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An Efficient and Scalable Synthesis of the Spirocyclic Glycine Transporter Inhibitor GSK2137305

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Abstract:

An efficient and scalable synthesis of a glycine transporter inhibitor is presented. The key steps in the synthetic sequence are the formation of a spirocyclic imidazolidinone from an α-amino nitrile and a cyclic ketone and an arylation of 4-methyl imidazole under 'ligandless' Ullmann coupling conditions.

Introduction

GSK2137305 (**1**, Figure 1) is a potent and selective Glycine transporter type-1 (GlyT1) inhibitor and, thus, has potential for treating neurological and neuropsychiatric disorders.[1] A key structural feature of GSK2137305 is the spirocyclic imidazalone core.

The initial route for the synthesis of GSK2137305, used to prepare the first *ca*. 50 g of drug substance, is depicted in Scheme 1.[2] A number of factors made this approach unsuitable as the long-term supply route capable of delivering substantial quantities of **1**. For example, the eight-step synthesis provided crude **1** in <5% yield and had to be further purified by preparative HPLC to remove a regioisomeric impurity **2**, which originates from the copper-catalysed cross-coupling of aryl bromide **8** with 4-methyl imidazole. Furthermore, safety concerns due to the evolution of hydrogen cyanide during the Bucherer−Bergs reaction to form hydantoin **4** precluded the rapid operation of this chemistry in large scale equipment. We herein report the identification and development of a new, concise route to **1** that enabled its safe and rapid manufacture on a multikilogram scale.

Results and Discussion

It was postulated that it might be possible to go directly to the spirocyclic imidazolidinone **7** by conducting a Strecker reaction with 4-bromobenzaldehyde (**3**) and condensing the resulting amino nitrile **12** with cyclopentanone (Scheme 2). Initial reaction of the amine **12** with cyclopentanone would form the hemiaminal **13**, which could then undergo an intramolecular Pinner reaction to form the cyclic imidate **14**. Base catalysed rearrangement of **14** would then provide the desired imidazolidinone **7**. Indeed, there is limited literature precedent for the condensation of amino nitriles with ketones to generate imidazolidinone heterocycles,[3] which encouraged us to evaluate this approach further.

Hence, employing standard Strecker conditions the desired amino nitrile **12** was formed from 4-bromobenzaldehyde (**3**) in *ca.* 4 h at ambient temperature.[4] The product was then extracted into *tert*-butylmethyl ether (TBME) and washed with water to remove all cyanide waste. Since the reaction and waste streams remain basic throughout, the potential for hydrogen cyanide formation is avoided. Subjection of purified **12** to the literature conditions for the cyclisation, a neat reaction at elevated temperature with catalytic sodium methoxide,[3a] did generate imidazolidinone **7**, albeit as a minor component in the reaction mixture (Table 1, entry 1). Encouraged by this preliminary result, we sought to rapidly optimize the reaction conditions. By running the reaction in methanol a significantly cleaner reaction profile was obtained, with imidazolidinone **7** now observed as the major component (entry 2). Crystallisation occurred upon cooling the methanol solution to 0−5 °C, with **7** isolated in 14% yield and with high purity. A similar reaction profile was obtained with ethanol, and the lower solubility of **7** in ethanol led to a higher isolated yield (entry 3). The use of stoichiometric base offered no advantage (entry 4), and little or no desired product was observed in the absence of base or with sodium acetate or a range of organic bases (entries 5−9). A further improvement in both reaction profile and recovery was obtained on switching to 1-butanol, with little difference in reaction profile when run at either 90 or 120 °C (entries 10 and 11), but other solvents screened proved less effective (entries 12−16).

