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Development of Scalable Manufacturing Routes to AZD1981. Application of the Semmler–Wolff Aromatisation for Synthesis of the Indole-4-amide Core

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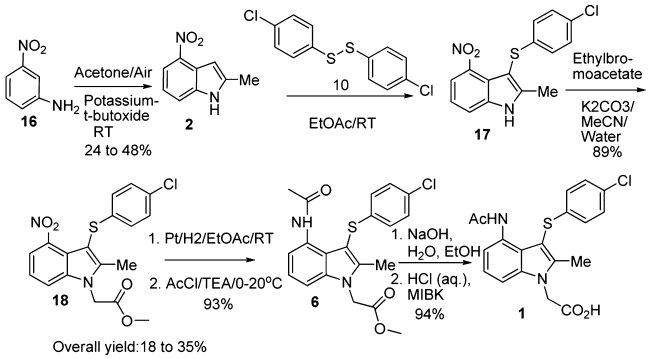
Supporting Information

ABSTRACT: A safe and efficient synthesis of AZD1981 is described in which the indole 4-amide core is formed by a Semmler–Wolff aromatisation of a cyclohexenone oxime fused to a pyrrole ring. The substrate was obtained via Paal–Knorr pyrrole synthesis, followed by incorporation of the key 3-arylthio substituent by reaction with 4-chlorophenylsulfenyl chloride. In this manner, the 1,2,3,4-substitution pattern of the AZD1981 core was regiospecifically established in a concise and efficient telescoped sequence. Accordingly, AZD1981 was obtained in 40% overall yield in six chemical steps, with two isolated crystalline intermediates.

INTRODUCTION

AZD1981 (**1**) is being developed in the Respiratory and Inflammation portfolio within AstraZeneca.[1] The evolution of the first generation supply route, which relied upon a sequential elaboration of 2-methyl-4-nitro-1*H*-indole (**2**), itself was prepared through Makosza reaction from 3-nitroaniline[2] (Scheme 1).

Scheme 1. AZD1981 Early Development



Although this route proved robust and scalable in early development, we had concerns over the long-term economic viability of the route and certain aspects of process safety regarding specifically the preparation and thermal stability of **2** which failed the Koenen tube test (2 mm diameter).

Moreover, Makosza chemistry for the synthesis of **2** is carried out above the flash point of acetone in the presence of air which could be a potential safety issue. In addition to this, there was inconsistency in the yield of **2** due to poor control over the Makosza chemistry. This prompted a search for alternative means of manufacturing **1** that did not proceed through **2**. The invention and development of a next generation synthetic route to AZD1981 is the subject of this paper.

Having critically evaluated a number of established routes to substituted indoles that relied on annelating a benzenoid ring, an alternative construction which established the five-membered ring prior to elaboration of the benzenoid ring appeared to offer a superior opportunity to avoid the intermediacy of **2**. The Semmler–Wolff aromatisation is particularly appealing in this connection.[3]This reaction provides a method for conversion of cyclohexenone oximes into aromatic anilines or anilides by dehydration under acidic conditions.[4] Whereas the majority of published examples relate to the synthesis of isolated benzenoid rings, a number of fused heterocyclic systems have also been prepared by this method, including an amino carbazole,[5] an oxindole-4-amide,[6] and a 4-amino benzoxazole.[7]To the best of our knowledge, this reaction has not been applied to the synthesis of an indole, but were it to prove feasible, it would enable the direct preparation of the 4-amidoindole core of AZD1981, as illustrated in Scheme 2.

To minimise the overall number of steps, our goal was to use a substrate which allowed early introduction of the indole N-substituent from a glycine derivative and for concomitant acetylation of the amino group during the Semmler–Wolff

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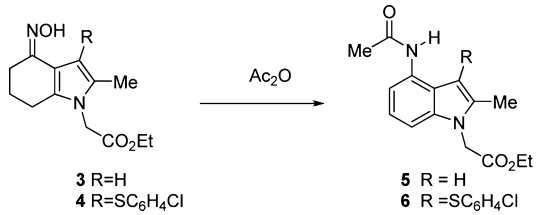
Scheme 2. Semmler–Wolff Synthesis of Indole-4-amides



3 R=H
4 R=SC_6H_4Cl

5 R = H
6 R =SC_6H_4Cl

reaction itself. One development aspect of this alternative route to AZD1981 was defining the order in which the transformations would be carried out, particularly the point at which the Semmler–Wolff aromatisation would be implemented. Consequently, a choice between using either substrate **3** or **4** was a key consideration in establishing this new approach. Whereas conditions for sulfenylation of indole **5** had already been established, the possibility of side reactions of **3** with electrophilic acylating agents was apparent. To mitigate this risk, compound **4** was targeted as a key substrate.

RESULTS AND DISCUSSION

Synthesis of the Pyrrolocyclohexenone Substrate. A straightforward route to the required pyrrolocyclohexenone **9** was devised utilising a Paal–Knorr pyrrole synthesis on trione **8**, itself made in a straightforward manner by alkylation of cyclohexane-1,3-dione **7** using chloroacetone, as illustrated in Scheme 3.[8] Initial studies into the synthesis of **8** using sodium

Scheme 3. Synthesis of the Pyrrolocyclohexanone 9

7 **8** **9** **9a**

or potassium hydroxides as base in aqueous ethanol confirmed the extensive reaction time reported. Under such conditions, at ambient temperature, around 80% conversion to **8** was achieved after 20 h. It was possible to accelerate the reaction by switching to potassium *tert*-butoxide in neat ethanol, but these conditions led to formation of unacceptably high levels of furan **9a**.

