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Process Research for the Synthesis of RWJ-51204, A Novel Anxiolytic Agent

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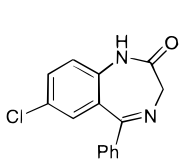
Abstract:

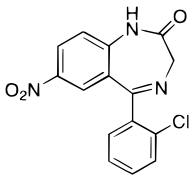
RWJ-51204, the lead compound in our pyrido [1,2-*a*] benzimidazole (PBI) series, was shown to exhibit anxiolytic efficacy in animal models at doses which did not cause central nervous system side effects commonly observed with other anxiolytic agents. To prepare supplies of drug substance for early toxicological and clinical studies, we needed to develop a safe and scaleable synthesis. Our main focus was to improve the last two steps of the process which involved formation of the penultimate carboxamide intermediate followed by alkylation using potentially toxic chloromethyl ethyl ether. Due to safety issues concerning storage and handling of this reagent during the large scale synthesis, we investigated alternate routes to minimize potential exposure risks. The process research carried out for the final steps that led to the safe and cost-effective multi-kilogram synthesis of RWJ-51204 is described herein.

Introduction

Benzodiazepines, such as diazepam and clonazepam, are recognized as very effective drugs for treating anxiety related disorders.[1] However, all of these currently marketed drugs cause unwanted central nervous system (CNS) side effects including motor and memory impairment, sedation, muscle relaxation, and physical dependency. Recently, our Drug Discovery group focused on identifying new therapeutic agents that were as efficacious as the marketed benzodiazepine drugs without the unwanted CNS side effects.

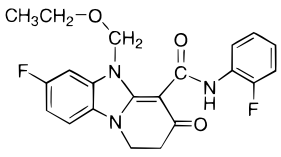


Diazepam



Clonazepam

As a result of this effort, we identified a novel class of compounds collectively referred to as pyrido[1,2-*a*]benzimidazoles (PBIs) which were shown to be active in animal models as anxiolytic agents.[2] In vitro and in vivo data indicate these compounds fit into the class of $GABA_A$ receptor modulators commonly termed as partial agonists. We selected the lead compound in this series, RWJ-51204 (**1**), as a development candidate for several reasons: (1) it is orally active, (2) it possesses a high level of anxiolytic efficacy in animal models, (3) it shows very good in vitro activity ($IC_{50} = 0.3$ nM), and most importantly, (4) the large therapeutic index in animal models and overall profile suggests RWJ-51204 (**1**) might have efficacy in human anxiety-related disorders at doses that should not cause CNS side effects. For complete biological evaluation, we needed to prepare multi-kilogram quantities of drug substance for early development studies. This paper describes some of the process research which led to the large scale, safe, and cost-effective synthesis of highly pure RWJ-51204 (**1**).



RWJ-51204 (**1**)

Initially, we evaluated the medicinal chemistry based synthesis as outlined in Scheme 1. Treatment of commercially available 4-fluoro-2-nitroaniline (**2**) with acrylonitrile[3] in the presence of an excess of Triton B afforded the cyanoethyl derivative **3** in 93% yield. Selective reduction of the nitro group via catalytic hydrogenation and subsequent reaction with ethyl 3-amino-3-ethoxyacrylate hydrochloride (**5**) led to the formation of 1-(2-cyanoethyl)-2-carbethoxymethyl-5-fluorobenzimidazole (**6**) in 75% yield. Ethanolysis of the cyano group in ethanolic HCl gave the diester intermediate **7** which upon treatment with freshly prepared sodium ethoxide in ethanol underwent Dieckman cyclization to afford the pyrido[1,2-*a*]benzimidazole ester **8** in 66% yield for the combined two steps. Reaction with 2-fluoroaniline led to the isolation of penultimate amide intermediate **9** in 58% yield after chromatographic purification. Deprotonation of **9** with NaH in DMF followed by treatment with chloromethyl ethyl ether (CMEE) in the presence of 15-crown-5 afforded crude RWJ-51204 (**1**). The pure product was obtained after column chromatography on silica gel in 35% yield from intermediate **8**. The overall yield for the eight-step synthetic route is 15%.