To allow efficient processing on a plant scale, it was desirable to telescope the Strecker reaction with the imidazolidinone formation, since amino nitrile **12** proved to be difficult to isolate and showed limited stability. Hence, after aqueous washes of the TBME solution of **12**, the reaction was dried by azeotropic distillation and concentrated to *ca*. 2 volumes by vacuum distillation. Although the imidazolidinone formation reaction

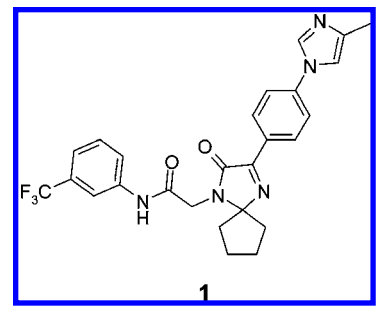

Figure 1. **GSK2137305 (1).**

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(1) (a) Blunt, R.; Cooper, D. G.; Porter, R. A.; Wyman, P. A. Patent Application WO 2009/034061 A1, 2009. (b) For a recent review on inhibitors of GlyT1 for the treatment of schizophrenia, see: Bridges, T. M.; Williams, R.; Lindsley, C. W. *Curr. Opin. Mol. Ther.* **2008**, *10*, 591.

(2) The chemistry as detailed in ref 1a was adapted by Simone Spada and Roberto Profeta at GSK Verona for the preparation of the first 50 g of GSK2137305.

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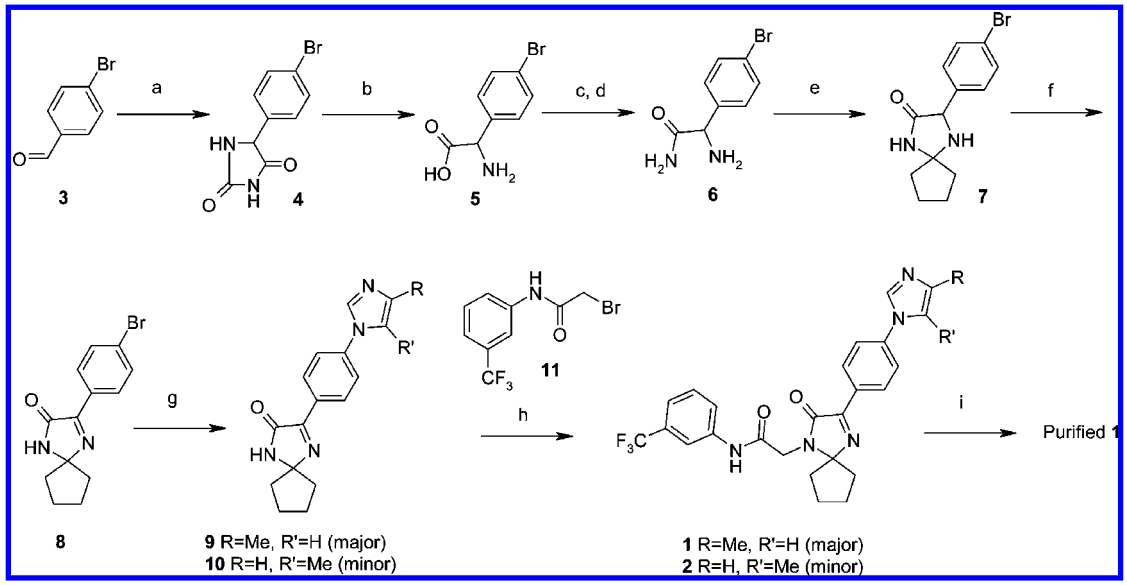
Scheme 1. **Initial route to GSK2137305**[a]



[a] Reagents and conditions: (a) KCN, $(NH_4)_2CO_3$, EtOH, H_2O, 68%; (b) H_2SO_4, 81%; (c) $SOCl_2$, MeOH, 91%; (d) NH_3 (aq), 66%; (e) cyclopentanone, H−Y zeolite, methanol, 63%; (f) NBS, CH_2Cl_2, 56%; (g) 4-methyl imidazole (6 equiv), CuI (0.6 equiv), L-histidine (1.2 equiv), K_2CO_3, DMSO, 50%; (h) KO*t*Bu, DMF, 81%; (i) preparative HPLC, *ca.* 65%.