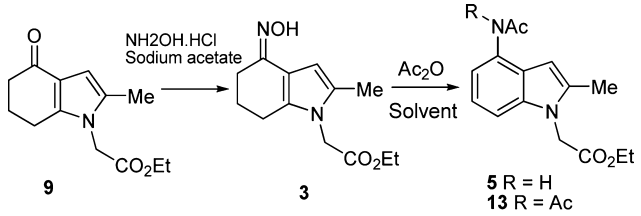
We studied the reaction using in situ mid-IR monitoring (employing aqueous ethanol as reaction solvent and potassium hydroxide as base). This demonstrated that the rate of reaction was essentially independent of solvent composition over quite a wide range at 20 °C. Further formation of **9** by reaction of **8** with glycine ethyl ester hydrochloride in the presence of sodium acetate at elevated temperature was found to be highly tolerant of water and potassium chloride. Accordingly, neither isolation of **8** nor drying solutions of this intermediate was imperative for a successful pyrrole synthesis. This encouraged us to look at water alone as reaction solvent for the preparation of **8**. Under these conditions, an acceptable 85 area % conversion was achieved after an overnight stir at 20 °C. However, the product was observed to separate out as oil[a] and could not be recovered completely in this form or by extraction into a water-immiscible solvent. Therefore, the aqueous–organic mixture was progressed directly into the Pall–Knorr pyrrole synthesis following addition of an organic cosolvent. This facilitated removal of the aqueous potassium chloride at the end of the reaction whilst enabling isolation of **9** by partition into the organic phase, from which it could be crystallised. Ethyl acetate and isopropyl acetate proved acceptable for this purpose; however, seeding was found necessary to generate the product with an adequate physical form. Demonstration of the ethyl acetate process by scale up to 500 g scale (input dione) afforded **9** in 62% yield. However, MTBE ultimately proved a better choice of cosolvent since the product could be crystallised from this solvent without seeding.

The process defined for scale up used a small excess of chloroacetone and required a reaction time of 20 h at 30–35 °C to achieve less than 3% (area by HPLC) of **7** remaining. Following addition of MTBE, sodium acetate, and glycine ethyl ester, pyrrole formation took place over 6–8 h at 50–55 °C. A sodium bicarbonate wash was introduced into the workup to remove a small amount of the de-esterified product, which was routinely observed as a low level impurity. On a 130 kg input scale, by this process, **9** was produced in overall yield of 62–67% with very high purity.[b]

Semmler–Wolff Aromatisation of 3. Conditions traditionally used for the Semmler–Wolff aromatisation involve heating the oxime substrate and acetic anhydride in acetic acid whilst passing gaseous hydrogen chloride through the mixture, and their use for the preparation of acetanilides is well precedented.[9] In combination with acetic anhydride, other acids such as phosphoric[10] and methane sulfonic[11] acids promote the reaction under milder conditions. Whilst acetic anhydride alone,[12] or in the presence of acetic acid,[13] has been used, reported reaction times are lengthy. Alternatively, acetyl chloride with acetic anhydride in the presence of pyridine,[14] ketene,[15] or 1-ethoxyvinyl acetate[16] promoted the Semmler–Wolff aromatisation under milder conditions. The proposed mechanism of Semmler–Wolff reaction encompasses several individual steps, commencing with O-acetylation of the oxime. Subsequent aromatisation occurs by loss of acetic acid together with N-acetylation.[17]

Development of Semmler–Wolff transformation of **3** started with a one-pot "all-in" process (Scheme 4) in which the

Scheme 4. Semmler–Wolff Reaction of 3



9 **3** **5** R = H
13 R = Ac

reaction was allowed to proceed to its full extent without isolation of any intermediate. The required oxime **3** was synthesized by refluxing ketone with hydroxyl amine hydrochloride and sodium acetate in ethanol with overall yield of 54%. To begin with, **3** was subjected to many typical reported conditions (Table 1) for the Semmler–Wolff aromatisation, aiming for in situ N-acetylation to get **5**.

As shown in Table 1, palladium/carbon as a catalyst gave very little conversion for the desired product along with many impurities (entry 1). Other conditions mainly resulted in imide product instead of amide (entry 3–7). With acetic anhydride alone as reagent, the reaction was found to require quite harsh conditions, e.g., temperatures of 140–160 °C, to achieve some conversion (entry 2), although shorter reaction times were achievable using microwave heating at similar temperatures (entry 7). In principle, the requisite amide **5** could be

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Table 1. Initial Screening for the Aromatising Reagents and Catalysts

entry	aromatising reagents/ catalyst	**5** by LC area %	**13** by LC area %	remarks
1	Pd/C[a]	19	---	Aromatisation with many impurities
2	Ac_2O[b]	35	2	Low conversion
3	TFAA[c]	3	53	Aromatisation but mainly imide **13**
4	Ac_2O/HBr/xylene[d]	4	45	Aromatisation with many impurities
5	Ac_2O/thiol/xylene[e]	4	45	Major imide with other impurities
6	Ac_2O/AcOH[f]	3	53	Closed vial reaction, but mainly imide **13**
7	Ac_2O/microwave[g]	24	54	Aromatisation with major imide component
8	xylene/*S*-phenyl thioacetate[h] (2.0 equiv)	60	---	48% isolated yield
9	1-acetyl imidazole[i] (2.0 equiv) and thiophenol	66	---	Product not isolated
10	Ac_2O/xylene/TBAI[j]	77	---	45% isolated yield

[a]Diethylene glycol dimethylether/150−180 °C. [b]Reflux. [c]Neat/110 °C. [d]110 °C. [e]110 °C. [f]110 °C. [g]145 °C/40 min. [h]Xylene/140 °C/40 min. [i]140−150 °C. [j]110 °C.

regenerated from the imide **13** under the basic conditions, but in practice, this complicated isolation of intermediates and impacted yield through losses to liquors. Therefore, minimising the formation of imide **13** became an important objective of the development studies.