We determined that this synthetic sequence could be used to prepare the desired drug substance with some modification. We identified the following safety and chemical issues as limitations to the large-scale synthesis of this product:

(1) Dunn, R. W.; Flanagan, D. M.; Martin, L. L.; Kerman, L. L.; Woods, A. T.; Camacho, F.; Wilmot, C. A.; Cornfeldt, M. L.; Effland, R. C.; Wood, P. L.; Corbett, R. *Eur. J. Pharmacol.* **1992**, *214*, 207.

(2) Reitz, A. B.; Jordan, A. D.; Sanfilippo, P. J.; Scott, M. K.; Vavouyios-Smith, A. U.S. Patent 5,817,668, 1998.

(3) Acrylonitrile is a genotoxic material and is systemically absorbed through the skin; therefore, proper personal protective equipment and monitoring were used.

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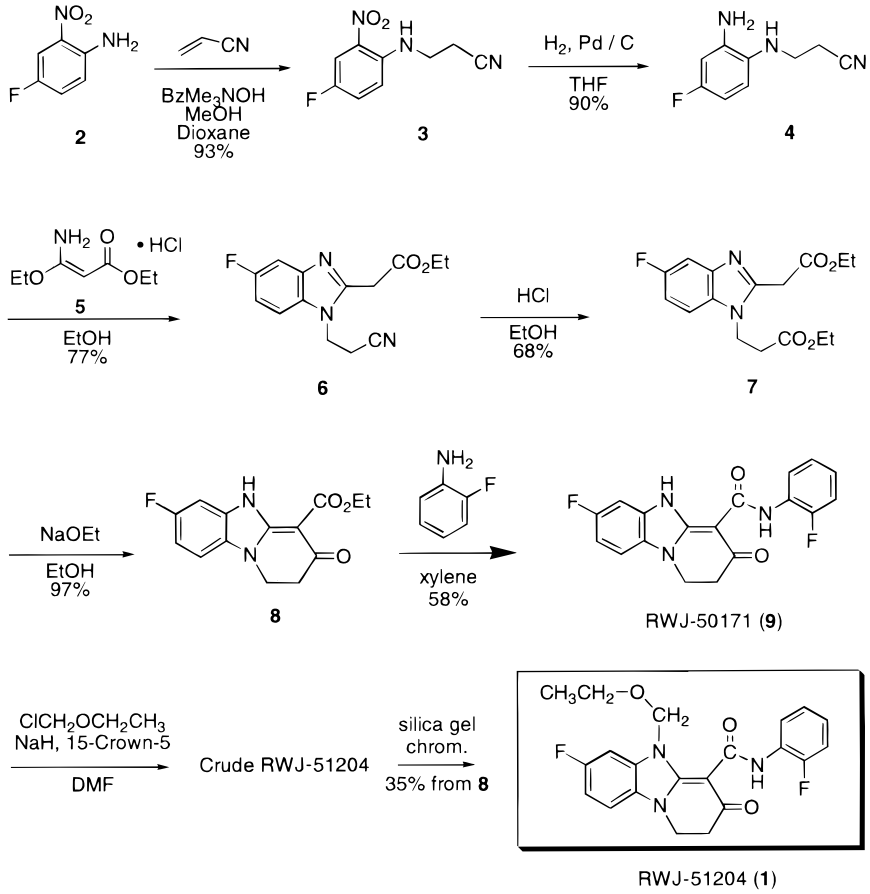
Scheme 1



1. Reaction of ester intermediate **8** with 2-fluoroaniline was carried out in xylene at elevated temperature. Due to the poor solubilities of both **8** and **9**, the reaction mixture was heterogeneous, leading to difficulties with stirring, reaction monitoring, and isolation of purified product. All of these factors contributed to the low yield and throughput for this step.

