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Process Development and Large-Scale Synthesis of MK-6186, a Non-Nucleoside Reverse Transcriptase Inhibitor for the Treatment of HIV

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ABSTRACT: A new synthetic route has been developed to drug candidate **1**, a second-generation NNRTI being developed as a potential treatment of HIV. Regiocontrol in a key alkylation step was achieved by selective *N*-alkylation of hydrazone **13**. After a deprotection and cyclisation sequence, **1** was isolated in six steps in 35% overall yield from readily available starting materials.

INTRODUCTION

Inhibition of the reverse transcriptase (RT) enzyme present in the human immunodeficiency virus (HIV) represents a key method for the treatment of the HIV infection. The emergence of non-nucleoside reverse transcriptase inhibitors (NNRTIs) has provided a welcome boost against the resistance experienced by the older class of nucleoside reverse transcriptase inhibitors (NRTIs) by viral mutation. However, recently marketed NNRTI treatments such as efavirenz, nevirapine, and delavirdine have themselves met with viral mutation and resistance.[1] Second-generation NNRTIs, such as etravirene[2] have recently been developed specifically for treatment-experienced adult patients with HIV resistance to an NNRTI. Merck recently reported on the discovery and development of a novel class of second-generation NNRTIs containing the pyrazolo[3,4-*b*]pyridine and biaryl ether key structural features.[3,4] In a further elaboration of this sequence, compound **1**, now with a central indazole moiety was brought forward for development.[5] Herein, the evolution of a robust synthesis of **1** which is amenable to scale, will be discussed.

Medicinal Chemistry Synthesis of 1. The initial Medicinal Chemistry route to **1** is outlined in Scheme 1.[5] Key to this synthetic sequence was the formation of the indazole ring system **6** by cyclisation of the aryl hydrazone formed between aldehyde **5** and hydrazine hydrate.[6] A palladium-mediated cyanation of **6** gave nitrile **7**, and subsequent alkylation with bromide **8** gave the penultimate **9**. Finally, Boc deprotection of **9** afforded the desired compound **1** in 5% overall yield.

Although successful for the generation of gram quantities of **1**, a number of limitations rendered the Medicinal Chemistry route unsuitable for larger-scale deliveries. First the use of toxic reagents such as metallic cyanides and hydrazine hydrate are highly undesirable for a long-term route. Second, poor regiocontrol in the N-alkylation of **7** coupled with the tendency of **9** to undergo Boc-deprotection followed by further alkylation with bromide **8** resulted in the need for a chromatographic separation of **9**. This depressed the yield of this step to a modest 40%. Finally, the low overall yield of just 5% over the six steps was not viable for a long-term synthesis.

Proposed Process Chemistry Approach to 1. In designing a second-generation route to **1**, the primary goal was achieving regiocontrol in the N-alkylation. The direct indazole alkylation had been shown to be nonselective, and thus, an alternative strategy was required. It was postulated that the desired outcome could be achieved through alkylation of a hydrazone such as **13** to give an open hydrazone precursor **14** to the required indazolone (Scheme 2). Once formed, **14** could then be treated with aqueous acid to invoke a tandem acid hydrolysis and cyclisation, to afford the desired indazole product **1** regio-selectively. Bromo compound **8** was readily available using chemistry previously described at Merck.[4] Hydrazone **13** was anticipated to be formed by palladium mediated cross-coupling of bromide **12** with benzophenone hydrazone. Bromide **12** itself would be accessed by an adaptation of the medicinal chemistry route to **5**.

RESULTS AND DISCUSSION

Synthesis of Intermediate 17. The synthesis began with the preparation of biaryl ether **17** using the commercially available 4-bromo-1-chloro-2-fluorobenzene **10** as the starting material (Scheme 3). Using the Medicinal Chemistry formylation conditions as a starting point, **10** was deprotonated using LDA at −50 °C in THF. The resulting anion **10′** was treated with DMF at −50 °C to form the intermediate aminal **15**. Quenching the reaction with water and extraction into MTBE gave a solution of aldehyde **16**. Crystallisation of the aldehyde could then be effected by solvent switch to hexane followed by cooling to −10 °C to maximise recovery. In the laboratory, a modest 76% yield was obtained when employing this protocol. Two key pieces of data provided the insight required for the optimization of this process. First, examination of the reaction profile by reverse phase HPLC showed that >99% conversion to **15** had been achieved. Second, when an MTBE solution of **16** (post water quench) was left to stand at 20 °C overnight, 30% of **10** was reformed. The inference was