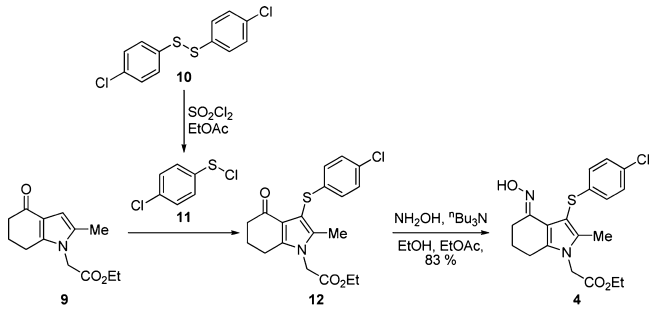
An initial breakthrough arose during evaluation of alternative acetylating agents in place of acetyl chloride or acetic anhydride. Use of *S*-phenyl thioacetate in xylene (entry 8) was found to give better conversion than acetic anhydride alone under comparable reaction conditions and provided the starting point for a catalyzed Semmler−Wolff aromatisation reaction. Noting that a reaction using acyl imidazole (entry 9) was enhanced upon addition of thiophenol, the hypothesis that the thiol may be acting as a nucleophile, either by activating the acetylating agent or through having an alternative role in the reaction, prompted investigation of iodide salts as promoters (entry 10).[18]

Indeed, when using acetic anhydride in xylene in the presence of tetrabutylammonium iodide (TBAI), a good conversion of oxime **3** was observed over a short period of time (3−4 h) at reflux to form indole amide **5** cleanly. The removal of TBAI had some problems, and finally the product was isolated with 45% yield.

Though the results were encouraging, the formation of **13** in considerable amount along with some of the unidentified impurities raised concerns about control of product quality at scale. This prompted examination of substrate **4** under similar conditions.

Synthesis of Oxime 4. Conversion of thiols or disulfides to the corresponding sulfenyl chlorides has precedence using reagents such as sulfuryl chloride or chlorine. Indeed, 4-chlorophenylsulfenyl chloride **11** has been prepared by such means from both the thiol[19] and disulfide.[20] Of these, the easily handled solid disulfide **10** was selected due to ready availability with very good purity. Initially, chlorination of this substrate was carried out using trichloroisocyanuric acid (TCCA) in ethylacetate; however, the heterogeneous nature of the resulting reaction mixture prompted replacement by sulfuryl chloride in the same solvent. Complete conversion of **10** under these conditions was confirmed by undertaking a study in D_8-EtOAc and analysis of the mixture directly by ^{1}H NMR spectroscopy, which provided a spectrum consistent with the formation of the sulfenyl chloride. Reaction of **11** with pyrrole **9** conveniently also proceeded in ethyl acetate, providing thioether **12** as a solution in ethyl acetate (Scheme 5). Under such conditions, thioether **12** could be obtained in 80% yield by solution assay on a small laboratory scale.

Scheme 5. Synthesis of the Semmler−Wolff Substrate



Isolation of intermediate **12** by crystallisation proved difficult, and low recoveries resulted. These observations focused development upon a telescoped process whereby a solution of thioether **12** in ethyl acetate was progressed directly into oxime formation. A basic aqueous workup was introduced principally to remove the HCl produced, before transition into the oxime formation. Oximation being water sensitive, concentration of thioether solution in ethyl acetate by distillation dried the solution sufficiently to enable efficient conversion to the oxime **4**. To begin with, this was achieved quite simply by heating a solution of the substrate in ethyl acetate or ethanol with hydroxylamine hydrochloride[c] in the presence of sodium acetate. However batches of oxime prepared this way tended to have low and variable assays, presumably due to contamination with inorganic materials. Therefore, a screen of common inorganic and organic bases was carried out and identified tri-*n*-butylamine as a better alternative, for which the soluble hydrochloride salt remained in solution upon isolation of oxime **4**, in 53 and 54% yields from either ethyl acetate or ethanol, respectively. Upon the basis of the results that oxime formation worked equally well in either ethyl acetate or ethanol alone, use of a mixed solvent system in fact provided the simplest process.

Thus, following thioether formation in ethyl acetate and concentration, ethanol was added, followed by hydroxylamine hydrochloride and tri-*n*-butylamine. Following a 4 h stir-out at 60 °C and cooling to 20 °C, **4** was collected by filtration and obtained in around 80% yield on a small laboratory scale. Investigation of various reaction parameters for the two-stage telescope was undertaken by a single combined factorial experimental design (FED) prior to the first pilot plant scale up and covered, amongst other aspects, temperatures, volumes, stoichiometries, addition, rate, and solvent composition for the oxime stage (Table 2).