Scheme 2. **Postulated preparation of imidazolidinone 7**

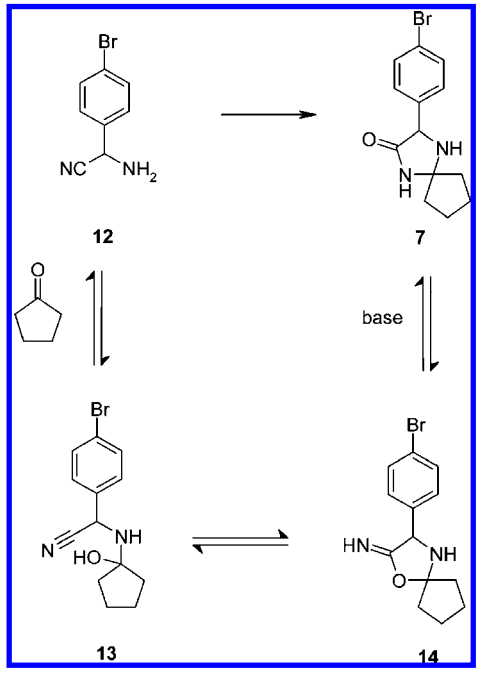


Table 1. **Solvent and base screen for reaction of amino nitrile 12 with cyclopentanone**

Entry[a]	Solvent	Base	Product[b] (%)
1	—[c]	NaOMe	6
2	MeOH	NaOMe	50 (14)
3	EtOH	NaOEt	54 (32)
4	EtOH	NaOEt[d]	50
5	EtOH	—	<5
6	EtOH	NaOAc	<5
7	EtOH	Et_3N	<5
8	EtOH	Pyridine	<5
9	EtOH	DBU	14
10	1-BuOH	NaOEt	63 (45)
11	1-BuOH[e]	NaOEt	60
12	2-BuOH	NaOEt	25
13	EtOAc	NaOEt	<5
14	Toluene	NaOEt	<5
15	THF	NaOEt	<5
16	Acetonitrile	NaOEt	<5

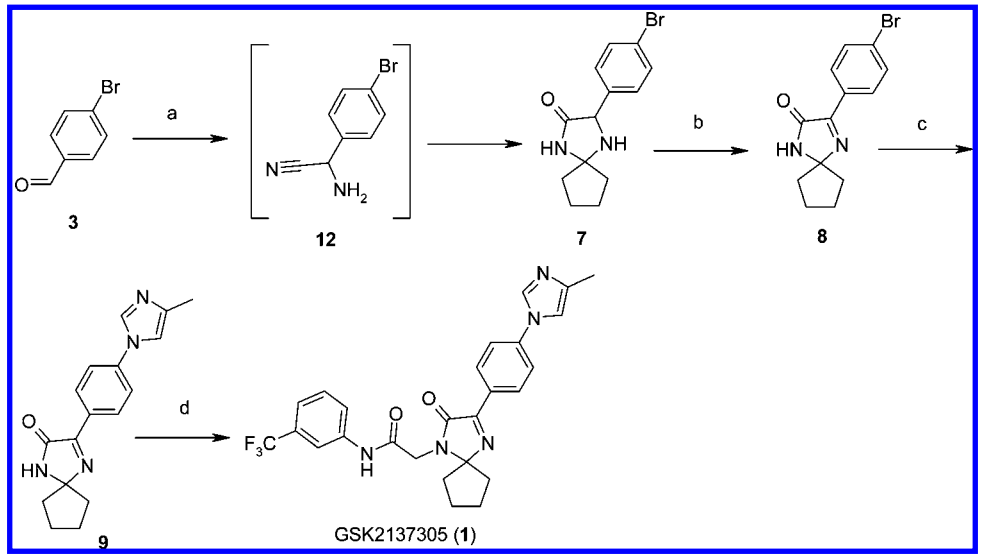
[a] Reactions run in Radley's carousel tubes as 0.5 M solutions of amino nitrile **12**, with 2.4 equiv of cyclopentanone and 0.1 equiv of base, and heated with a block temperature of 90 °C for 6−12 h. [b] Percentage a/a **7** in the reaction mixture, determined by HPLC. Isolated yields in parentheses. [c] Reaction performed neat, with 5 equiv of cyclopentanone. [d] 1.1 equiv of base used. [e] 120 °C block temperature.

