). The organic layer was dried over sodium sulfate and heated to reflux for 30 min. Then 10 mL of a 45% sodium hydroxide solution was added and the mixture was heated for a further 30 min. The organic layer was separated, dried over sodium sulfate and evaporated. The residue was purified by column chromatography (dichloromethane) to yield 660 mg (39%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 3.39$ (br s, 2H), 3.72 (s, 3H), 6.45 (m, 2H); LC-MS: m/z 160 $[M+H]^+$.
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17. (2,6-Difluoro-4-methoxyphenyl)carbamic acid *tert*-butyl ester **7a**: 3.00 g (15.9 mmol) of **6a** was heated in 20 mL thionyl chloride and two drops DMF at reflux for 2 h. The excess of reagent was removed in vacuo and the residue was dissolved in 10 mL acetone and cooled to 0 °C. A solution of 1.45 g (22.3 mmol) sodium azide in water (3 mL) was added dropwise. A white solid precipitated and was collected after addition of water by suction. The residue was dissolved in 50 mL toluene, extracted with brine and dried over sodium sulfate. After filtration, the toluene solution was heated to 100 °C for 1 h. Then, at 70 °C, 3.0 mL (32 mmol) of *t*-butanol was added and the mixture was heated at 70 °C for 36 h. The mixture was filtered and evaporated to yield 1.94 g (47%) of the desired compound. ^{1}H NMR (200 MHz, DMSO-d_6) $\delta = 1.41$ (s, 9H), 3.77 (s, 3H), 6.76 (m, 2H), 8.50 (br s, 1H); MS (DCI): m/z 277 $[M+NH_4]^+$. (2,6-Difluoro-4-methoxyphenyl)carbamic acid ethyl ester **7b**: 509 mg (2.71 mmol) of the benzoic acid **6a** was dissolved in 8 mL dioxane. DPPA 0.70 mL (3.25 mmol) and 0.55 mL (400 mmol) triethylamine were added and the mixture was stirred at rt for 30 min. 2.0 mL (35 mmol) methanol was added and the reaction was heated to reflux for 2 h. After evaporation the residue was dissolved in dichloromethane. The solution was washed with 5% citric acid, 5% sodium bicarbonate solution and brine, then dried over sodium sulfate and evaporated. The residue was treated with cyclohexane and white crystals were collected by suction. Yield 422 mg (68%). ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 1.29$ (t, $J = 7.1$ Hz, 3H), 3.78 (s, 3H), 4.21 (q, $J = 7.1$ Hz, 2H), 5.81 (br s, 1H), 6.50 (m, 2H); MS (ESI): m/z 232 $[M+H]^+$.
18. 1-Benzyloxy-3,5-difluorobenzene **5b**: To a solution of 10.0 g (76.9 mmol) of 3,5-difluorophenol in 100 mL ethanol, 31.0 mL of a 10% aqueous sodium hydroxide solution and subsequently 14.6 g (115 mmol) of benzyl chloride were added dropwise. Afterwards the mixture was heated to 100 °C for 1 h. The ethanol was removed and the residue treated with ethyl acetate/water. The organic phase was washed twice with water, dried over sodium sulfate and evaporated to yield 15.1 g (89%) of the desired product. ^{1}H NMR (300 MHz, DMSO-d_6) $\delta = 5.13$ (s, 2H), 6.74–6.85 (m, 3H), 7.30–7.47 (m, 5H).
19. 4-Benzyloxy-2,6-difluorobenzoic acid **6b**: The compound was synthesized analogously to **6a** in 42% yield. ^{1}H NMR (200 MHz, DMSO-d_6) $\delta = 5.19$ (s, 2H), 6.92 (m, 2H), 7.32–7.49 (m, 5H), 13.5 (br s, 1H); MS (DCI): m/z 282 $[M+NH_4]^+$.