As noted above from Table 2, the stoichiometry of sulfuryl chloride and disulfide **10** was matched on a molar basis, as was that for tributylamine and hydroxylamine hydrochloride. The sulfenyl chloride formation and reaction with pyrrole **9** were

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Table 2. Factorial Experiment Design (FED) Range versus Proposed Conditions

entry	factors	design range	proposed condition
1	sulfenyl chloride mol equiv	0.5−0.55 mol equiv	0.53
2	temperature of ketone formation	0−40 °C	0 °C
3	NH_2OH·HCl and Bu_3N equiv	0.9−1.1 equiv	1.0 equiv
4	total solvent volume for oxime formation	5−9 rel. vol.	6 rel. vol.
5	solvent composition for the oxime formation	33−67% v/v EtOH	33% v/v EtOH
6	temperature for the oxime formation	50−70 °C	60 °C
7	temperature of the oxime isolation	10−30 °C	20 °C

best done at low temperature (0 °C). The stoichiometry of hydroxylamine hydrochloride was chosen to keep the excess of this reagent to a minimum. In this manner, sulfenyl chloride **11** reacted with pyrrole **9** to afford thioether **12** cleanly in 90% yield by solution assay on a large laboratory scale. Subsequent conversion to oxime **4** at a reaction temperature of 60 °C achieved complete reaction in 4 h in a solvent system comprising a 2:1 mixture of ethyl acetate and ethanol. Oxime **4** was isolated simply by filtration at the end of reaction in 88% yield. Upon scale up of these conditions to pilot plant scale (90 kg input of pyrrole **9**), the yield was 84% with good purity.

Semmler−Wolff Aromatisation of 4. Applying here our learnings of Semmler−Wolff aromatisation of **3**, an initial screening of reaction of **4** was done using acetic anhydride in xylene using TBAI as promoter (Scheme 6, Table 3). The

Scheme 6. Semmler−Wolff Aromatisation

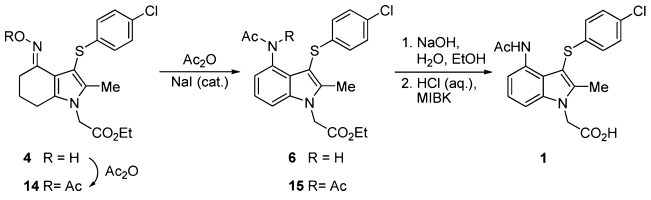

Table 3. Series of Experiments to Compare Certain Aspects of the Reaction Conditions

entry[a]	conditions	**6** by LC area %	remarks
1	Ac_2O/TBAI/110 °C	87.4	TBAI removal needed purification using IPA
2	Ac_2O/KI/95−100 °C	92.3	Isolated yield 65%
3	Ac_2O/NaI/85−95 °C	86.3	Isolated yield 65%
4	Ac_2O/	3.0	**15** (imide) >80% by LC area
5	Ac_2O/xylene[b]	70	**15** (imide) 8.9% by LC area
6	Ac_2O/toluene[b]	71	**15** (imide) 6.9% by LC area
7	Ac_2O/anisole[b]	67	**15** (imide) 7.6 by LC area
8	Ac_2O/mesitylene[b]	64	**15** (imide) 5.3% by LC area
9	2-MeTHF/Ac_2O[b]	68	**15** (imide) 6.9% by LC area
10	xylene:AcOH(1:1)/NaI (10%)/80 °C	90	18 h for the reaction completion
11	xylene:AcOH(1:1)/NaI (10%)/95 °C	93	Unreacted **4** less than 1.0% by LC area after 2 h
12	xylene:AcOH(1:1)/NaI (5%)	93	86% solution yield

[a]Note: entries 5−9: Ac_2O(4.0 mol equiv), solvent (5 rel. vol.), temperature 107 °C (oil bath). [b]No catalyst used.

reaction required an elevated temperature (110 °C) to proceed at a reasonable rate. Unfortunately, the downside of using a homogeneous source of iodide was separation from the product at the end of the reaction, which was exacerbated by the large amount (up to 1 mol equivalent) used (entry 1). To facilitate removal of the additive, inorganic iodide salts (potassium iodide, entry 2, and sodium iodide, entry 3) were assessed, and these compared favorably during small lab-scale trials in terms of reaction profile. Further high levels of imide **15** formation from use of a large excess of acetic anhydride (entry 4) as both reagent and solvent demonstrated the requirement for inert diluents. Those which were shortlisted, having met the required criteria, were acetic acid, anisole, mesitylene, xylene, toluene, and 2-methyltetrahydrofuran as shown in Table 3 (entries 5−9).

In acetic acid, complete consumption of acetylated oxime **14** was achieved within 18 h at 80 °C (entry 10). However, use of a 50:50 xylene/acetic acid mixture at 95 °C (entry 11) achieved complete reaction within 2 h with better purity when compared with reactions in xylene alone. Further assessment of mixed solvent systems with acetic acid led to the conclusion that xylene was indeed the nonpolar component of choice since it was only surpassed by mesitylene, which was less readily available and potentially more difficult to remove from the product due to its higher boiling point. The acetic anhydride stoichiometry was a balance between benefit on rate of reaction and controlling overacetylation to generate imide **15**, and consequently 4 mol equiv was used, whereby a reaction time of 4−6 h was observed at a temperature of 85 °C. Up until this point in time, the amount of catalyst was maintained at 50 mol %, and the main benefit of such a high level was a short time to reach end of reaction. By implementing less of the additive (10 mol %), it appeared that substantial removal from reaction mixtures during work up was now possible, and although the reaction time was increased, the ultimate extent of reaction remained essentially unchanged.