tolerated the carryover of TBME, it did slow the reaction, so upon dilution with 1-BuOH and treatment with cyclopentanone and sodium ethoxide solution the reaction typically took about 12 h to reach completion at 80 °C. Upon cooling the reaction the desired product crystallised, providing imidazolidinone **7** in 35−40% isolated yield from 4-bromobenzaldehyde. Prior to transfer to plant the process was investigated by reaction calorimetry, with the exhaust gas monitored by mass spectroscopy due to the potential hazard of hydrogen cyanide evolution. We were not able to establish the absence of hydrogen cyanide during all of the process due to fragmentation of TBME in the mass spectrometer (a fragment with mass 27 masks that of HCN). However, the ratio between the main TBME signal and the fragment remained constant and no gas was evolved so we could infer that little or no hydrogen cyanide was generated. Hence, the construction of the aryl imidazolidinone spirocycle **7** from cheap, readily available starting materials employing an operationally simple and safe process was readily achieved. Although the yield was modest, it represented approximately a doubling of the yield when compared to the initial route and

(3) (a) David, A. C.; Levy, A. L. *J. Chem. Soc.* **1951**, 3479. (b) An imidazolidinone impurity was observed from the reaction of 1-amino-1-cyanocyclohexane in DMF under basic conditions, presumably formed by cyclisation/rearrangement with cyclohexanone, formed under the reaction conditions by adventitious water: Wendelin, W.; Kern, W.; Zmölnig, I.; Schramm, H. *Monatsh. Chem.* **1981**, 1091.

(4) Addition of ethanol to the procedure of Gaertner, M. *Photochem. Photobiol. Sci.* **2007**, 159. avoided material forming a gum in the reaction without adversely affecting the reaction profile.

Scheme 3. **New route to GSK2137305**[a]



[a] Reagents and conditions: (a) (i) NaCN, aq. NH_3, NH_4OAc, EtOH, 25 °C, 4 h; (ii) cyclopentanone, 1-BuOH, NaOEt, 80 °C, 35−40%; (b) DDQ, EtOAc, 60 °C, 80−85%; (c) 4-methyl imidazole, CuI, K_2CO_3, DMSO, 130 °C, 50−55%; (d) (i) NMP, aq. KOH; (ii) 3-aminobenzotrifluoride, chloroacetyl chloride, NMP, 75−80%.

significantly shortened the supply time for the preparation of the key intermediate **7**.

With a new, efficient route to imidazolidinone **7** in place, all that remained to complete the four-stage synthesis of GSK2137305 (**1**) was the oxidation of **7**, an Ullmann coupling with 4-methyl imidazole and an *N*-alkylation reaction (see Scheme 3). However, there were still many issues that needed to be addressed with these three steps in order to develop a route suitable for further scale-up. The oxidation of imidazolidinone **7** had initially been performed using *N*-bromosuccinimide (NBS) in dichloromethane. However, it was shown that the imidazolone product **8** competitively reacted with NBS, generating a range of decomposition products and limiting the isolated yield of **8** to about 50%. When 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) was used as oxidant, complete conversion to **8** was observed after 1 h at 60 °C in ethyl acetate. Furthermore, unlike the NBS process, the product remained stable to the reaction conditions. Excess DDQ was destroyed with aqueous sodium sulfite, and following removal of the aqueous waste and concentration of the organic phase, imidazalone **8** crystallised from solution and was isolated in 80−85% yield.

