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A Simplified Process for the Manufacture of AZD0530, a Potent SRC Kinase Inhibitor

Steven A. Raw,* Brian A. Taylor, and Simone Tomasi

Pharmaceutical Development, AstraZeneca, Charter Way, Macclesfield, SK10 2NA, U.K.

ABSTRACT: An efficient process for the manufacture of AZD0530 **1**, a potent SRC kinase inhibitor, has been developed. The key transformation, reaction of monofluoroanilide **7** with alcohol **8**, was much simplified between manufacturing campaigns. The development of a robust, efficient, and scalable process for this transformation drew on both a practical and theoretical understanding of the process and is described herein

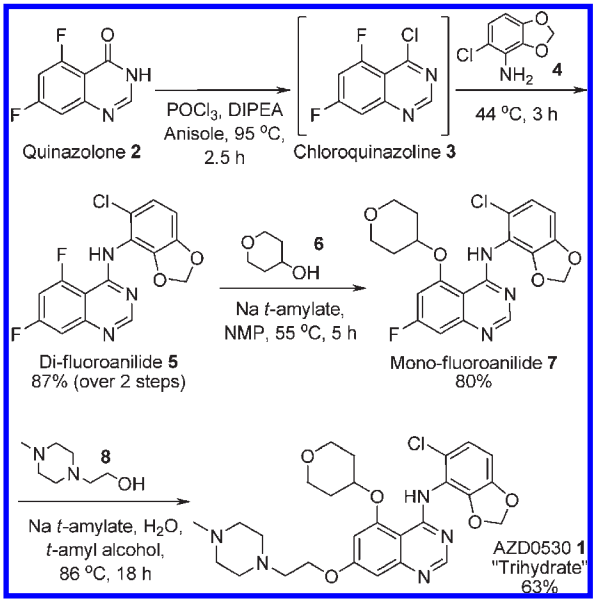
INTRODUCTION

Previous communications have disclosed the development of an expedient process[1] for the manufacture of multikilogram quantities of AZD0530 **1**, a potent SRC kinase inhibitor for the treatment of solid tumours.[2] This route comprised the conversion of readily accessible quinazolone **2** to the corresponding chloroquinazoline **3**, followed by three consecutive S_NAr reactions with **4**, **6**, and **8**, exploiting the differing reactivities of the halogens decorating chloroquinazoline **3** (Scheme 1). The synthesis outlined in Scheme 1 varies from that used for our first multikilogram-scale manufacture[1c] of AZD0530 **1** in one respect: that *tert*-amyl alcohol is employed as solvent in the transformation of **7** to **1** instead of diethoxyethane for toxicological and environmental reasons. This change was made between pilot plant campaigns, and the *tert*-amyl alcohol process was successfully carried out on a >100 kg scale.

This manufacturing route was concise, and most of the stages were considered satisfactorily robust for potential technical transfer to a commercial manufacturing unit. However, the final S_NAr reaction, transformation of monofluoroanilide **7** into AZD0530 **1**, was not fully optimized, primarily due to time constraints.

The key issues with the process as it stood at the time were: (1) use of a protic solvent of apparently similar pK_a to the alcohol **8**; (2) significant levels of unidentified byproducts, as observed by HPLC, if the batch temperature was allowed to rise above 90 °C; (3) a high charge of alcohol **8** (3.1 mol equiv) was required to achieve acceptable reaction times (contributory to this was the upper limit on reaction temperature); (4) the hitherto unexplained requirement for a charge of "magic water" equimolar to the charge of sodium *tert*-amylate to suppress byproduct formation (this water charge was also required when aprotic solvents such as diethoxyethane[1c] were employed); (5) the process was operationally complex, with a high number of operations, including two vacuum distillations, low minimum volumes, and an accurate pH adjustment; (6) a relatively low isolated yield (average of 63% over four batches) with an unacceptably high loss to liquors (approximately 8% of theoretical); and (7) the isolation of AZD0530 **1** as a trihydrate which dehydrated easily, became friable, and rehydrated to varying levels.

Scheme 1. Large-scale manufacturing route to AZD0530[1]



RESULTS AND DISCUSSION

The beginning of a further manufacturing campaign to support phase II and III trials, requiring delivery of 280 kg of API, gave us the opportunity to redevelop the synthesis of AZD0530 **1** from monofluoroanilide **7** and address some, if not all, of these issues.

A preliminary solvent screen showed that the aromatic solvents anisole, toluene, and chlorobenzene gave similar reaction profiles to that seen with *tert*-amyl alcohol, under comparable conditions. With little to choose between these solvents in terms of reaction profile, toluene was chosen for further study based on practical considerations (*e.g.*, toxicity, environmental impact, density, and boiling point).