Nevertheless, having optimised the solvent composition, re-evaluation of sodium iodide at a level of 5 mol % demonstrated a comparable time to reach the end of reaction (entry 12). An important observation was made during the course of this work in response to variability that was impacting time to achieve end of reaction and in some cases making the reactions stop with unusually high levels of substrate remaining. This was attributed to inadequate inertisation of the reaction, which perhaps resulted in oxidation of the iodide catalyst to iodine to variable extents. By inertisation of the reaction vessels prior to charging the reagents, reproducibility was ensured.

As a result of some concerns over degradation of acetyl oxime **14** at elevated temperature, the effect of separating out the initial oxime acetylation step from the remainder of the transformation was studied through investigation of a two-stage process. To accomplish this, a solution of acetylated oxime **14** was prepared in the first reaction vessel in a mixture of xylene and acetic acid at room temperature containing part of the acetic anhydride charge. This was subsequently added to a hot mixture of the remaining acetic anhydride, and the sodium iodide in the same mixed solvent system held at the required reaction temperature in the second vessel. This change resulted in a faster reaction and an increased yield in solution measured by assay at end of reaction from 83% to 93% and was therefore adopted as the standard method by which the process was operated.

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Further development of the reaction through investigation of process parameters and stoichiometry prior to pilot plant scale up was done by factorial experimental design (FED), encompassing solvent composition, amount and split of the acetic anhydride charge over the two parts of the process, and addition rate of the acetyl oxime to the hot reaction mixture (Table 4). This confirmed that an acetic acid rich solvent system was preferred; however, to balance this against the impact on yield of the isolated product, the proportion of this was limited to 50% v/v. The split of the acetic anhydride charge across the two reaction vessels (initially set at 3.8 mol equiv) was not important, as long as at least 1 equiv was present in vessel 1 to acetylate the oxime; therefore, an equal split was chosen. The amount of acetic anhydride was subsequently reduced to 2.5 mol equiv to better control over-reaction to imide **15**, but at the expense of a slightly lower yield in solution (87%) and longer reaction time. The reaction temperature for the second part of the process was increased to 100 °C, without detriment, to ensure a good margin above the lower limit of 95 °C, below which the rate of reaction was significantly impacted.

Table 4. Study on Process Parameters and Stoichiometry by Factorial Experimental Design (FED)

entry	parameters	range studied	proposed conditions
1	reaction temperature	90−115 °C	100 °C
2	mol equiv of NaI	0.025−0.1 mol equiv	0.05 mol equiv
3	addition rate of acyl oxime	0.05−0.3 mL/min	addition rate: no impact on quality
4	Ac_2O mol equiv	1.2−2.8 equiv (split between two vessels)	2.5 mol equiv
5	% of xylene wrt AcOH	30−90% v/v wrt AcOH	50:50

Isolation of the product with a good recovery depended upon effective removal of the acetic acid since high residual levels at the point of crystallisation led to loss of the product to liquors. Removal through washing was preferred over distillation, and consequently aqueous sodium chloride and dilute sodium thiosulfate washes were implemented to remove acetic acid and iodine arising from adventitious oxidation of the iodide salt. It was essential to carry out the workup at elevated temperature to maintain the product in solution, and after addition of heptane and cooling, crude amide **6** was isolated with a good physical form. Under these conditions on a 100 g laboratory scale, amide **6** was formed in 87% yield, measured by solution assay, and isolated in 76% yield. Scale up of these reaction conditions to pilot plant (73 kg input of oxime **4**) afforded the product in 76% yield.

Two effective systems for recrystallisation of amide ester were identified from screening studies, ethanol or aqueous acetonitrile, and the latter was chosen as a solvent of choice. The recrystallisation was scaled up successfully, affording purified indole amide **6** in 92% recovery.

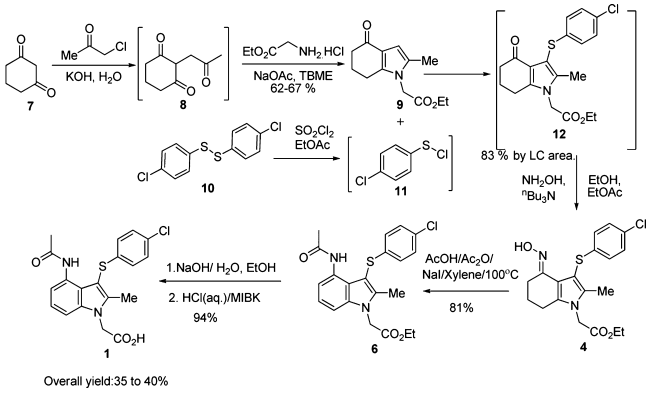
Further development of this stage therefore focused on use of around 10% v/v acetic acid, which offered product with better purity and allowed a simpler work up by removal of the first aqueous wash, in which around 4% yield was lost, and necessitating only the dilute aqueous sodium thiosulfate wash to remove iodine. Further optimisation of the reaction volumes and isolation procedure arrived at the improved process which afforded indole amide **6** in 81% yields on a 200 g scale.

The downstream chemistry of **6** to get AZD1981 (**1**) by de-estrification and further purification by crystallisation remains the same as in the case of the early developmental route.[4] However, an attempt to replace IPA with EtOH at the hydrolysis stage was successful and afforded AZD1981 (**1**) in 94% yield with a purity of 99.5 area % on a 100 kg input scale. The overall yield of **1** from the Semmler−Wolff aromatisation route is about 37−40% against 18−35% of the first generation supply route.