2. Conversion of carboxamide **9** to the final product, RWJ-51204 (**1**) was problematic for several reasons:

- The anion of intermediate **9** was generated with NaH in DMF. It has been reported in the literature that combinations of 15% NaH/DMF w/w pose a potential thermal hazard.[4,5] There have even been reports of plant-scale incidents using these reagents where they observed the onset of an exotherm at 40 °C followed by rapid self-heating and eventually explosion.[5]
- The ethoxymethylation was carried out in the presence of 15-crown-5. This reagent is very toxic as well as an irritant. For the final large-scale process, we needed to eliminate this hazardous reagent.
- The alkylating reagent for this step, chloromethyl ethyl ether, is expected to be highly toxic. Current OSHA guidelines indicate that chloromethyl methyl ether (a close analogue to chloromethyl ethyl ether in structure and reactivity) is a known human carcinogen. Therefore, we were concerned about using chloromethyl ethyl ether as the ethoxymethylating reagent due to the potential exposure risks during storage and handling.
- In addition to the hazardous reagents, the conversion of penultimate intermediate **9** to RWJ-51204 (**1**) was inefficient, requiring the crude product to be purified by silica gel chromatography. For large-scale synthesis, purification by chromatography is neither practical nor cost-effective.

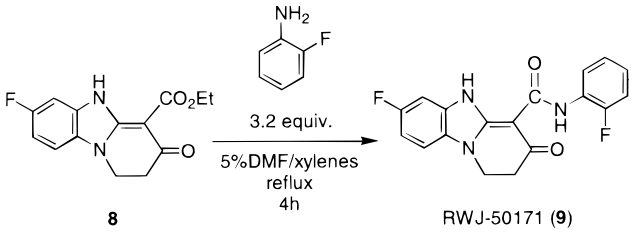
Our goal in devising an alternate route that avoided the problems highlighted above was to improve the last two steps of the synthesis starting with the ester intermediate **8**.

Results and Discussions

The aminolysis reaction to prepare penultimate intermediate **9** was typically carried out by treating ester intermediate **8** with excess 2-fluoroaniline in xylene at reflux temperature for 4 h. After purification by chromatography, the desired product was obtained in 58% yield. Due to the poor solubility of the starting ester **8** as well as that of the carboxamide product **9**, this reaction was difficult to reproduce. Upon scale-up, we encountered problems with inadequate stirring of the heterogeneous reaction mixture and caking on the sides of the reaction vessels. This led to difficulties with reaction monitoring, and as a result, the isolated product was contaminated with unreacted starting material and needed further purification. We investigated several alternate solvents for this step and found that a mixture of 5% (v/v) DMF/xylene greatly improved the reaction. Ester **8** was more soluble in this solvent combination; therefore, the reaction

(4) Buckley, J. *Chem. Eng. News* **1982**, *60*, 5.
(5) De Wall, G. *Chem. Eng. News* **1982**, *60*, 43.

Scheme 2

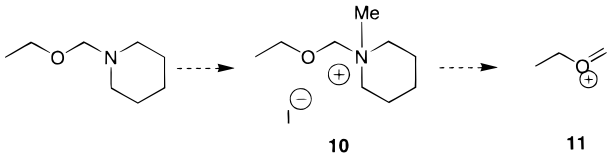


mixture was almost homogeneous at reflux temperature prior to product precipitation. After 4 h, the reaction mixture was filtered and washed with xylene to afford amide **9** in 93% yield. Most importantly, the isolated product was obtained in greater than 99% purity, thus eliminating any chromatographic purification. Increasing the amount of DMF in the solvent mixture did not afford any advantage; on the contrary, the isolated yield was lower. The 5% DMF in xylene conditions seemed to be optimum for this step (Scheme 2).