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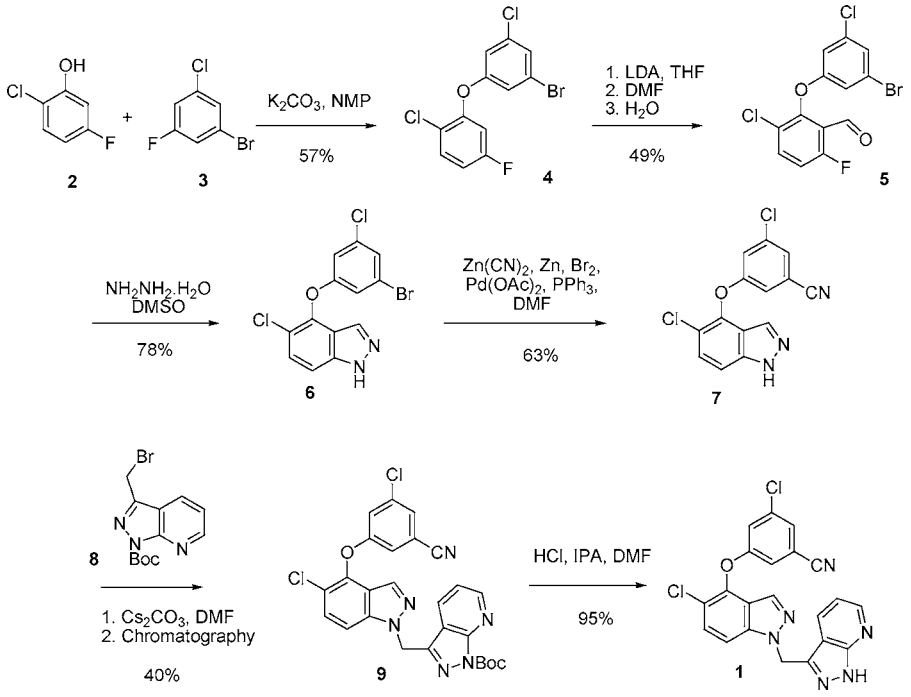
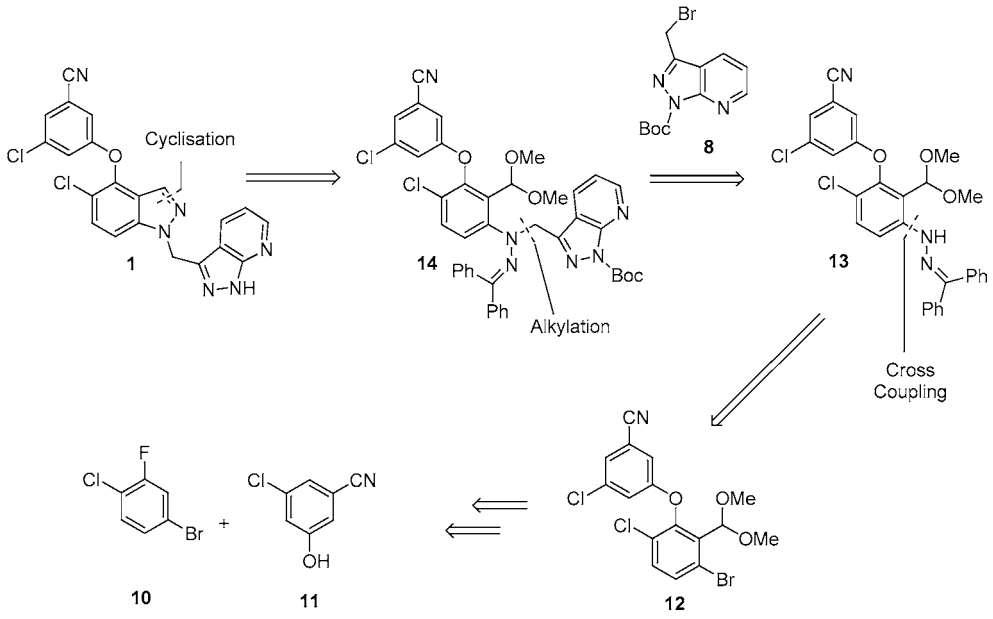
Scheme 1. Medicinal Chemistry synthesis of 1



Scheme 2. Proposed Process Chemistry route to 1



therefore that, after a water quench of **15**, the intermediate aminal could decompose via two competing pathways.

Upon quenching of **15** with water or a weak acid (acetic acid) the aminal can eliminate DMF to reform the stabilized anion **10′** which is then protonated to give the starting material **10** (Scheme 4). Alternatively the desired outcome of elimination of dimethylamine can occur to give aldehyde **16**. Working on the hypothesis that these decomposition pathways could be influenced by the electronic state of the aminal nitrogen, we reasoned that a quench with strong acid would lead to protonation of the nitrogen, thus favoring elimination of the dimethyl amino fragment to generate the desired product **16**. This was found to be the case. After a screen of suitable acids it was found that quenching with 4 M hydrochloric acid generated **16** exclusively. After further optimization, a protocol of an inverse addition of the reaction mixture to a biphasic mixture of 4 M hydrochloric acid and MTBE at 0 °C was designed. This was not only critical in affording complete conversion to **16** but also by using an addition controlled quench, the observed exotherm could be modulated by varying the addition rate.