CONCLUSIONS

A highly efficient, robust, and safe synthesis of AZD1981 from cheap, readily available building blocks, and which is suitable for large-scale manufacture, has been devised (Scheme 7). The key step, a Semmler−Wolff aromatisation, has been found to proceed under relatively mild reaction conditions using acetic anhydride in a mixture of acetic acid and xylene in the presence of a catalytic amount of sodium iodide. The solvent composition has been optimized. The exact role of the iodide has not yet been elucidated and is the subject of ongoing work within our laboratories.

Scheme 7. Overall Synthetic Scheme of AZD1981



EXPERIMENTAL DETAILS

General. All reactions were performed under a nitrogen atmosphere. Xylene refers to a commercially available mixture of *o*-, *m*-, and *p*-xylenes and ethyl benzene. Heptane refers to *n*-heptane (assay 99% w/w minimum). NMR spectra were recorded on Varian Unity Inova spectrometers operating at the specified proton frequencies on D6-DMSO solution with tetramethylsilane (TMS) as an internal reference. HPLC and UHPLC methods which can be used for purity and assay determination are given in the Supporting Information. Assays were performed against purified and fully characterised reference materials. LC−MS spectra were obtained using an Agilent 1100 series LC instrument and LC/MSD SL detector with +ve atmospheric pressure electrospray ionisation (APESI).

Ethyl (2-Methyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-1-yl)acetate (9). To a 1600 L glass-lined reactor was charged water (143 L) and cyclohexane-1,3-dione (130 kg, 1.16 kmol) at 27 °C, and then the mixture was cooled to 12 °C with stirring. To this, a solution of potassium hydroxide (76.6 kg, 90% w/w, 68.9 kg contained weight, 1.23 kmol) in water (117 L) was added over a period of 2 h 15 min at 11 °C (initial pH 5.0 increasing to 7.0 at the end of the addition), and then the mixture was maintained at this temperature for a further 30 min. Chloroacetone (126.2 kg, 1.36 kmol) was added slowly to

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the reaction mixture over 4 h at 11.5 °C, after which the temperature was allowed to rise to 32 °C and maintained for 20 h. Glycine ethyl ester hydrochloride (180.7 kg, 1.29 kmol) and MTBE (390 L) were added, and after continuing stirring at 30 ± 3 °C for 10 min, anhydrous sodium acetate (104.7 kg, 1.28 kmol) and water (260 L) were charged. Then the reaction mixture was heated to 52 ± 3 °C and maintained at this temperature for 6 h. The aqueous layer was separated and extracted with MTBE (260 L) at 52 ± 3 °C. The combined MTBE layers were washed with 5% aqueous sodium bicarbonate solution (520 L) at 52 ± 3 °C, and the aqueous phase was re-extracted with MTBE (130 L) at 53 °C. The combined MTBE layers were cooled slowly to 0−5 °C and held for 12 h, and then the solid product was collected by filtration, washed with water (260 L) followed by cold MTBE (260 L), and dried under vacuum at 40−45 °C to provide the title compound as a pale yellow solid, 183.7 kg (67% yield). Assay by ^{1}H NMR 98.8% w/w. Purity by UHPLC 99.4 area %. ^{1}H NMR (500 MHz): 6.04 (1H, s), 4.79 (2H, s), 4.17 (2H, q, J = 7.1 Hz), 2.65 (2H, t, J = 6.1 Hz), 2.27 (2H, t, J = 6.3 Hz), 2.10 (3H, s), 1.94−2.03 (2H, m), 1.22 (3H, t, J = 7.1 Hz). m/z 236 (MH+).

Ethyl [(4*E*/*Z*)-4-(Hydroxyimino)-2-methyl-4,5,6,7-tetrahydro-1*H*-indol-1-yl]acetate (3). *Procedure 1.* In 1.0 L of RBF, **9** (0.054 kg, 0.230 mol) was added in ethanol (0.54 L) with stirring followed by addition of water (0.050 L), hydroxylamine hydrochloride (0.024 kg, 0.344 mol), and sodium acetate trihydrate (0.047 kg, 0.344 mol) in one portion. Then the mixture was heated to reflux for approximately 3−5 h. After cooling to 10 °C, the solid was collected by filtration on a Buchner funnel, washed with water (0.05 L), and then dried under vacuum at temperature of 40 °C to provide the title compound as an off-white solid, 0.055 kg (95% yield not assay corrected). Purity by HPLC 98.98 are a% (together for both the isomers). ^{1}H NMR (300 MHz): 9.99 (1H, s), 9.886 (1H, s), 6.49 (1H, s), 5.89 (1H, s), 4.66−4.69 (4H, d), 4.11−4.19 (4H, m), 2.45−2.54 (6H, m), 2.24−2.29 (2H, m), 2.07−2.08 (6H, s), 1.72−1.86 (4H, m), 1.13−127 (6H, t). ^{1}H NMR spectrum showed signals for both isomers. m/z 251 (MH+).