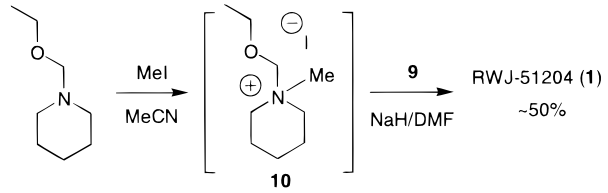
The final step of the synthesis is the ethoxymethylation of **9** with chloromethyl ethyl ether in the presence of 15-crown-5 to form RWJ-51204 (**1**). Due to the expected toxicity and carcinogenicity of chloromethyl ethyl ether, we investigated various approaches to replace it with a potentially less toxic reagent. Our options were to identify an alternate, less toxic alkylating reagent or to develop an in situ preparation of chloromethyl ethyl ether to minimize the occupational exposure risks during storage and handling. We determined early on that 15-crown-5 was not necessary for the alkylation, and thus, we eliminated the use of this toxic reagent.

Diethoxymethane, a safer alternative to chloromethyl ethyl ether, has been reported[6,7] to be an effective ethoxymethylating reagent for alcohols, phenols, and amines in the presence of acidic catalysts. Ozaki and co-workers[6] reported the alkylation of silylated fluorouracil derivatives using diethoxymethane in the presence of Lewis acids such as $SnCl_4$. Similarly, Schaper[7] reported alkylation of phenols using diethoxymethane in the presence of a Montmorillonite clay. However, all attempts at ethoxymethylation of intermediate **9** under acidic conditions based on these reports afforded none of the desired product, and only unreacted starting material was recovered. We also investigated alkylations under basic conditions (stoichiometric or catalytic) with various electrophiles including formaldehyde, dichloromethane, bromochloromethane, or Mannich-type bases. Again, we did not observe any product formation under these conditions. Reasons for the failure of these reactions include the limited solubility of the sodium salt of amide **9** in organic solvents less polar than DMF and the poor nucleophilicity of the carboxamide anion. In an effort to assess this, we subjected the sodium salt of **9** to reaction with methyl iodide (a very reactive alkylating reagent) in DMF. After 3 h at 60 °C in a sealed vessel only 40% conversion to the *N*-methyl compound was observed. In light of the poor reactivity of **9** with such reactive alkylating reagents, more reactive electrophilic ethoxymethylating reagents than those mentioned above were designed and tested.

Scheme 3



Scheme 4



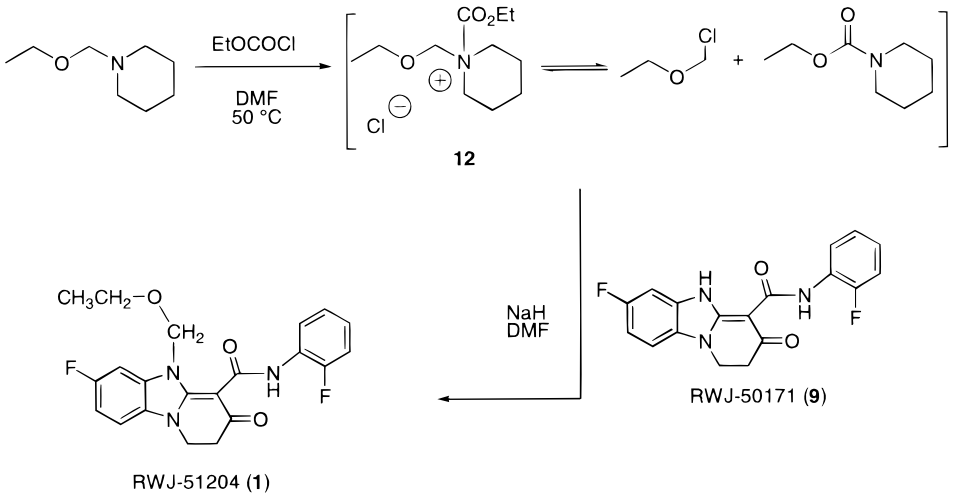
We proposed that oxonium intermediate **11** would be a very reactive ethoxymethylating reagent. One way we thought to prepare **11** was from quaternary ammonium salts such as **10** (Scheme 3). We hypothesized that under basic conditions **10** would convert to the reactive intermediate **11** upon elimination of *N*-methylpiperidine.