Next, our attention turned to the S_NAr coupling of **16** with phenol **11** to prepare biaryl ether **17**. Reviewing the Medicinal Chemistry procedures showed the reaction could be carried out

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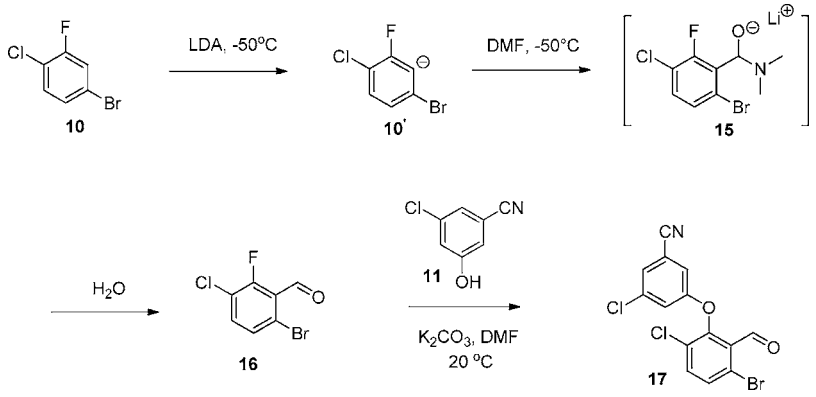
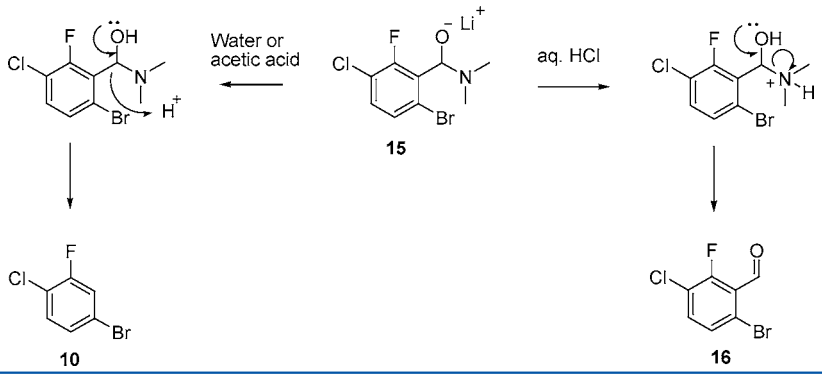
Scheme 3. Preparation of biaryl ether 17

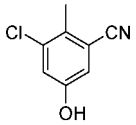


Scheme 4. Decomposition pathways of aminal 15



using K_2CO_3 in NMP at 60 °C. However, in our hands the reaction was found to stall at ~70% conversion, and also the generation of an unidentified, structurally related impurity at 3% was observed.[7] A change of solvent to DMF gave complete conversion within 2 h at 60 °C but still led to the generation of this unidentified impurity. After extensive optimisation of the conditions, we found that the reaction could be reproducibly performed on gram scale using 2 equiv K_2CO_3 and 8 volumes of DMF at 20 °C over 8 h, with less than 1% of the impurity generated. Biaryl ether **17** could then be isolated in 95% yield by simply adding water and filtering the resulting slurry.

Identification of a commercial source of **11** obviated the need to prepare this reagent in-house using zinc cyanide. Once bulk supplies of **11** had been received, it was found to contain a new impurity at 3%, assigned as methyl compound **18** by LC−MS. Close control over this impurity and subsequent methyl derivatives of our desired intermediates would be required as translation of **18** through the synthesis to the final product **1** could be envisaged.



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As the process was scaled up, it became progressively more difficult to drive the reaction to completion. One contributing factor was believed to be the change in agitation method from magnetic stir bar to overhead paddle stirrer. When employing a heterogeneous system such as K_2CO_3 in DMF, the solubility of the base would be influenced greatly by the particle size. It was likely that the stir bar imparted a beneficial grinding effect, therefore making more base available for reaction. As the scale of operation was increased, the stoichiometry of base required to achieve a satisfactory level of conversion also increased. For plant-scale operation, a protocol of portionwise addition of 5 equiv of K_2CO_3 was employed which ensured greater than 99% conversion to **17** after an overnight age at 20 °C.

Conversion of **10** to **17** on-scale was implemented in a single batch campaign. Deprotonation, reaction with DMF, and acid quench proceeded as expected to give **16** (7.50 kg, 95% assay yield). The stream was sufficiently pure to allow us to telescope the sequence. To this end the solution of **16** was solvent switched from MTBE into DMF and this solution was used directly in the S_NAr to generate a total of 7.82 kg of **17** in an 85% isolated yield. The main impurity was the methyl compound generated from reaction of **18** with **16** and was present at 2.8%.

Synthesis of Key Hydrazone Intermediate 13. In preparation for the coupling of the bromobiaryl ether **17** with benzophenone hydrazone **19**, it was first necessary to protect **17** to prevent any reaction through the aldehyde group. This was easily achieved by conversion of **17** into the acetal **12** using trimethylorthoformate in methanol (Scheme 5). Initially 0.1