20. (4-Benzyloxy-2,6-difluorophenyl)carbamic acid ethyl ester **7c**: The compound was synthesized from **6b** analogously to **7b** in 95% yield. ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 1.29$ (t, $J = 7.1$ Hz, 3H), 4.21 (q, $J = 7.1$ Hz, 2H), 5.02 (s, 2H), 5.83 (br s, 1H), 5.57 (m, 2H), 7.34–7.42 (m, 5H); MS (ESI): m/z 308 $[M+H]^+$.
21. 4-Benzyloxy-2,6-difluorophenylamine **2b**: 2.59 g (8.43 mmol) of **7c** was dissolved in 40 mL ethanol and 4.73 g (84.3 mmol) of potassium hydroxide was added. The mixture was heated to reflux for 18 h, evaporated, dissolved in water and extracted with diethyl ether (3×). The combined organic phases were dried over sodium sulfate and evaporated. The residue was purified by column chromatography (dichloromethane/petroleum ether 2:1) to yield 1.71 g (86%) of the desired aniline as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 3.40$ (br s, 2H), 4.95 (s, 2H), 6.52 (m, 2H), 7.30–7.42 (m, 5H); LC-MS (ESI pos.): m/z 236 $[M+H]^+$.
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23. (4-Benzyloxy-2,6-difluorophenyl)carbamic acid 2-trimethylsilanylethyl ester **7d**: The compound was synthesized from **6b** analogously to **7b** in 75% yield. ^{1}H NMR (300 MHz, DMSO-d_6) $\delta = 0.00$ (s, 9H), 0.94 (dd, $J = 8.2$, 7.7 Hz, 2H), 4.11 (dd, $J = 8.2$, 7.7 Hz, 2H), 5.11 (s, 2H), 6.85 (m, 2H), 7.32–7.45 (m, 5H), 8.68 (br s, 1H); MS (ESI): m/z 425 $[M+2Na]^+$.
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25. 3,5-Difluoro-4-(phenyldiazenyl)phenol **8**: 108 g (1.16 mol) of aniline was added to 500 g of hydrochloric acid (27%) at 0 °C. A solution of 95.2 g (1.38 mol) sodium nitrite in 280 mL of water was added dropwise and the temperature was kept below 5 °C. The precipitate was dissolved by addition of 200 mL hydrochloric acid (37%) and the resulting solution was stirred for 1 h at 0 °C. Excess sodium nitrite was quenched by addition of amidosulfuric acid. 101 g (0.77 mol) of 3,5-difluorophenol was dissolved in aqueous sodium hydroxide, prepared from 183 g (4.57 mol) sodium hydroxide and water (2.2 L). The solution was cooled to 5 °C and a freshly prepared solution of the diazonium salt was added dropwise. During addition the pH was controlled to remain strongly alkaline. The reaction mixture was stirred for 1 h at room temperature. The pH was adjusted to 4 by addition of 2 N hydrochloric acid. The precipitate was filtered and washed with water to yield 182 g (79%; purity approximately 80% by GC analysis) of the desired azo compound as an orange-brown solid. MS-EI: m/z 234 $[M]^+$. **Caution**! Solid diazonium salts are heat and shock sensitive towards explosion!
26. 4-Amino-3,5-difluorophenol **1**: 9.87 g (42 mmol) of 3,5-difluoro-4-(phenyldiazenyl)phenol was dissolved in ethanol. After addition of 100 mg of palladium on carbon (10%) the mixture was stirred under a hydrogen atmosphere at rt for 12 h. The catalyst was removed by filtration, the solvent evaporated and the residue was purified by column chromatography on silica gel (dichloromethane: ethyl acetate 1:1). Recrystallization from cyclohexane gave 4.5 g (73%) of the desired aminophenol as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) $\delta = 4.33$ (br s, 2H), 6.34 (m, 2H), 9.20 (s, 1H); GC–MS (TOF MS CI^+): m/z 146 $[M+H]^+$.