The next challenge was to develop a scalable coupling of aryl bromide **8** with 4-methyl imidazole. There has been a resurgence of interest in recent years in the Ullmann-type copper-catalysed arylation of nucleophiles, in particular around the *N*-arylation of azoles, since these have proved difficult to couple under palladium catalysed conditions.[5] Indeed, the chemistry utilised in the initial route used a CuI/L-histidine system to affect the coupling. Although this was successful in preparing **9**, high loadings of CuI (0.6 equiv) and L-histidine (1.2 equiv) were employed and several side reactions competed, including the coupling of L-histidine with the aryl bromide. This meant that the isolation of **9** from the reaction mixture was not trivial. Additionally, a *ca*. 4:1 mixture of the 4- and 5-methyl imidazole regioisomers (**9** and **10**, respectively) was formed in the reaction, a ratio similar to other known examples of the coupling of 4-methyl imidazole with aryl bromides that do not possess ortho-substituents,[6,7] with the 4-methyl isomer formed as the major product due to steric factors.[6a] The undesired 5-isomer **10** converts through to the corresponding regioisomer of drug substance (**2**), and this impurity needed to be controlled to very low levels. In the initial route, preparative HPLC was used to remove this isomer from drug substance, and this was unsuitable for the long-term supply of GSK2137305 (**1**). Improving the regioselectivity of the Ullmann coupling reaction was considered; however, given the literature precedent for coupling of 4-methyl imidazole with aryl bromides, it was regarded that any significant improvements within a short time frame would be unlikely. Instead, the focus remained on developing facile chemistry that is easy to scale and to gain the desired purification through control of the crystallisation processes.

An initial screen of the CuI catalysed coupling of **8** with 4-methyl imidazole in different solvents and with a range of commercially available ligands identified several useful leads, particularly for alcoholic solvents with diamine ligands.[8] However, it proved difficult to quickly identify a facile method to isolate **9** free from the catalyst, ligand, and other impurities.[9] We reasoned that the presence of 4-methyl imidazole might render an additional ligand superfluous and that 'ligandless' conditions would simplify the isolation of **9**. Gratifyingly, the

(5) For recent reviews on the copper-catalysed arylation of nucleophiles, see: (a) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed* **2008**, *47*, 3096. (b) Sorokin, V. I. *Mini-Rev. Org. Chem*. **2008**, *5*, 323.

(6) (a) Altman, R. A.; Koval, E. D.; Buchwald, S. L. *J. Org. Chem*. **2007**, *72*, 6190. (b) Zhu, L.; Guo, P.; Li, G.; Lan, J.; Xie, R.; You, J. *J. Org. Chem*. **2007**, *72*, 8535. (c) Huang, W.; Shakespear, W. C. *Synthesis* **2007**, 2121. (d) Kiyomori, A.; Marcoux, J.; Buchwald, S. L. *Tetrahedron Lett*. **1999**, *40*, 2657. (e) Lo, Y. S.; Nolan, J. C.; Maren, T. H.; Welstead, W. J., Jr.; Gripshover, D. F.; Shamblee, D. A. *J. Med. Chem*. **1992**, *35*, 4790.

(7) A recent example of the coupling of an aryl iodide with 4-methyl imidazole under mild conditions has reported a 17:1 ratio of regioisomers; see: Zhu, L.; Guo, P.; Li, G.; Lan, J.; Luo, L.; You, J. *J. Org. Chem*. **2009**, *74*, 2200.

'ligandless' CuI catalysed reaction between aryl bromide **8** and 4-methyl imidazole proceeded cleanly in DMSO at 130 °C to afford a *ca*. 4:1 mixture of regioisomers **9** and **10**,[10] albeit with a slightly extended reaction time of *ca*. 36 h.[11] Addition of aqueous L-cysteine solution and isopropyl acetate allowed the removal of the inorganics, including copper, in the aqueous layer, and **9** was crystallised from the organic phase in 50−55% yield as a *ca*. 20:1 mixture of regioisomers. Although we had identified milder conditions from our initial screen, these 'ligandless' conditions meant that the process was cheap, operationally simple, and suitable for supplying **9** in high purity on a multikilogram scale.

The final chemistry stage required the *N*-alkylation of imidazalone **9**. The reaction proved to be more efficient using 2-chloro-*N*-[3-(trifluoromethyl)phenyl]acetamide rather than the bromo analogue **11**, with the optimal reaction profiles obtained in a polar aprotic solvent and with a strong base. Using NMP as solvent, it was possible to directly telescope the alkylation with the preparation of 2-chloro-*N*-[3-(trifluoromethyl)phenyl]acetamide, from 3-aminobenzotrifluoride and chloroacetyl chloride.[12] Crystallisation of **1** was achieved by addition of water to the reaction mixture, with **1** isolated in 75−80% yield in high purity and <1% of the imidazole regioisomer **2**. Further upgrade in the purity of **1** could be readily obtained by recrystallisation from a DMSO/1-propanol solvent system in 80% yield.