Scheme 5. Preparation of acetal 12

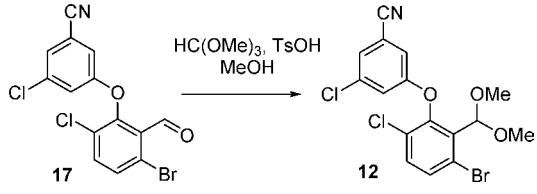

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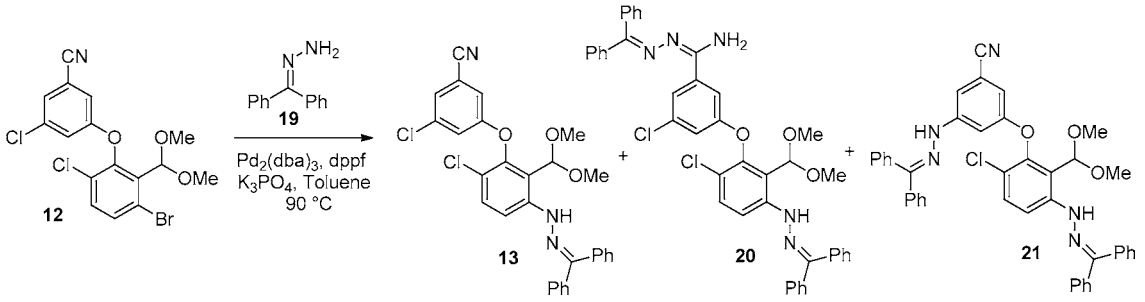
Table 1. Catalyst and ligand screening for the cross coupling to 13



entry	solvent	base	ligand	conversion to **13** (area %)[a]	bis-adduct **21** (area %)[a]
1	2-Me THF	Cs_2CO_3	Xantphos	95	6.5
2	2-Me THF	Cs_2CO_3	DPEphos	97	3.0
3	2-Me THF	Cs_2CO_3	BINAP	93	2.7
4	2-Me THF	Cs_2CO_3	dppf	96	2.0
5	2-Me THF	K_3PO_4	dppf	93	1.6
6	CPME	Cs_2CO_3	dppf	91	1.3
7	CPME	K_3PO_4	dppf	93	1.4

[a]Determined by HPLC analysis.

equiv of PTSA monohydrate catalyst was required, but subsequently with bulk supplies of **17** exhibiting a higher water content, an increase to 0.4 equiv was necessary to drive the reaction to completion. Workup was performed by neutralisation of the tosic acid with triethylamine, followed by the addition of water to effect crystallisation. Acetal **12** was isolated as an off-white solid in 95% yield.

At this point in the project, evaluation of the downstream chemistry demonstrated that rejection of methyl impurities derived from compound **18** would become progressively more difficult. It was therefore decided to perform an upgrade of **12**. A recrystallisation screen demonstrated that alcoholic solvents, in particular 2-propanol, gave the best combination of impurity rejection and recovery. On scale a 92% recovery of **12** was achieved with a 50% reduction in the level of the methyl impurity from 2.8 to 1.4%. Evaluation of the upgraded acetal **12** in the downstream chemistry confirmed the levels of impurities derived from **18** would conform to the desired API specifications.

The focus then turned towards the generation of the hydrazone **13**. This could be accomplished by a palladium-catalysed cross-coupling of the upgraded aryl bromide **12** with an aryl hydrazone such as benzophenone hydrazone **19**.[8] Compound **19** is a cheap, readily available commercial material that is significantly easier and safer to handle on scale than the hydrazine hydrate which had been previously employed in the Medicinal Chemistry synthesis. In-house catalyst screening identified that the use of strong bases such as sodium *tert*-butoxide (*t*-BuONa) promoted hydrazone addition to the nitrile, giving rise to the amidine **20**, and as such, their use was precluded. Switching to milder bases such as Cs_2CO_3 or K_3PO_4 resulted in the formation of the desired product **13** when used in combination with commonly used amination ligands (such as Xphos, Davephos, Ruphos, and BINAP).[9,10] However, these highly active ligands were also found to promote the formation of the undesired bis-addition product **21** through chloride activation (Table 1, entries 1−3). Less active ligands were then screened with $Pd_2(dba)_3$/dppf in a biphasic mixture of CPME and saturated K_3PO_4 (Table 1, entry 7) in particular giving good conversion whilst minimizing the formation of bis-adduct **21**. Optimization of this initial hit highlighted that, although switching from saturated to 2 M K_3PO_4 resulted in a much slower reaction, if used in combination with preformed $PdCl_2(dppf)\cdot CH_2Cl_2$ complex (2 mol %) a much improved reaction rate was observed, with complete conversion being obtained after 18 h at 90 °C. In addition, the reaction profile was much cleaner when compared to the original catalyst screening hit.

A screen of alternative reaction solvents showed similar conversion in CPME, toluene, and THF. Toluene was ultimately chosen since robust crystallisations of **13** from toluene/heptane or toluene/2-propanol had been identified. Further optimisation of the reaction protocol showed that thorough subsurface nitrogen degassing of the solution of **12** and **19** in toluene and the 2 M aqueous potassium phosphate solution were required before combination and charging of the catalyst. Effective mixing was also crucial to ensure constant suspension of the base, thus maximising mass transfer and achieving >95% conversion. Control of residual metals (Pd and Fe) was also important at this stage to ensure compliance with the specification at the final drug candidate. To this end a 60 wt % MP-TMT (macroporous polystyrene-2,4,6-trimercaptotriazine)[11] resin treatment of the organic phase was employed during workup, prior to isolation by crystallisation from toluene/2-propanol, allowing **13** to be isolated in 79% yield from **12**.