We prepared the quaternary ammonium iodide **10** by treating *N*-(ethoxymethyl)piperidine with methyl iodide and reacted it with the sodium salt of **9** in DMF (Scheme 4). At ambient temperature, we detected no reaction; however upon heating to reflux temperature for 2 h, we observed 50% conversion to RWJ-51204 (**1**). We were concerned that at elevated temperatures the alkylation proceeded through the in situ formation of iodomethyl ethyl ether. This could occur from nucleophilic attack by the iodide ion on the quaternary ammonium salt and subsequent elimination of *N*-methylpiperidine. To test this hypothesis, we prepared the quaternary ammonium salt by treating *N*-(ethoxymethyl)piperidine with methyl tosylate and repeated the ethoxymethylation reaction. Even at elevated temperatures, we observed no conversion to the desired product. This suggests that under the reaction conditions, the quaternary ammonium salt does not convert to oxonium intermediate **11** and that the active alkylating reagent for the first reaction is iodomethyl ethyl ether formed in situ under basic conditions.

Since we were unable to identify a less toxic ethoxymethylating reagent to carry out the alkylation, we investigated the in situ formation of chloromethyl ethyl ether to reduce the risk associated with exposure in handling and storage of this reagent. On the basis of our previous results, we examined the use of ethyl chloroformate to form quaternary ammonium salt **12** which upon heating would eliminate ethyl 1-piperidinecarboxylate to form chloromethyl ethyl ether (Scheme 5). Treatment of *N*-(ethoxymethyl)-piperidine with 1 equiv of ethyl chloroformate in DMF at 50 °C generated a mixture of the quaternary ammonium salt **12** and chloromethyl ethyl ether. However, after addition of the sodium salt of carboxamide **9**, the reaction only proceeded 60% (with the formation of many impurities) and no further product was observed even upon prolonged heating. This route would be problematic for large-scale production for several reasons. The yield was low, and the

(6) Ozaki, S.; Watanabe, Y.; Fujisawa, H.; Hoshiko, T. *Chem. Pharm. Bull.* **1986**, *34*, 150.
(7) Schaper, U.-A. *Synthesis* **1981**, 794.

Scheme 5



isolated product was contaminated with impurities and unreacted starting material so that chromatographic purification was still necessary. Also, *N*-(ethoxymethyl)piperidine is not commercially available; therefore, we would need to prepare it, thus adding another step to the synthesis. Therefore, we investigated other in situ preparations of chloromethyl ethyl ether.

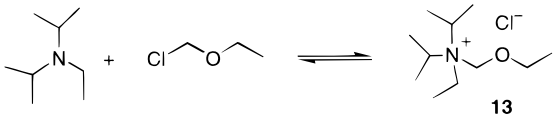
In 1995, Bailey and co-workers[8] reported the cleavage of cyclic formaldehyde acetals with acetyl chloride in the presence of Lewis acids to afford the corresponding chloromethyl ethers which were then reacted with alcohols under basic conditions to afford the desired products in high yield. On the basis of this report, we investigated the formation of chloromethyl ethyl ether from diethoxymethane and acetyl chloride in the presence of catalytic sulfuric acid. A similar approach was reported[9] for the synthesis of chloromethyl methyl ether from dimethoxymethane and acid chlorides in methanol. Treatment of a slight excess (10 mol %) of diethoxymethane with acetyl chloride and catalytic sulfuric acid at 40 °C for 3 h resulted in complete conversion to chloromethyl ethyl ether and ethyl acetate. Addition of the sodium salt of **9** (generated from NaH in DMF) afforded approximately 80% conversion to RWJ-51204 after 16 h at ambient temperature. Addition of excess NaH completed the reaction but led to dialkylated impurities confirmed by MS. This was an important observation and the first time that the reaction could be forced to completion. An aqueous quench at the end of the reaction precipitated the product as a tan solid in high yield. It also destroyed the residual chloromethyl ethyl ether, thus eliminating the potential exposure risk during workup. In order for this process to be suitable for scale-up, we needed to replace the hazardous NaH/DMF combination. Most importantly, to avoid any chromatographic purification, we needed to completely consume the difficult-to-remove starting material **9** without forming any dialkylated impurities. Results of a survey of

