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An Efficient, Direct Bis-ortho-chlorination of 4-(Difluoromethoxy)-aniline and Its Application to the Synthesis of BMS-665053, a Potent and Selective Pyrazinone-Containing Corticotropin-Releasing Factor-1 Receptor Antagonist

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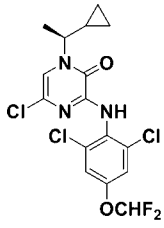
ABSTRACT: An efficient scale-up synthesis of (*S*)-5-chloro-1-(1-cyclopropylethyl)-3-(2,6-dichloro-4-(difluoromethoxy)-phenylamino)-pyrazin-2(1*H*)-one, **1** (**BMS-665053**), is described. This new process features a one-step direct bis-ortho-chlorination of 4-(difluoromethoxy)aniline with HCl and H_2O_2, and a palladium-catalyzed coupling of 2,6-dichloro-4-(difluoromethoxy)aniline **2** and (*S*)-3,5-dichloro-1-(1-cyclopropylethyl)pyrazin-2(1*H*)-one **3**. The process was applied to the preparation of batches of **1** for preclinical toxicology studies.

INTRODUCTION

Novel pharmacological approaches leading to the development of improved treatments for stress-related diseases, such as anxiety and depression, are of significant interest to the pharmaceutical industry. Despite the availability of currently marketed anxiolytic and antidepressant drugs, issues with currently available therapies, such as a delayed onset of action, undesirable side effects, and a lack of efficacy in subgroups of patients, stimulate continued interest in novel treatments. One such potential novel method of treatment for stress-related disorders includes corticotropin-releasing factor-1 (CRF_1) receptor antagonists.[1−6]

During our discovery program,[7] (*S*)-5-chloro-1-(1-cyclopropylethyl)-3-(2,6-dichloro-4-(difluoromethoxy)-phenylamino)-pyrazin-2(1*H*)-one, **1** (**BMS-665053**), Figure 1,



1 (BMS-665053)

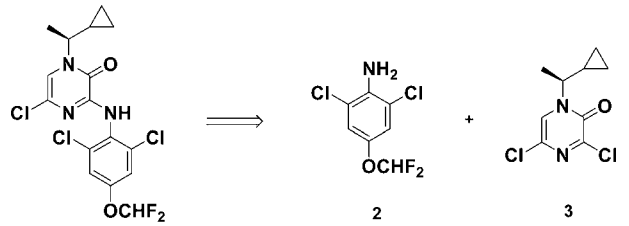
Figure 1. (*S*)-5-Chloro-1-(1-cyclopropylethyl)-3-(2,6-dichloro-4-(difluoromethoxy)phenylamino)-pyrazin-2(1*H*)-one, **1**.

was identified as a novel pyrazinone-containing CRF_1 receptor antagonist.[7] Compound **1** is a high-affinity CRF_1 receptor antagonist with an IC_{50} of 1.0 nM and is a potent inhibitor of CRF-stimulated cyclic adenosine monophosphate (cAMP) production in human Y-79 retinoblastoma cells (IC_{50} = 4.9 nM). It was selected as our lead candidate for further evaluation. Herein, we describe a new and efficient scale-up synthesis of **1** to support preclinical toxicology studies.

RESULTS AND DISCUSSION

Original Synthesis of 2,6-Dichloro-4-(difluoromethoxy)aniline, 2. The preparation of (*S*)-5-chloro-1-(1-cyclopropylethyl)-3-(2,6-dichloro-4-(difluoromethoxy)-phenylamino)-pyrazin-2(1*H*)-one, **1**, is a convergent synthesis developed by our medicinal chemists. It requires two advanced intermediates, 2,6-dichloro-4-(difluoromethoxy)aniline, **2**, and (*S*)-3,5-dichloro-1-(1-cyclopropylethyl)pyrazin-2(1*H*)-one, **3** (Scheme 1).[7]