Alkylation and Indazole Formation: Preparation of Drug Substance 1. With the issue of regiocontrol during N-alkylation now solved by the use of intermediate hydrazone **13**, there still remained the possibility of Boc-deprotection to give **22** followed by over-alkylation leading to **23**. A review of the Medicinal Chemistry alkylation conditions highlighted the use of DBU or Cs_2CO_3 in DMF or DMSO. An extensive base screen was carried out; selected results are presented in Table 2. Alkoxide bases in DMF or NMP gave reasonable conversion but with high levels of **22** and **23** seen. A trend was noted in that the lithium base performed better than the sodium or potassium base. Switching to hexamethyl disilazane (HMDS) bases, the same trend was apparent in DMF or NMP. When the solvent was changed to THF, both KHMDS and NaHMDS performed poorly (Table 2, entries 9 and 10). However, the combination of LiHMDS with THF gave a very clean reaction (Table 2, entry 11) with very low levels of over-alkylation.

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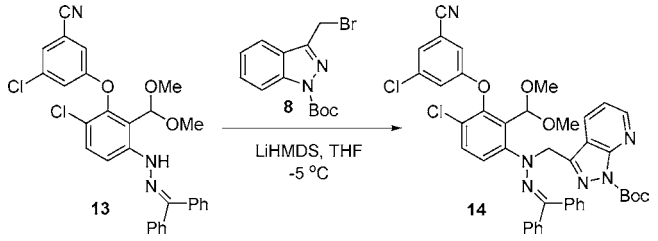
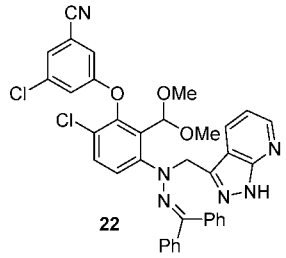
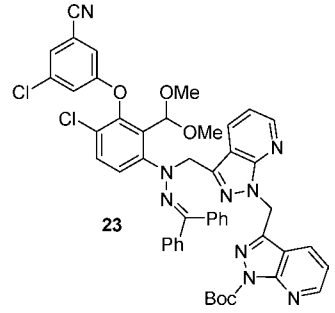
Table 2. Screening results for alkylation of 13 with 8



entry	base	solvent	product **14** (area %)[a]	de-Boc product **22** (area %)[a]	over-alkylated **23** (area %)[a]
1	KOtBu	DMF	71.4	10.9	10.3
2	KOtBu	THF	55.8	5.4	10.6
3	NaOtBu	DMF	80.1	5.8	7.6
4	NaOtBu	NMP	79.4	0	9.8
5	LiOtBu	DMF	92.4	0.6	5.7
6	KHMDS	NMP	78.5	0	12.3
7	NaHMDS	DMF	83.7	5.1	10.3
8	LiHMDS	NMP	89.6	0	5.4
9	KHMDS	THF	36.5	26.0	9.6
10	NaHMDS	THF	58.1	6.0	3.6
11	LiHMDS	THF	96.2	3.4	0.5
12	Cs_2CO_3	NMP	97.0	0	3.0
13	K_3PO_4	DMAc	88.0	1.0	1.0

[a]Determined by HPLC analysis.



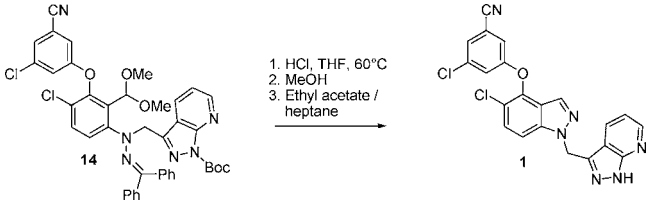


This combination was therefore chosen to go forward for further development.

Following a DOE study of reaction stoichiometry, concentration, and temperature, optimised conditions were implemented, whereby deprotonation of a THF solution of **13** using 1.15 equiv of LiHMDS at −5 °C was followed by addition of 1.15 equiv of **8** at −5 °C. Complete conversion to **14** was obtained after 1 h with none of the over-alkylation product **23** seen.

An early incarnation of the acid-catalysed hydrolysis/cyclisation sequence to afford drug candidate **1** was performed using PTSA monohydrate in ethanol at elevated temperature. However, concerns over the generation of tosylate esters as potential genotoxic impurities meant that a reagent change was required.[12] One set of Medicinal Chemistry conditions involved the use of concentrated HCl in DMF to effect this transformation and this was applied to the current reaction by carefully charging 2 M hydrochloric acid to the completed alkylation reaction mixture in THF and then heating to 65 °C (Scheme 6). Complete conversion was achieved after 4 h at this temperature. After extractive workup, **1** could be crystallised from ethyl acetate in 75% yield by adding heptane antisolvent. This however produced a waxy solid of low purity (~70 wt %) due to cocrystallisation of benzophenone. Also noted was an increased propensity of the product to oil out as scale of

Scheme 6. Preparation of desired compound 1



operation was increased. These factors meant that a new robust crystallisation was required. A screen identified methanol as an ideal solvent for the crystallization of **1** which could overcome these problems. Benzophenone was found to have relatively high solubility (>200 mg/mL), whilst the desired product was found to have low solubility (0.3 mg/mL) in this system. Thus, after extraction of the product into ethyl acetate and solvent switching into methanol, **1** could be reproducibly crystallised as a pale-yellow solid in 79% yield.