Ethyl [3-(4-Chlorophenylsulfanyl)-4-(hydroxyimino)-2-methyl-4,5,6,7-tetrahydro-1*H*-indol-1-yl]acetate (4). *Procedure 1.* In reaction vessel 1, bis-(4-chlorobenzene)-disulfide (57.15 kg, 199 mol) was suspended in ethyl acetate (278.2 kg) with stirring, and the mixture was cooled to 0 ± 3 °C. Sulfuryl chloride (26.9 kg, 199 mol) was added in one portion, followed by an ethyl acetate line rinse (39.7 kg), and then the mixture was stirred at 0 °C for approximately 2.5 h. Meanwhile, **9** (90.0 kg, 382 mol) and ethyl acetate (351.3 kg) were charged to reaction vessel 2, and the mixture was stirred at 20 ± 3 °C. The contents of reaction vessel 1 were added to the mixture in reaction vessel 2 over approximately 30 min, washing the residues with ethyl acetate (84.5 kg). After holding overnight at 20 °C, a solution of sodium carbonate (anhydrous, 57.7 kg, 544 mol) in water (487.3 kg) was added over a period of 30 min (gas evolution), and then stirring was continued for 45 min. The layers were allowed to separate, and the lower aqueous phase was discarded. A solution of sodium chloride (31.75 kg) in water (424.5 kg) was added to the organic phase. The mixture was stirred for 40 min, and then the layers were separated, discarding the lower aqueous phase. The organic layer was transferred to a clean reaction vessel, followed by an ethyl acetate line rinse (39.0 kg), and then concentrated by distillation at atmospheric pressure until 540 kg of distillate had been collected. After cooling the concentrate to 20 °C, hydroxylamine hydrochloride (26.1 kg, 376 mol) and tributylamine (69.8 kg, 376 mol) were added followed by ethanol (140.9 kg), and then the resulting mixture was heated at 60 ± 3 °C for 3.5 h. After cooling to 20 °C, the solid was collected by centrifugation, washed with ethyl acetate (218 kg), and then dried under vacuum at a maximum jacket temperature of 40 °C to provide the title compound as a white solid, 125.8 kg (84% yield). Purity by HPLC 96.3 area %. Assay by HPLC 97% w/w. ^{1}H NMR (400 MHz): 10.30 (1H, s), 7.21−7.25 (2H, m), 6.89−6.93 (2H, m), 4.85 (2H, s), 4.17 (2H, q, J = 7.1 Hz), 2.52−2.59 (4H, m), 2.12 (3H, s), 1.76−1.84 (2H, m), 1.21 (3H, t, J = 7.1 Hz). m/z 393 (MH+).

Procedure 2. In reaction vessel 1, bis-(4-chlorobenzene)-disulfide (12.7 g, 44.2 mmol) was suspended in ethyl acetate (80 mL) with stirring, and the mixture was cooled to 5 °C. Sulfuryl chloride (3.55 mL, 43.9 mmol) was added in one portion, and the mixture was stirred at 5 °C for approximately 2 h. **9** (20.0 g, 98% w/w, 19.6 g contained weight, 83.3 mmol) and ethyl acetate (100 mL) were charged to reaction vessel 2, and the mixture was stirred at 20 °C. The contents of reaction vessel 1 were added to the mixture in reaction vessel 2 over approximately 30 min, washing in the residues with ethyl acetate (10 mL). After stirring at briefly at 20 °C, triethylamine (11.6 mL, 83.2 mmol) was added over a period of 12 min, and then the mixture was held overnight. The solid byproduct was removed by filtration; the filter cake was washed with ethyl acetate (20 mL); and the combined filtrates were evaporated in vacuo. The residue was dissolved in a mixture of ethyl acetate (80 mL) and ethanol (40 mL), and then hydroxylamine hydrochloride (5.79 g, 83.3 mmol) and tributylamine (19.9 mL, 83.6 mmol) were added. After heating at 60 °C for 4 h, the mixture was cooled to 20 °C, and then the product was collected by filtration, washed with ethyl acetate (2 × 40 mL), and dried under vacuum at 40 °C to provide the title compound as a white solid, 27.2 g (83% yield). Purity by HPLC 96.5 area %.

Ethyl [4-Acetylamino-3-(4-chlorophenylsulfanyl)-2-methyl-1*H*-indol-1-yl]acetate (6). *Procedure 1.* In reaction vessel 1, acetic anhydride (23.9 kg, 234 mol) was added over a period of 10 min to a stirred slurry of **4** (73.0 kg, 186 mol) in a mixture of xylene (64.0 kg) and acetic acid (77.2 kg) at 22 ± 3 °C. Meanwhile, a mixture of sodium iodide (1.39 kg, 9.3 mol), xylene (64.0 kg), acetic acid (77.5 kg), and acetic anhydride (23.6 kg, 231 mol) was heated to 100 ± 3 °C in reaction vessel 2 with stirring. After stirring the contents of reaction vessel 1 for 2.5 h, this was added to the solution in reaction vessel 2 over 50 min, maintaining the temperature at between 97 and 103 °C. Reaction vessel 1 was rinsed with a mixture of xylene (16.2 kg) and acetic acid (19.2 kg), which was added to reaction vessel 2. The reaction mixture was held at 100 ± 3 °C for a further 1.5 h then cooled to 60 °C. Additional xylene (59.2 kg) was added, followed by a hot (60 °C) solution of sodium chloride (13.7 kg) in water (106.8 kg), maintaining the temperature at 60 °C. After stirring for 15 min, the aqueous layer was separated and discarded. A hot (60 °C) solution of sodium thiosulfate (2.94 kg, 18.6 mol) in water (37.2 kg) was added, and after mixing for 20 min, the aqueous layer was separated and discarded. Heptane (143.2 kg) was added to the organic layer, whilst maintaining the temperature at 60 ± 3 °C, causing crystallisation of the product. The resulting slurry was cooled to 20 °C over 1 h, and then the product was collected by centrifugation, washed with ethanol (96.1 kg), and dried

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under vacuum at a maximum jacket temperature of 40 °C to afford the crude product **6** as an off-white solid, weight 59.0 kg (76% yield). Assay by UHPLC 94.4% w/w. Purity UHPLC 96.9 area %.