All stages of the synthetic sequence performed as expected during a pilot plant campaign, with a total of 19.5 kg of **1** prepared in a 12% overall yield, representing a 4-fold increase in yield compared to the initial route.

Conclusions

A facile and scalable four-stage synthesis of the glycine transporter inhibitor GSK2137305 (**1**) has been developed. The new route considerably lowers the cost and delivery time required to prepare multikilogram quantities of **1**, through the rapid access to the imidazolidinone intermediate **7** and control of the chemistry and isolations in the oxidation, Ullmann coupling, and alkylation steps. The scope and utility of the key reaction to form the imidazolidinone structure from amino nitrile and carbonyl compounds are currently being explored and will be reported in due course.

Experimental Section

3-(4-Bromophenyl)-1,4-diazaspiro[4.4]nonan-2-one 7. A slurry of 4-bromobenzaldehyde (**3**) (29.6 kg, 1 equiv) in ethanol (75 L) was charged to a solution of ammonium acetate (37.5 kg, 3.0 equiv) and sodium cyanide (8.7 kg, 1.1 equiv) in water (27 L) and aqueous ammonia (35% w/w, d = 0.88; 63 L), washing in with further ethanol (15 L). The resultant reaction mixture was stirred at 20 ± 3 °C for *ca.* 4 h until the reaction was deemed complete by HPLC analysis. TBME (150 L) was added, and the aqueous layer was removed. The organic phase was washed with water (2 × 150 L), aqueous sodium chloride solution (20% w/w; 2 × 150 L), and further water (60 L). The organic phase was azeotropically dried by atmospheric distillation and concentrated to *ca.* 50 L at 20−30 °C under reduced pressure. To the concentrate of amino nitrile **12** were charged 1-BuOH (300 L), cyclopentanone (36 L, 2.5 equiv), and NaOEt (21% wt in ethanol, 6 L, 0.1 equiv), and the reaction was warmed to 80 ± 5 °C for *ca*. 12 h until deemed complete by HPLC analysis. The reaction was cooled to 20 ± 3 °C, and the resulting crystals were isolated by filtration, washed with cold ethanol (5 ± 3 °C; 2 × 60 L), and dried under vacuum at 50 ± 5 °C to provide an off-white solid of **7** (16.3 kg, 35% yield) with 97% area purity by HPLC. ^{1}H NMR (400 MHz; d_6-DMSO) δ 8.54 (s, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 4.53 (d, J = 8.4 Hz, 1H), 3.62 (d, J = 8.4 Hz, 1H), 1.85−1.60 (m, 8H). ^{13}C NMR (100 MHz; d_6-DMSO) δ 173.4, 139.8, 130.7, 129.4, 120.1, 81.6, 61.1, 40.3, 38.7, 22.5, 22.4. HRMS (ES +ve) calcd for $C_{13}H_{16}N_2OBr$ 295.0446, found 295.0452.

3-(4-Bromophenyl)-1,4-diazaspiro[4.4]non-3-en-2-one 8. To a slurry of **7** (14.0 kg, 1 equiv) in EtOAc (280 L) at 20 ± 5 °C was charged DDQ (11.9 kg, 1.1 equiv). The resultant reaction mixture was heated to 60 ± 5 °C until the reaction was deemed complete by HPLC analysis. The reaction was washed twice at 60−65 °C with aqueous sodium sulfite solution (10%w/w; 140 and 70 L) and then with water (70 L). The organic phase was concentrated to *ca*. 140 L by distillation at atmospheric pressure, and the resulting slurry cooled to 0 ± 3 °C. The solids were isolated by filtration, washed with cold EtOAc (0 ± 3 °C; 2 × 28 L), and dried at 50 ± 5 °C under vacuum to afford off-white crystals of **8** (11.7 kg, 84% yield) with 99% area purity by HPLC. ^{1}H NMR (400 MHz; d_6-DMSO) δ 10.10 (s, 1H), 8.28 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 8.8 Hz, 2H), 1.99−1.81 (m, 8H). ^{13}C NMR (100 MHz; d_6-DMSO) δ 163.9, 159.0, 131.6, 129.8, 125.2, 89.7, 37.0, 23.8. HRMS (ES +ve) calcd for $C_{13}H_{14}N_2OBr$ 293.0289, found 293.0298.