Scheme 1. Convergent synthesis of 1



1 (BMS-665053) 2 3

In the original synthesis, aniline intermediate **2** was prepared from commercially available 3,5-dichlorophenol **4** (Scheme 2).[7] Nitration of **2** with sodium nitrite in H_2SO_4 and water at reflux afforded a mixture of 2- and 4-nitro regiomeric products **5** and **6** in a 2:1 ratio, from which the desired 4-nitro isomer **6** was isolated by selective crystallization in 25% yield. Reaction of **6** with methyl difluorochloroacetate in DMF in the presence of K_2CO_3 gave 1,3-dichloro-5-(difluoromethoxy)-2-nitrobenzene, **7**, in 72% yield. Hydrogenation of **7** with palladium over charcoal in methanol provided **2** in 47% yield after chromatographic separation.

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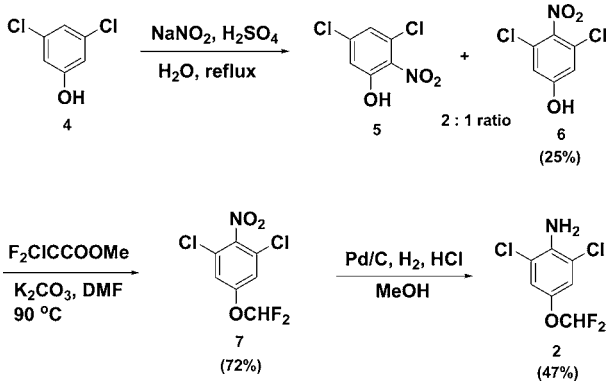
Scheme 2. Original synthesis of 2,6-dichloro-4-(difluoromethoxy)aniline intermediate, 2



The original synthesis of intermediate **2** was amenable for small-scale preparation. However, there were several issues pertaining to scale-up. First, the nitration at an elevated temperature was a safety concern, and the yield was low due to poor regioselectivity. Second, while the difluoromethylation of **6** gave satisfactory yield of the desired product **7**, the possibility exists for a potential competitive side reaction (polymerization through nucleophilic aromatic substitution, i.e., phenolate displacing chlorines which are activated by the *o*-nitro group)[8] under the reaction conditions especially during scale-up. Third, des-halogenation occurred in the hydrogenation step, and tedious column purification was required resulting in the low isolated yield. Thus, a more efficient alternative scale-up synthesis of 2,6-dichloro-4-(difluoromethoxy)aniline **2** was desired.

Alternative Synthesis of 2,6-Dichloro-4-(difluoromethoxy)aniline, 2. Our focus in the development of an alternative synthesis of **2** was on the direct bis-ortho-chlorination of 4-(difluoromethoxy)aniline, **8**, which is commercially available (Table 1). The direct ortho chlorination

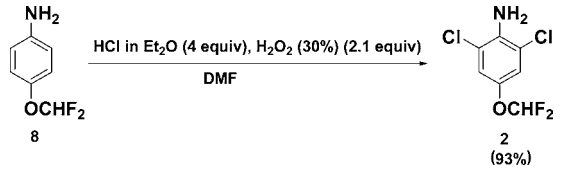
Table 1. HCl source and solvent screen for the direct bis-ortho-chlorination of 4-(difluoromethoxy)aniline, 8

entry	HCl source	solvent	temperature	time (h)	yield (%)
1	1 N in water	MeOH	rt to reflux	16	no product
2	6 N in water	MeOH	rt to reflux	16	trace
3	12 N in water	MeOH	0 °C to reflux	24	11
4	12 N in water	MeOH	rt to reflux	16	22
5	2 N in Et_2O	MeOH	rt to 38 °C	8	43
6	2 N in Et_2O	DMF	rt to 38 °C	2	93

of aniline derivatives is a well-known reaction. A number of chlorination reagents or systems such as Cl_2,[9] HCl/H_2O_2,[10] $ZnCl_2/NaBiO_3$,[11] $NaOCl/FeCl_3$,[12] and NCS[13] have been utilized for this transformation. Despite the fact that there was no specific method reported for the direct chlorination of *p*-alkoxyanilines, we were attracted by the potential efficiency of this new transformation (one step vs three in the original synthesis). We were particularly interested in using the combination of HCl/H_2O_2 for the direct bis-ortho-chlorination of 4-(difluoromethoxy)aniline, **8**, because both HCl and H_2O_2 are readily available and environmentally benign.