Recrystallisation of 6. Crude **6** (87.3 kg, 209 mol) was dissolved in a mixture of acetonitrile (622 kg) and water (396.1 kg) by heating to 80 ± 3 °C with stirring. After holding for 20 min, the solution was cooled to 15 ± 3 °C, and then the resulting solid product was collected by centrifugation, washed with ethanol (116.3 kg), and dried under vacuum at a maximum jacket temperature of 40 °C to afford purified **6** as an off-white solid, weight 80.2 kg (92% yield). Assay by UHPLC 99.2% w/w. Purity by UHPLC 99.4 area %. ^{1}H NMR (400 MHz): 9.51 (1H, br s), 7.46 (1H, d, J = 7.6 Hz), 7.26−7.35 (3H, m), 7.11 (1H, t, J = 8.0 Hz), 6.97 (2H, d, J = 8.5 Hz), 5.24 (2H, s), 4.18 (2H, q, J = 7.1 Hz), 2.39 (3H, s), 1.86 (3H, s), 1.21 (3H, t, J = 7.1 Hz). m/z 417/419 (MH+).

Procedure 2. A mixture of sodium iodide (3.82 g, 25.5 mmol), xylene (400 mL), acetic acid (50 mL), and acetic anhydride (67.4 mL, 713 mmol) was heated to 100 °C in vessel 1 with stirring. In vessel 2, acetic anhydride (67.4 mL, 713 mmol) was added to a stirred slurry of **4** (200 g, 509 mmol) in xylene (450 mL) and acetic acid (50 mL) at rt. After stirring for 45 min, this mixture was added to the contents of reaction vessel 1 over 140 min, maintaining the temperature at 100 °C. The reaction was held at this temperature for a further 2.5 h and then cooled to 20 °C and left overnight. The suspension was reheated to 60 °C, and then sodium thiosulfate (8.05 g, 50.9 mmol) and water (100 mL) were added. After mixing and allowing the layers to separate, the lower aqueous layer was discarded, and then the organic layer was concentrated by distillation under vacuum, removing around 370 mL of distillate. The temperature was adjusted to 95 °C and heptane (600 mL) added. The resulting suspension was cooled to 20 °C over 1 h, and then the solid product was collected by filtration, washed with ethanol (400 mL), and dried under vacuum at 40 °C to afford **6** as a pale yellow solid, weight 171.8 g (81% yield). Purity by UHPLC 98.8 area %.

[4-Acetylamino-3-(4-chlorophenylsulfanyl)-2-methyl-1*H*-indol-1-yl]acetic Acid (1). A mixture of **6** (99.9 kg, 240 mol), ethanol (393 kg), water (450 kg), and aqueous NaOH (10 M, 72.3 kg) was heated to 62 ± 3 °C and held at this temperature for 30 min. The resulting solution was cooled to 20 ± 3 °C and then filtered to remove particulate matter, and the filter was rinsed with water (50.9 kg). MIBK (403 kg) was added to the combined filtrates, and the mixture was heated to 60 ± 5 °C. A mixture of aqueous hydrochloric acid (10 M, 65.0 kg) in water (296 kg) was added to the hot solution over a period of around 45 min, maintaining the reaction temperature within the specified range. The resulting slurry was cooled to 15 ± 3 °C over approximately 60 min and held at this temperature overnight. The solid product was collected by centrifugation, washed with water (386 kg) followed by ethanol (249 kg), and then dried under vacuum at a maximum jacket temperature of 60 °C to give the title compound as a white solid: 79.1 kg (94%). Assay by HPLC 99.8% w/w. Purity by HPLC 99.5 area %. ^{1}H NMR (400 MHz): 13.20 (1H, br s), 9.51 (1H, s), 7.46 (1H, d, J = 7.5 Hz), 7.35−7.26 (3H, m), 7.11 (1H, t, J = 8.0 Hz), 6.98 (2H, d, J = 8.6 Hz), 5.12 (2H, s), 2.39 (3H, s), 1.85 (3H, s). m/z 389/391 (MH+).

■ ASSOCIATED CONTENT

Supporting Information

HPLC and UHPLC methods for AZD1981 and intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

TBAI (tetrabutyl ammonium iodide); Ac_2O (acetic anhydride); MIBK (methyl isobutyl ketone); MTBE (methyl-*t*-butyl ether); TCCA (trichlorocyanuric acid); NH_2OH·HCl (hydroxyl amine hydrochloride); EtOH (ethanol); NaBr (sodium bromide); NaI (sodium iodide); TFAA (trifluoroacetic acid); $ZnCl_2$ (zinc chloride).

■ ADDITIONAL NOTES

[a]We feel the intermediate **8**, being carbocyclic, is hydrophobic in nature. The compound exists as salt in basic pH probably because of the hydrophobic nature, and even in salt form, the solubility of this is not there in both organic and aqueous medium. As these facts are not confirmed, we have not added any comments on the reason for oiling. Further telescoping resulted in **3** without any problem. Therefore, our attention did not go into addressing this issue.

[b]The reaction aimed to have the cyclohexane-1,3-dione consumption up to around 97%, but the conversion of **7** to **8** is around 85% by LC area. Some amount of **9a** is also observed at this stage along with de-esterified impurity which was removed during the workup. Hence, the overall yield is around 62−67% for this two-stage process, starting from cyclohexane-1,3-dione.

[c]Hydroxylamine hydrochloride is used for the reaction instead of the free base to minimise the thermal hazard. Further, the reaction calorimetric study of the oximation reaction had shown no exotherm, indicating the safety of the process.

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