Table 1. **Ethoxymethylation of 9 with alternate bases**[a]

base	solvent	CMEE (equiv)	RWJ-51204 (**1**) area % HPLC	RWJ-50171 (**9**) area % HPLC
KOH	DMF	1.5	0	100
NaOEt	DMF	2.0	38	56
Bu_4NOH	DMF	1.0	0	100
Bu_4NOH	THF	1.0	23	77
KO*t*-Bu	DMF	1.0	55	45
KHMDS	THF/DMF	1.1	75	25
DIPEA	THF	1.7	6	94
DIPEA	DMF	1.7	82	18
DIPEA	DMF	2.3	100	0
DIPEA/DBU	**DMF**	**2.3**	**100**	**0**

[a] Progress of reaction monitored by HPLC.

Scheme 6



alternate bases used for the *N*-ethoxymethylation of carboxamide **9** with chloromethyl ethyl ether are shown in Table 1.

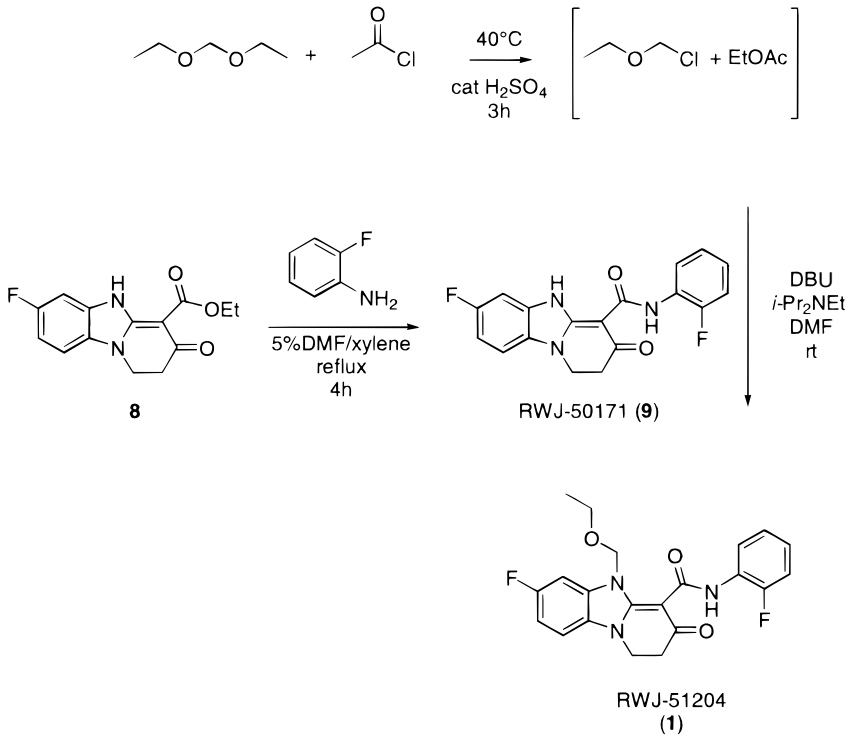
As shown in Table 1, we achieved the best results using diisopropylethylamine (DIPEA) as the base. Addition of carboxamide **9** and DMF to an in situ generated solution of chloromethyl ethyl ether followed by slow addition of DIPEA (2.75 equiv) afforded clean conversion to RWJ-51204 (**1**). Quenching with water after 16 h at ambient temperature precipitated the crude product as an off-white solid in 85−95% yield, > 99% purity.