3-[4-(4-Methyl-1*H*-imidazol-1-yl)phenyl]-1,4-diazaspiro-[4.4]non-3-en-2-one 9. A slurry of **8** (10.5 kg, 1 equiv), 4-methyl imidazole (10.5 kg, 3.6 equiv), potassium carbonate (10.5 kg, 2.1 equiv), and copper(I) iodide (1.5 kg, 0.15 equiv) in DMSO (52 L) was heated to 130 ± 3 °C until the reaction was deemed complete by HPLC (∼36 h). The reaction mixture

(8) Ullmann coupling screen conditions: Aryl bromide **8** (0.34 mmol), 4-methylimidazole (0.68 mmol), CuI (0.068 mmol), Cs_2CO_3 (0.68 mmol), ligand (0.14 mmol), and solvent (1.2 mL) heated to 110 °C for 30 h under an atmosphere of nitrogen, monitoring by HPLC. Ligands screened: L-proline; ethylene glycol; 1,10-phenanthroline; ninhydrin; (±)-*trans*-1,2-diaminocyclohexane; 2-dimethylaminoethanol; *N*,*N*′-dimethylethylenediamine; *trans*-*N*,*N*′- dimethylcyclohexane-1,2-diamine; 8-hydroxyquinoline. Solvent screened: DMSO; *o*-xylene; toluene; 1,4-dioxane; proprionitrile; NMP; *n*-butyl acetate; DMPU; 1-butanol; 1-pentanol.

(9) Residual copper levels of ≤10 ppm in drug substance **1** were required. To achieve this specification, copper levels of <100 ppm were targeted in **9**.

(10) Regioisomeric ratio determined by ^{1}H NMR. See Supporting Information for further details.

(11) Only DMSO was investigated as solvent for the 'ligandless' reaction, since it is a preferred dipolar aprotic solvent for use on scale and some success in isolating **9** from a DMSO solution had previously been achieved. For other examples of copper-catalysed coupling of imidazoles with aryl halides that do not require a separate ligand, see refs 6b,e, and 7.

(12) 3-Aminobenzotrifluoride, chloroacetyl chloride, and 2-chloro-*N*-[3-(trifluoromethyl)phenyl]acetamide were all flagged as potential genotoxic impurities. Chloroacetyl chloride will be hydrolysed to chloroacetic acid under the reaction conditions, and this, together with 3-aminobenzotrifluoride and 2-chloro-*N*-[3-(trifluoromethyl)phenyl]acetamide, was nonmutagenic when tested in a bacterial mutation screening assay (Ames test).

was cooled to 60−70 °C and treated with isopropyl acetate (73 L) and 3% w/w aqueous L-cysteine solution (73 L). The layers were separated, and the lower aqueous phase was back-extracted with isopropyl acetate (73 L) at 60 ± 5 °C. The organic phases were combined, diluted with ethanol (42 L), and then washed twice with a mixture of 3% w/w aqueous L-cysteine solution (31 L) and 10% w/w K_2CO_3 solution (31 L), followed by water washes (2 × 52 L). Isopropyl acetate (73 L) was charged, and the reaction was concentrated by atmospheric distillation to *ca.* 105 L, during which time the product crystallised. The slurry was cooled to 20 ± 3 °C, and the solids were isolated by filtration, washed with isopropyl acetate (52 L then 26 L), and dried under vacuum at 50 ± 5 °C to provide an off-white solid of **9** (5.65 kg, 54%) with 97% area purity by HPLC and *ca.* 5% regioisomer **10** by ^{1}H NMR. ^{1}H NMR (400 MHz; d_6-DMSO) δ 10.05 (s, 1H), 8.43 (d, J = 9.2 Hz, 2H), 8.26 (d, J = 1.2 Hz, 1H), 7.76 (d, J = 9.2 Hz, 2H), 7.54 (s, 1H), 2.18 (s, 3H), 2.00−1.82 (m, 8H). ^{13}C NMR (100 MHz; d_6-DMSO) δ 164.1, 158.8, 138.9, 138.8, 134.7, 129.4, 128.5, 119.3, 113.8, 89.6, 37.1, 23.8, 13.6. HRMS (ES +ve) calcd for $C_{17}H_{19}N_4O$ 295.1559, found 295.1561.