Review of the analytical data for the crude API highlighted a discrepancy between the 90 wt % assay and the 98 area % profile (both by HPLC). Correcting the wt % assay for solvents and inorganics only accounted for approximately 2% of the difference. It was known that the bromide **8** had less than ideal stability under the reaction conditions, and it was theorised that **8** could polymerise via a de-Boc/alkylation sequence. In order

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to remove the polymeric material thus produced and achieve a pharmaceutically acceptable purity specification, a further upgrade was required. An extensive screen of recrystallisations, carbons, adsorbents, and resin treatments was performed. It was found that by dissolution in ethyl acetate, filtration through a silica pad, and crystallisation with heptane, pure **1** could be obtained in 92% recovery (98 wt %, 99 area % purity).

■ CONCLUSION

A new and practical synthesis of **1** has been developed and demonstrated on multikilogram scale. Key to the success of this route was the formation of the indazole core via a regioselective N-alkylation of a benzophenone derivative. This strategy enabled an improvement in the overall yield from 5 to 35% over six linear steps. In addition, control of impurities generated by the supply of an impure starting material has been established. The chemistry employed may form the basis of a future manufacturing route; however, further work would be required to resolve the formation of polymeric impurities in the final stage and thus remove the requirement for a silica treatment.

■ EXPERIMENTAL SECTION

General. Starting materials were obtained from commercial suppliers and were used without further purification. HPLC analyses were performed on an Agilent Series 1100 liquid chromatograph equipped with a UV detector (wt % and area % purity). NMR spectra were obtained at 400 MHz for ^{1}H and 100 MHz for ^{13}C. All coupling constants are reported in hertz (Hz).

*6-Bromo-3-chloro-2-fluorobenzaldehyde (**16**).* LDA was prepared by charging *n*-butyllithium (23% in hexane, 10.7 kg, 38.4 mol) to a mixture of diisopropylamine (4.0 kg, 40.1 mol) and THF (35 L) at 0−10 °C in a 400 L vessel. The LDA solution was then charged to a solution of **10** (7.0 kg, 33.4 mol) in THF (35 L) at −60 °C over 1 h and aged at −60 °C for a further hour. DMF (40 kg, 100.0 mol) was then added at a rate sufficient to maintain the temperature at −50 to −55 °C and aged for 1 h. HPLC analysis was used to confirm the reaction was complete. The reaction was quenched by transferring into a vigorously stirred mixture of water (45 kg), concentrated HCl (33 kg), and MTBE (70 L), maintaining the temperature at 0−5 °C. The batch was warmed to 15 °C, and the phases were separated. The aqueous was re-extracted with MTBE (35 L), and the organics were combined and concentrated under reduced pressure to a volume of 10−15 L. DMF (35 L) was charged and the solution concentrated under reduced pressure to remove the remaining MTBE. Aldehyde **16** was obtained as a solution in DMF (54 kg, 7.50 kg of **16** by assay, 95% assay yield).

*3-(3-Bromo-6-chloro-2-formylphenoxy)-5-chlorobenzonitrile (**17**).* Phenol **11** (3.7 kg, 24.1 mol), K_2CO_3 (6.7 kg, 19.2 mol), and the DMF solution of aldehyde **16** (54 kg, 13.9 wt %, 26.5 mol) were charged to a 160 L vessel and aged at 21 °C for 20 h. Further charges of K_2CO_3 (3.35 kg) were made at 2, 5, and 8 h (total charge 16.8 kg, 48.2 mol). The reaction was confirmed complete by HPLC analysis and then cooled to 5 °C. Water (29.6 kg) was charged at such a rate as to maintain the temperature below 25 °C. The resulting slurry was aged for 1 h at 25 °C and filtered, and the wet cake was washed with water (10.0 kg). The filter cake was dried in vacuo to afford biaryl ether **17** (7.82 kg, 85% yield from **11**). Mp 176−179 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.93 (1 H, m), 7.09 (1 H, m), 7.37 (1 H, s), 7.61 (1 H, d, J = 8.4 Hz), 7.67 (1 H, d, J = 8.4 Hz), 10.23 (1 H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 188.5, 158.2, 149.5, 136.5, 135.8, 132.8, 129.3, 129.2, 126.4, 124.5, 120.7, 116.9, 116.8, 114.6.