Thus, **8** was treated with 4 equiv of 1 N aqueous HCl at room temperature followed by addition of 30% H_2O_2 in methanol, and the mixture was heated at reflux overnight, the most frequently used conditions for *o*-chlorination of anilines. Surprisingly, no product was detected by LC/MS. The starting material, **8**, mostly decomposed to a complex mixture (Table 1, entry 1). The use of 6 N aqueous HCl resulted in a trace amount of product (Table 1, entry 2). Further increasing the HCl concentration to 12 N and adding the HCl solution at 0 °C (to minimize the escape of HCl gas) afforded the isolated product **2** in 11% yield (Table 1, entry 3). Addition of the concentrated HCl and 30% H_2O_2 at rt followed by refluxing for 16 h gave **2** in 22% isolated yield (Table 1, entry 4). From the above experiments, we observed the following important phenomena: (1) a higher concentration of HCl gave a better yield; (2) the reaction was slightly exothermic and occurred above room temperature; (3) both the addition of HCl and H_2O_2 were exothermic, and prolonged aging above 50 °C resulted in excessive oxidation of the aniline **8**. Disappointed by these results, we decided to use a different source of HCl for the reaction. Thus, the commercially available 2 N HCl in ether instead of aqueous HCl was used in the reaction. To our delight, the reaction was much cleaner, and the desired product dichloroaniline **2** was isolated in 43% yield (Table 1, entry 5). Next, we decided to explore any potential solvent effects on this reaction. When DMF was used as the solvent instead of methanol, the reaction was very clean and was completed in less than 2 h. The product 2,6-dichloro-4-(difluoromethoxy)-aniline, **2**, was isolated in 93% yield after extractive workup and crystallization from hexane (Scheme 3 and Table 1, entry 6).

Scheme 3. New improved synthesis of 2,6-dichloro-4-(difluoromethoxy)aniline, 2



Synthesis of (*S*)-3,5-Dichloro-1-(1-cyclopropylethyl)-pyrazin-2(1*H*)-one, 3, and Final Coupling of 2 and 3. With the one-step synthesis of intermediate **2** in place, we turned our focus to the synthesis of intermediate **3** and the final coupling of **2** with **3** (Scheme 4). It was reported that substituted 3,5-dichloro-2(1*H*)-pyrazinones were prepared by treatment of hydrochlorides of 2-*sec*-aminoalkanenitriles with oxalyl chloride in *o*-dichlorobenzene at 80−100 °C.[14] The 2-*sec*-aminoalkanenitriles were obtained by Strecker synthesis. However, this method has some scale up issues, such as the use of potassium cyanide, the high boiling point and hazardous solvent *o*-dichlorobenzene and column chromatography for purification. We decided to attempt the nucleophilic substitution of chloroacetonitrile **10** with commercially available (*S*)-1-cyclopropylethylamine hydrochloride, **9**, to give intermediate **11** and subsequently to optimize the reaction conditions of **11** to **3** (Scheme 4).

Reaction of **9** with **10** in the presence of potassium iodide and potassium carbonate in acetonitrile at 50 °C for 16 h afforded the free base of **11** as an oil after aqueous workup which contained ~5% dialkylated product based on ^1H NMR. The crude oily free base was treated with 2 N HCl in ether to give pure (*S*)-2-(1-cyclopropylethylamino)acetonitrile hydrochloride, **11**, as a white crystalline solid in 91% yield. The reaction of **11** with oxalyl chloride was carried out in toluene at 55 °C for