Interestingly, we observed an initial rapid consumption of the amide starting material **9** (~90%) and conversion to RWJ-51204 (**1**) in the first minutes after the reagents were combined followed by an apparent slower but complete disappearance of the remaining starting material over several hours. Since we were concerned about the possible side reaction between DIPEA and chloromethyl ethyl ether during the prolonged reaction times, we examined this by ^{1}H NMR and observed a rapid reaction ($t_{1/2}$ < 15 min) to form a new

(8) Bailey, W. F.; Zarcone, L. M. J.; Rivera, A. D. *J. Org. Chem.* **1995**, *60*, 2532.

(9) (a) Weinstock, L. M.; Karady, S.; Sletzinger, M. U.S. Patent 3,972,947, 1975. (b) Amato, J. S.; Karady, S.; Sletzinger, M.; Weinstock, L. M. *Synthesis* **1979**, 970. (c) Linderman, R. J.; Jaber, M.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6499.

Scheme 7



species, presumably the quaternary ammonium salt **13** (Scheme 6). Our current hypothesis is that the reaction between these two reagents (DIPEA and CMEE) is fast but reversible and that the quaternary ammonium salt **13** serves as a source of chloromethyl ethyl ether to complete the reaction in the presence of excess base. This is consistent with our partial successes in generating chloromethyl ethyl ether from other aminomethyl ethyl ethers on quaternization.

In preliminary studies on recrystallization of crude RWJ-51204, we found that isopropyl alcohol improved the color and provided good recovery of the solid with high throughput. We were concerned about possible loss of the ethoxymethyl side chain thermally in alcoholic solvent; however, we found no evidence of dealkylation or decomposition of product after 17 h at reflux in isopropyl alcohol.

For the final process, there was only one outstanding issue, the poor solubility of intermediate **9** in DMF. After we prepared the chloromethyl ethyl ether, the reaction flask had to be opened and the amide added as a solid. To avoid the risk associated with possible exposure to chloromethyl ethyl ether upon opening the reaction vessel, we investigated alternate methods of addition. Our first approach involved in situ formation of chloromethyl ethyl ether in the presence of amide intermediate **9** which upon addition of DIPEA would afford RWJ-51204 in a "one-pot" reaction. However, once all the reagents were combined in the presence of catalytic acid, the reaction mixture became very thick and difficult to stir. Since this would be problematic for large-scale production, we examined formation of the anion of carboxamide **9** with various bases (other than DIPEA) in DMF in hopes of improving solubility. After investigating several bases, we found that treatment of intermediate **9** with 1 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMF yielded a homogeneous solution. Addition of this homogeneous solution to a closed reaction vessel containing chloromethyl ethyl ether under inert conditions followed by slow addition of excess DIPEA afforded clean conversion to RWJ-51204 (**1**). Quenching with water precipitated the product as an off-white solid in 95% yield. The crude product was recrystallized from isopropyl alcohol to give RWJ-51204 (**1**) in 92% yield for the two steps and >99% purity (Scheme 7).

In summary, we have successfully developed a safe large-scale synthesis of RWJ-51204 which avoids the safety challenges of the original medicinal chemistry route. We increased the yield and throughput for the aminolysis step to prepare carboxamide **9** by addition of 5% DMF to the reaction mixture. We improved the final alkylation step by developing an in situ preparation of chloromethyl ethyl ether to minimize the potential exposure risks during storage and handling. We also eliminated the use of 15-crown-5 and replaced the hazardous combination of NaH/DMF with DIPEA/DBU/DMF. As a result, we increased the yield for the final step after purification from 60% to 92%, while eliminating chromatography. With these improvements, we prepared RWJ-51204 (**1**) in 36% overall yield and applied this process to synthesize drug substance for use in early development toxicological and clinical studies.

Experimental Section

General Procedures. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM 300, 300 MHz spectrometer. The chemical shifts were expressed as δ units with Me_4Si as the internal standard (multiplicities in ^{1}H NMR are referred to as follows: s for singlets, d for doublets, t for triplets, q for quartets, and m

for multiplets). All reactions are carried out under a nitrogen or an argon atmosphere. Solvents and reagents were obtained from commercial sources and used without further treatment or purification.