2-{3-[4-(4-Methyl-1*H*-imidazol-1-yl)phenyl]-2-oxo-1,4-diazaspiro[4.4]non-3-en-1-yl}-*N*-[3-(trifluoromethyl)phenyl]acetamide 1. Chloroacetyl chloride (3.15 kg, 1.1 equiv) was charged to a solution of 3-aminobenzotrifluoride (4.73 kg, 1.15 equiv) in NMP (30 L), maintaining a temperature in the range 25 ± 5 °C. The reaction solution was stirred at 25 ± 5 °C until the reaction was deemed complete by HPLC (*ca.* 10 min). This solution was then charged to a stirred solution of **9** (7.5 kg, 1 equiv) and 45% wt. aqueous KOH solution (5.5 L, 2.5 equiv) in NMP (30 L), rinsing in with NMP (7.5 L). The reaction was stirred at 25 ± 5 °C until deemed complete by HPLC (*ca.* 6 h). Product was crystallised by addition of water (37 L), and the slurry temperature cycled to 70 ± 3 °C before isolation by filtration at 20 ± 3 °C. The solids were washed sequentially with 2:1 v/v NMP/water (22 L vol), water (2 × 22 L), and 1-propanol (22 L). The cake was reslurried in 1-propanol (75 L), then filtered, and dried under vacuum at 50 ± 5 °C to provide white crystals of GSK2137305 (**1**) (9.8 kg, 78%) with 99% area purity by HPLC. Mp 258−260 °C. ^{1}H NMR (500 MHz; d_6-DMSO) δ 10.57 (s, 1H), 8.46 (d, J = 8.5 Hz, 2H), 8.28 (d, J = 1.0 Hz, 1H), 8.11 (s, 1H), 7.80 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 8.5 Hz, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.56 (s, 1H), 7.44 (d, J = 8.0 Hz, 1H), 4.38 (s, 2H), 2.19 (s, 3H), 2.16−1.68 (m, 8H). ^{13}C NMR (100 MHz; d_6-DMSO) δ 166.3, 162.6, 157.5, 139.4, 139.1, 138.9, 134.8, 130.1, 129.5 (q, J_{CF} = 31.6 Hz), 129.4, 128.3, 124.1 (q, J_{CF} = 272 Hz), 122.8, 119.9 (q, J_{CF} = 3.5 Hz), 119.4, 115.2 (q, J_{CF} = 3.8 Hz), 113.8, 93.3, 43.4, 34.4, 23.6, 13.6. HRMS (ES +ve) calcd for $C_{26}H_{25}F_3N_5O_2$ 496.1955, found 496.1937.

Recrystallisation of 1. Crude **1** (9.65 kg) was dissolved in DMSO (48 L) at 80 ± 5 °C, filtered, and charged with 1-propanol (96 L). The solution was cooled to 65 ± 3 °C and seeded with a slurry of **1** (9.6 g) in 1-propanol (100 mL). The slurry was cooled to 20 ± 3 °C, and the solids were isolated by filtration, washed with 1-propanol (2 × 29 L), and dried under vacuum at 50 ± 5 °C to provide a white, crystalline solid of **1** (7.74 kg, 80%) with >99% area purity by HPLC and <0.3% of the imidazole regioisomer **2**.

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Supporting Information Available

^{1}H and ^{13}C NMR, LC/MS, and HPLC data of the final product (**1**), isolated intermediates (**7**, **8**, and **9**), and the regioisomeric impurity **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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