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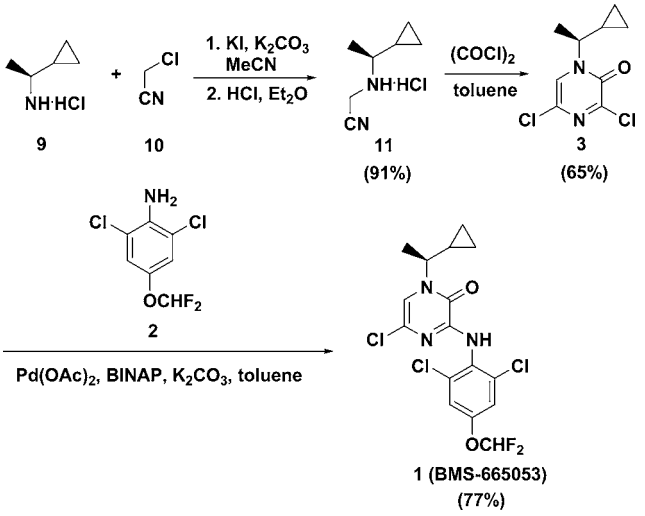
Scheme 4. Improved synthesis of 11 and (*S*)-5-chloro-1-(1-cyclopropylethyl)-3-[2,6-dichloro-4-(difluoromethoxy)-phenylamino]-pyrazin-2(1*H*)-one, 1 (BMS-665053)



18 h. After extractive workup, the crude product was purified by crystallization from 70% ethanol to give the product **3** in 65% yield with 98% HPLC purity.

With substantial amounts of key intermediates **2** and **3** in hand, screening was performed to determine the optimal coupling conditions of **2** and **3** (Table 2). In the absence of a base, heating of **2** and **3** at 120 °C for 1.5 h did not provide any product (Table 2, entry 1). Using excess amount of K_2CO_3 as the base, the reaction was carried out in toluene at reflux for 16 h, however, only a trace amount of the product was detected by LC/MS (Table 2, entry 2). Treatment of compound **2** with NaHMDS in THF and subsequent reaction with **3** for 16 h only yielded 50% of the desired API (Table 2, entry 3). Using $Pd(OAc)_2$ and BINAP as the catalyst and Cs_2CO_3 as the base, the reaction in toluene at reflux for 16 h afforded the product **1** in 28% yield. By switching the base to K_2CO_3, the reaction went to completion (Table 2, entry 5). After workup, trituration with heptane and crystallization from EtOH, the final product (*S*)-5-chloro-1-(1-cyclopropylethyl)-3-[2,6-dichloro-4-(difluoromethoxy)phenylamino]-pyrazin-2(1*H*)-one, **1** (**BMS-665053**), was isolated in 76% yield with 99.5% HPLC purity.

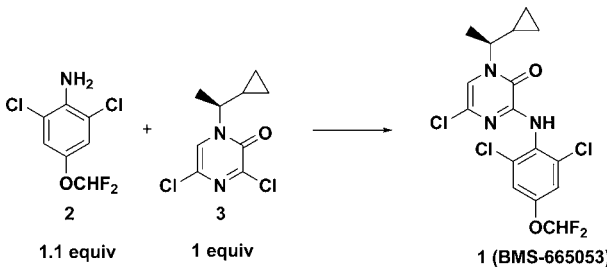
In conclusion, an efficient and direct bis-ortho-chlorination of 4-(difluoromethoxy)aniline, **8**, with HCl and H_2O_2 was developed. Subsequent palladium-catalyzed coupling of 2,6-dichloro-4-(difluoromethoxy)aniline, **2**, with (*S*)-3,5-dichloro-1-(1-cyclopropylethyl)pyrazin-2(1*H*)-one, **3**, was found to be superior to other base-mediated reaction conditions to give **1**. This process was successfully applied to the larger-scale preparation of CRF1 receptor antagonist, **BMS-665053**.

EXPERIMENTAL SECTION

All reagents were obtained from Aldrich Chemical Co. and used without further purification unless otherwise stated. All reactions were performed under a nitrogen atmosphere. All glassware was dried and purged with nitrogen or argon before use. All reactions were monitored by Shimadzu LC/MS system using the following method: Phenomenex C18 column 10 μm 4.6 mm × 50 mm. Solvent: A = 10% methanol/90% water with 0.1% TFA; B = 90% methanol/10% water with 0.1% TFA. Gradient: 0−100% B over 4 min. Flow: 4 mL/min, wavelength: 220 nm. HPLC analyses were performed using a Shimadzu system (model SPD 10AV). All ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 300 or 400 MHz spectrometer using DMSO-d_6 or $CDCl_3$ as the solvents.