Pyrido[1,2-*a*]benzimidazole-4-carboxamide, 7-Fluoro-*N*-(2-fluorophenyl)-1,2,3,5-tetrahydro-3-oxo (9). To a stirred suspension of ethyl pyrido[1,2-*a*]benzimidazole-4-carboxylate, 7-fluoro-1,2-dihydro-3-oxo (**8**)[2] (27.6 g, 0.10 mol) in DMF (22 g) and xylene (384 g) under a nitrogen atmosphere was added 2-fluoroaniline (36.0 g, 0.32 mol), and the suspension was brought to a gentle reflux. The reaction mixture was stirred at reflux for 4 h and then cooled to 20 °C. The solid was collected by filtration and washed with xylene (70 g) and then air-dried to yield **9** (31.58 g, 92.6%) as a tan solid: mp = 266−268 °C; ^{1}H NMR (DMSO-d_6) δ (ppm) 2.79 (2H, t), 4.31 (2H, t), 7.00 (1H, m), 7.12−7.29 (3H, m), 7.41 (1H, dd), 7.57 (1H, m), 8.50 (1H, t), 12.18 (1H, s, NH), 12.72 (1H, s, NH). MS (ESI) *m*/*z* 342 (MH^+). Anal. Calcd for $C_{18}H_{13}F_2N_3O_2$: C, 63.34; H, 3.84; N, 12.31. Found: C, 63.29; H, 3.81; N, 12.35.

Pyrido[1,2-*a*]benzimidazole-4-carboxamide, 5-(Ethoxymethyl)-7-fluoro-*N*-(2-fluorophenyl)-1,2,3, 5-tetrahydro-3-oxo (1). To a stirred solution of diethoxymethane (28.6 g, 0.27 mol) and acetyl chloride (19.6 g, 0.25 mol) under a nitrogen atmosphere was added sulfuric acid (0.30 g, 0.003 mol). The resulting clear solution was warmed to 40 °C for 3 h, and the reaction mixture was then cooled to ambient temperature. A solution of pyrido[1,2-*a*]benzimidazole-4-carboxamide, 7-fluoro-*N*-(2-fluorophenyl)-1,2,3,5-tetrahydro-3-oxo (**9**) (34.1 g, 0.10 mol) and 1,8-diazabicyclo[5.4.0]-undec-7-ene (15.2 g, 0.10 mol) in DMF (97.0 g) was prepared and added to the reaction mixture slowly to maintain the temperature between 25 and 35 °C. Diisopropylethylamine (22.6 g, 0.17 mol) was added, and the reaction mixture was stirred for 3 h at ambient temperature. The reaction mixture was cooled in a water bath, and water (60 g) was added slowly. The resulting suspension was stirred for 30 min. The solid was collected by filtration and washed with water (250 g). The solid was dried in vacuo at ambient temperature to afford the desired crude product **1** (38.0 g, 95.0%) as a light yellow, granular, free-flowing powder.

The crude product was dissolved in isopropyl alcohol (196 g) and heated to reflux. The hot solution was filtered to remove particulates and washed with hot isopropyl alcohol (8 g). The filtrate was concentrated to remove isopropyl alcohol (90 g) via distillation. The clear solution was cooled to ambient temperature slowly, resulting in crystallization. The solid was collected by filtration, washed with isopropyl alcohol (50 g), and then dried in vacuo at 25 °C to afford **1** (35.7 g, 94%) as a tan solid: mp 153−155 °C; ^{1}H NMR ($CDCl_3$) δ (ppm) 1.08 (3H, t), 2.85 (2H, t), 3.33 (2H, q), 4.15 (2H, t), 5.75 (2H, s), 6.97 (1H, m), 7.10−7.13 (1H, m), 7.22 (1H, m), 7.35 (1H, dd), 8.38 (1H, t), 12.01 (1H, s). MS (ESI) *m*/*z* 400 (MH^+). Anal. Calcd for $C_{21}H_{19}F_2N_3O_3$: C, 63.15; H, 4.79; N, 10.52. Found: C, 63.03; H, 4.66; N, 10.40.

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