*3-(3-Bromo-6-chloro-2-dimethoxymethylphenoxy)-5-chlorobenzonitrile benzhydrylidene-hydrazine (**12**).* A mixture of biaryl ether **17** (7.8 kg, 21.0 mol), PTSA (1.6 kg, 8.4 mol), trimethylorthoformate (6.7 kg, 63.0 mol), and methanol (30.8 kg) was heated to 65 °C for 30 min. The reaction was confirmed complete by HPLC and cooled to 25 °C. Triethylamine (1.1 kg, 10.5 mol) was charged and the mixture further cooled to 5 °C. Water (39.0 kg) was charged over 1 h, maintaining the temperature below 25 °C. The resulting slurry was aged for 1 h and filtered, and the wet cake was washed with water (20.0 kg). After drying in vacuo at 50 °C for 12 h, 7.66 kg of acetal **12** was obtained as an off-white solid (92% yield, 99 wt % purity).

Upgrade of 12. Acetal **12** (7.6 kg) was charged to a vessel followed by 2-propanol (60.0 kg). The slurry was heated to 82 °C to dissolve the solids, the batch was cooled to 5 °C, and the resulting slurry aged for 1 h. The batch was filtered and the cake washed with 2-propanol (20.0 kg). The solid was dried in vacuo at 50 °C with a nitrogen sweep for 12 h to afford 6.96 kg of **12** as an off-white solid (92% yield). Mp 108−110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.36 (6 H, s), 5.62 (1 H, s), 6.93 (1 H, m), 7.07 (1 H, m), 7.31 (1 H, m), 7.37 (1 H, d, J = 8.4 Hz), 7.54 (1 H, d, J = 8.4 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 158.8, 148.6, 135.9, 133.3, 131,9, 131.8, 128.7, 125.5, 122.0, 120.9, 117.4, 117.2, 114.0, 105.3, 56.0.

*3-[3-(N′-Benzhydrylidene-hydrazino)-6-chloro-2-dimethoxymethylphenoxy]-5-chlorobenzonitrile (**13**).* To a 400 L vessel was charged acetal **12** (6.96 kg, 16.7 mol), benzophenone hydrazone **19** (3.43 kg, 17.5 mol), and toluene (33.0 kg). The resulting solution was degassed with subsurface nitrogen for 1 h. Potassium phosphate tribasic (14.2 kg) was dissolved in water (32.0 kg) and the resulting solution degassed with subsurface nitrogen for 1 h. $PdCl_2(dppf)\cdot CH_2Cl_2$ (272 g) was charged to the toluene solution of **12** and **19** and the mixture degassed with subsurface nitrogen for a further 30 min. The potassium phosphate solution was then charged to the 400 L vessel and the vigorously agitated biphasic mixture heated to reflux for 19 h. The reaction was confirmed complete by HPLC analysis. The mixture was cooled to 20 °C, diluted with toluene (33 kg), and stirred for 10 min. The phases were separated, and the toluene solution was washed with water (25 kg) and saturated aqueous brine (25 L). MP-TMT resin (5.0 kg) was charged and the mixture agitated for 17 h at 20 °C. The resin was removed by filtration and the cake washed with toluene (20.0 kg). The toluene solution was concentrated by distillation under reduced pressure at <45 °C to a volume of ∼20 L and then diluted by addition of 2-propanol (76 kg) over 30 min. The resulting slurry was aged at 20 °C for 2 h, cooled to 0 °C for 1 h ,and then filtered. The cake was washed with 2-propanol (20 kg) and then dried at 55 °C under vacuum with a nitrogen sweep for 16 h to afford hydrazone **13** as a pale-yellow solid (7.0 kg, 79% yield, 94.0 area% purity, 11 ppm Pd, 12 ppm Fe). Mp 160−164 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.01 (6 H, s), 5.29 (1 H, s), 6.98 (1 H, m), 7.07 (1 H, m), 7.36 (7 H, m), 7.54 (1 H, m), 7.62 (4 H, m), 7.80 (1 H, d, J = 9.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 158.5, 147.1, 146,6, 144.2, 138.0, 136.3, 133.7, 131.7, 129.4, 129.1, 129.0, 128.4, 128.3, 126.7, 125.8, 120.6, 117.1, 117.0, 115.8, 114.6, 114.4, 112.2, 101.3, 54.2.

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3-Chloro-5-[5-chloro-1-(1H-pyrazolo[3,4-b]pyridin-3-yl-methyl)-1H-indazol-4-yloxy]benzonitrile (1). Hydrazone **13** (7.0 kg, 13.1 mol) was dissolved in THF (50 kg) in a 400 L vessel and cooled to −5 °C. LiHMDS (13.5 kg, 1.0 M solution in THF, 15.2 mol) was charged over 15 min, maintaining the temperature at −5 °C. The dark-red solution was aged at −5 °C for 10 min, and then a solution of bromide **8** (4.72 kg, 15.2 mol) in THF (13 kg) was charged over 15−30 min (maintaining the reaction temperature at −5 °C). The reaction was warmed to 20 °C over ∼1 h. The reaction was confirmed complete by HPLC analysis. Hydrochloric acid (2 M, 26.5 kg, 53 mol) was charged slowly to the vessel and the mixture heated to 65 °C and aged for 4 h. The reaction was confirmed complete by HPLC analysis. The phases were separated, and the aqueous layer was extracted with ethyl acetate (27 kg). The organic phases were combined, diluted with ethyl acetate (54 kg), and then washed with 1 M NaOH (23 kg) followed by two water washes (39 kg each). The solution was concentrated to 30 L at reduced pressure, and then methanol was (100 kg) charged. The solution was concentrated to 30 L under reduced pressure. The resulting slurry was cooled to −5 °C and aged for 2 h. The product was filtered and the cake washed with methanol (15 kg). After drying in vacuo at 50 °C for 16 h, crude **1** was obtained as a yellow solid (4.5 kg, 90 wt % purity, 70% yield corrected for assay).