2,6-Dichloro-4-(difluoromethoxy)aniline, 2. 4-(Difluoromethoxy)aniline, **8** (63.7 g, 0.4 mol), was dissolved in dry DMF (800 mL). To the solution was added a solution of 2 N HCl in diethyl ether (800 mL, 1.6 mol) over a period of 0.5 h (rt to ∼32 °C). After cooling to rt, a solution of 30% H_2O_2 (95.2 mL, 0.84 mol) was added dropwise over a period of 1 h (temperature rose to 38 °C). After stirring at ∼38 °C for 2 h, the reaction mixture was cooled to rt and diluted with water (2 L). The mixture was then extracted with heptane (2 × 1 L). The combined organic extracts were washed with brine (2 L) and concentrated in vacuo (∼30 mmHg) at 50 °C to give the crude product (92.0 g) which was crystallized from heptane (200 mL) at −20 °C to afford 85.0 g of 2,6-dichloro-4-(difluoromethoxy)aniline, **2**, as an off-white solid (98% HPLC area purity, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (s, 2H), 6.36 (t, J = 72.0 Hz, 1H), 4.40 (s br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 138.5, 120.8, 119.4, 115.8 (t, J = 260.4 Hz). LRMS (ESI) m/e 225.9 [(M − H)$^-$, calcd for $C_7H_4NOCl_2F_2$ 226.0]. (*Authors urge readers to follow MSDS sheet regarding safe handling of 30% peroxide as well as related waste stream.*)

Table 2. Reagent and condition screening for coupling 2 and 3



entry	reagent and condition	isolated yield % (conversion %)
1	NMP, 120 °C, 1.5 h	no product
2	K_2CO_3 (6.7 equiv), toluene, reflux, 16 h	trace amount
3	NaHMDS (2 equiv), THF, rt, 16 h	50 (57)
4	3 mol % $Pd(OAc)_2$, 3 mol % BINAP, Cs_2CO_3 (6.7 equiv), toluene, reflux, 16 h	28 (40)
5	3 mol % $Pd(OAc)_2$, 3 mol % BINAP, K_2CO_3 (6.7 equiv), toluene, reflux, 16 h	76 (100)

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(*S*)-2-(1-Cyclopropylethylamino)acetonitrile Hydrochloride, 11. To a suspension of (*S*)-1-cyclopropylethylamine hydrochloride, **9** (41.4 g, 340.2 mmol), in anhydrous acetonitrile (900 mL) at room temperature was added potassium carbonate (141.3 g, 1024 mmol), potassium iodide (62.4 g, 376 mmol), and chloroacetonitrile, **10** (21.6 mL, 341.3 mmol). The reaction mixture was heated at 50 °C for 16 h with vigorous stirring. The resulting mixture was then cooled to room temperature and was filtered through a pad of Celite with acetonitrile rinsing (100 mL). The filtrate was concentrated in vacuo (~30 mmHg) at 50 °C, and the residue was partitioned between CH_2Cl_2 (1 L) and water (1 L). The organic phase was separated, washed with water (1 L) and brine (1 L), dried over Na_2SO_4, filtered, and concentrated in vacuo (~30 mmHg) at 40 °C to give a brown oil. The oil was dispersed in diethyl ether (900 mL), and the solution was treated with 2 N HCl in ether (300 mL). The resulting suspension was cooled to 10 °C and then filtered, and the filter cake was rinsed with cold ether (80 mL). After drying by house vacuum for 2 h, the product (*S*)-2-(1-cyclopropylethylamino)acetonitrile hydrochloride, **11** (49.6 g, 91% yield), was collected as an off-white solid. Mp 115−116.1 °C; $[\alpha]^{25}_D$ −25.0 (*c* 0.779, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (s br, 2H), 4.14 (s, 2H), 2.41−2.36 (m, 1H), 1.25 (d, *J* = 6.8 Hz, 3H), 0.91−0.82 (m, 1H), 0.62−0.55 (m, 1H), 0.55−0.41 (m, 2H), 0.24−0.18 (m, 1H). LRMS (ESI) *m*/*e* 125.0 [(M + H)$^+$, calcd for $C_7H_{13}N_2$ 125.1]. Anal. Calcd for $C_7H_{13}ClN_2$: C, 52.34; H, 8.16; N, 17.44. Found: C, 52.03; H, 8.24; N, 17.16.

(*S*)-3,5-Dichloro-1-(1-cyclopropylethyl)pyrazin-2(1*H*)-one, 3. (*S*)-2-(1-Cyclopropylethyl-amino)acetonitrile hydrochloride (**11**) (49.5 g, 309 mmol) was suspended in dry toluene (1.5 L). The mixture was cooled to 5 °C with an ice bath. Oxalyl chloride (133.8 mL, 1542 mmol) was added. The reaction mixture was then heated to 55 °C for 18 h. After cooling to rt, the reaction mixture was concentrated in vacuo (~30 mmHg) at 60 °C to 200 mL. The mixture was then added slowly to a cold (5 °C) saturated solution of KH_2PO_4 (1.0 L). The mixture was diluted with CH_2Cl_2 (1 L) and then stirred for 20 min. The organic phase was separated and concentrated in vacuo (~30 mmHg) at 40 °C. The yellow residue was crystallized from 70% aqueous ethanol (60 to 0 °C) to afford 46.5 g of the product (*S*)-3,5-dichloro-1-(1-cyclopropylethyl)pyrazin-2(1*H*)-one (**3**) as a white solid (65% yield, 98% HPLC area purity). $[\alpha]^{25}_D$ +27.6 (*c* 0.476, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (s, 1H), 4.26−4.20 (m, 1H), 1.46 (d, *J* = 6.6 Hz, 3H), 1.13−1.06 (m, 1H), 0.85−0.77 (m, 1H), 0.64−0.59 (m, 1H), 0.58−0.50 (m, 1H), 0.39−0.32 (m, 1H). LRMS (APCI) *m*/*e* 233.0 [(M+H)$^+$, calcd for $C_9H_{11}N_2OCl_2$ 233.0].

(*S*)-5-Chloro-1-(1-cyclopropylethyl)-3-[2,6-dichloro-4-(difluoromethoxy)phenylamino]-pyrazin-2(1*H*)-one, 1 (BMS-665053). A mixture of $Pd(OAc)_2$ (0.72 g, 3.21 mmol) and BINAP (2.0 g, 3.21 mmol) in toluene (1 L) was stirred at rt for 10 min. 2,6-Dichloro-4-(difluoromethoxy)aniline, **2** (26.9 g, 118 mmol), (*S*)-3,5-dichloro-1-(1-cyclopropylethyl)pyrazin-2(1*H*)-one, **3** (25.0 g, 107 mmol and K_2CO_3 [100.0 g, 725 mmol]), were added, respectively. The mixture was heated to reflux for 16 h. After cooling to rt, the mixture was filtered through a Celite pad and rinsed with EtOAc (500 mL). The filtrate was washed with brine (2 × 1 L) and then concentrated in vacuo (~30 mmHg) at 50 °C to give the crude product, which was triturated with heptane and then crystallized from EtOH (150 mL, 70 °C to −20 °C) to afford 34.5 g of the product, **1** (**BMS-665053**), as a slightly pink solid (99.5% HPLC area purity, 76% yield). Mp 164−165 °C; $[\alpha]^{25}_D$ +20.2 (*c* 0.353, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.21 (s, 2H), 6.90 (s, 1H), 6.52 (t, *J* = 72.6 Hz, 1H), 4.31−4.25 (m, 1H), 1.44 (d, *J* = 6.7 Hz, 3H), 1.12−1.04 (m, 1H), 0.79−0.73 (m, 1H), 0.61−0.54 (m, 1H), 0.51−0.45 (m, 1H), 0.41−0.35 (m, 1H). HRMS (ESI) *m*/*e* 424.0181 [(M + H)$^+$, calcd for $C_{16}H_{15}N_3O_2Cl_3F_2$ 424.0198].

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