Purification of 1. To a 400 L vessel were charged **1** (4.5 kg) and ethyl acetate (81 kg). The contents were heated to 60 °C until all the solid had dissolved. The solution was cooled to 20 °C and filtered through a bed of silica gel (22.5 kg). The silica was washed with ethyl acetate (203 kg) until all product had been recovered. The solution was concentrated under reduced pressure to a volume of 40 L (maintaining the batch temperature below 40 °C). The resulting slurry was cooled to 20 °C and heptane (92 kg) charged over 30 min. The slurry was cooled to −5 °C and aged for 2 h, and the product was filtered. The wet cake was washed with ethyl acetate/heptane (1:3, 20 L) followed by heptane (20 L). After drying in vacuo at 50 °C for 16 h, pure **1** was obtained as a pale-yellow solid (3.75 kg, 98 wt % purity, 92% yield corrected for assay). Mp 190−192 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.01 (2 H, s), 6.95 (1 H, m), 7.16 (2 H, m), 7.35 (1 H, t), 7.41 (1 H, d, J = 9.0 Hz), 7.51 (1 H, d, J = 9.0 Hz), 7.80 (1 H, s), 8.03 (1 H, d, J = 9.0 Hz), 8.63 (1H, d, J = 9.0 Hz), 12.88 (1 H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 158.1, 152.7, 149.3, 141.7, 140.7, 140.3, 136.5, 130.3, 130.2, 129.1, 126.3, 121.3, 119.3, 118.6, 117.6, 117.4, 116.9, 114.6, 113.8, 108.7, 47.6; HRMS (ESI$^+$) calcd for $C_{21}H_{12}Cl_2N_6O$ 434.0450, found 434.0528.

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REFERENCES

(1) Tarby, C. M. *Curr. Top. Med. Chem.* **2004**, *4*, 1045−1057.
(2) http://www.tibotec.com/bgdisplay.jhtml?itemname1/4HIV_tmc125.
(3) (a) Tucker, T. J.; Saggar, S.; Sisko, J. T.; Tynebor, R. M.; Williams, T. M.; Felock, P. J.; Flynn, J. A.; Lai, M. T.; Liang, Y.; McGaughey, G.; Liu, M.; Miller, M.; Moyer, G.; Munshi, V.; Perlow-Poehnelt, R.; Prasad, S.; Sanchez, R.; Torrent, M.; Vacca, J. P.; Wan, B. L.; Yan, Y. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2959−2966. (b) Tucker, T. J.; Sisko, J. T.; Tynebor, R. M.; Williams, T. M.; Felock, P. J.; Flynn, J. A.; Lai, M. T.; Liang, Y.; McGaughey, G.; Liu, M.; Miller, M.; Moyer, G.; Munshi, V.; Perlow-Poehnelt, R.; Prasad, S.; Reid, J. C.; Sanchez, R.; Torrent, M.; Vacca, J. P.; Wan, B. L.; Yan, Y. *J. Med. Chem.* **2008**, *51*, 6503−6511.
(4) Kuethe, J. T.; Zhong, Y. L.; Alam, M.; Alorati, A. D.; Beutner, G. L.; Cai, D.; Fleitz, F. J.; Gibb, A. D.; Kassim, A.; Linn, K.; Mancheno, D.; Marcune, B.; Pye, P. J.; Scott, J. P.; Tellers, D. M.; Xiang, B.; Yasuda, N.; Yin, J.; Davies, I. W. *Tetrahedron* **2009**, *65*, 5013−5023.
(5) Gomez, R.; Jolly, S. J.; Williams, T.; Vacca, J. P.; Torrent, M.; McGaughey, G.; Lai, M. T.; Felock, P.; Munshi, V.; DiStefano, D.; Flynn, J.; Miller, M.; Yan, Y.; Reid, J.; Sanchez, R.; Liang, Y.; Paton, B.; Wan, B. L.; Anthony, N. *J. Med. Chem.* **2011**, *54*, 7920−7933.
(6) Lokhande, P. D.; Raheem, A.; Sabale, S. T.; Chabukswar, A. R.; Jagdale, S. C. *Tettrahedron Lett.* **2007**, *48*, 6890−6892.
(7) Not identified. No ionization by LC−MS or GC−MS. This was not the methyl impurity related to **18**.
(8) Szmant, H. H.; McGinnis, C. *J. Am. Chem. Soc.* **1950**, *72*, 2890−2892.
(9) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27−50.
(10) Hartwig, J. F. *Synlett* **1997**, *4*, 329−340.
(11) Purchased from Biotage Ltd.
(12) Robinson, D. I. *Org. Process Res. Dev.* **2010**, *14*, 946−959.