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We then undertook a factorial experimental design study, intended to optimize the reaction parameters in toluene, using Fractional Factorial Design with 4 factors, each set at 2 levels, Resolution IV, with 2 centre points, a total of 10 experiments.[3] The results from this are summarized below:

- The charge of base had little effect on reaction outcome when above 2.20 mol equiv. The range explored was 2.20 to 3.60 mol equiv.
- The stoichiometry of the water charge is crucial. Charges greater than equimolar to base stoichiometry significantly reduce the rate of reaction.
- Higher temperatures give an increased rate of reaction but higher levels of impurities. This can be tempered by slight increases in water charge.
- Increasing the stoichiometry of alcohol **8** increases the reaction rate. Ideally, however, this charge would be minimized to minimize cost.

With this basic understanding of the practicalities of the reaction, we sought to explore the nature of the species present in an effort to fully comprehend the process. To do this, we embarked upon the *in silico* modeling of the species involved. Relative basicities in the gas phase and in toluene were computed using Density Functional Theory (DFT). Solvation effects were estimated using PCM (Polarizable Continuum Model). The calculations were performed for a range of temperatures, but only the results for 363 K (90 °C) are reported here:

Alcohol 8. *tert*-Amyl alcohol was found to be a weaker acid, compared to alcohol **8**. Its deprotonation in toluene is 4.7 kcal/mol more energetic than that of **8**, corresponding to a ΔpK_a of 2.8 units. Since *tert*-amyl alcohol is the weaker acid, its conjugate base, *tert*-amylate, is capable of deprotonating **8**. Further to that, we found that internal chelation operating in the alkoxide of **8** (*vide infra*) plays an important role in the stability of the sodium alkoxide (Figure 1), contributing to increasing the acidity of **8** beyond that expected for a standard primary alcohol.

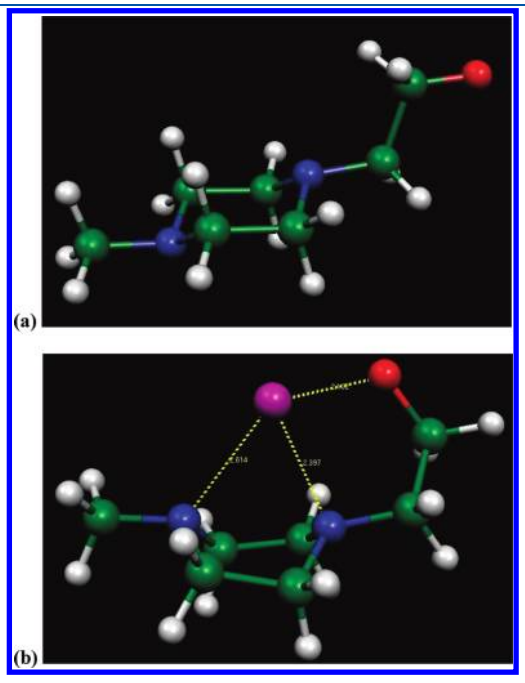


Figure 1. Conformational stability in the alkoxide of side chain **8**.

A thorough conformational analysis revealed that the most stable geometry of neutral **8** was the chair conformation, with both the methyl and the $-CH_2CH_2OH$ substituents equatorial. The same geometry is found in the alkoxide of **8**, if the sodium cation *is not* considered, as shown in Figure 1 a. When the cation is included explicitly in the calculations, another conformation for the alkoxide of **8** is found to be most stable. This has the piperazine ring in a boat conformation, with the two ring substituents *pseudo*-equatorial and the $-CH_2CH_2ONa$ group folded onto itself, bringing the Na^+ into a position where it is capable of interacting with the lone pairs of both nitrogen atoms, as shown in Figure 1 b. This chelation provides enhanced stability to the alkoxide of **8** relative to the non-chelated mode, calculated as a $\Delta G°$ of 2.8 kcal/mol at 363 K, or 1.7 pK_a units.

Sodium *tert*-Amylate. Whilst sodium *tert*-amylate is clearly an adequate base for the deprotonation of **8** in pure toluene, the presence of water equimolar to the base makes it questionable that sodium *tert*-amylate is present in the reaction environment. It is much more likely that NaOH is actually present, due to the hydrolysis of sodium *tert*-amylate to *tert*-amyl alcohol and NaOH. It is well known that hydroxide is a weaker base than alkoxides in aqueous solution,[4] with high solvation in water mitigating its basicity. This is not the case for other solvents, which are not as capable of solvating it. Table 1 shows the proton affinities of hydroxide and *tert*-amylate anions in the gas phase and in toluene solution. In all cases the effect of the cation is ignored.

Table 1. Calculated proton affinities at 298 K

	OH^-	*tert*-Amylate	ΔG (or $\Delta\Delta G_{Solv}$)
Gas phase (calc)	−384.9	−367.2	17.7
Gas phase (expt)[5]	−383.7	−366.5	17.2
Toluene	−334.6	−335.7	−1.1
ΔG_{Solv} toluene	−51.4	−32.6	18.8

In the gas phase the hydroxide anion is a much stronger base than *tert*-amylate. Comparison with accurate experimental proton affinities[5] demonstrates the reliability of the gas-phase *in silico* results. In toluene, the two bases are of approximately equal strength (*tert*-amylate being marginally stronger). This is due to the much larger solvation energy of hydroxide. In a highly polar solvent like water, the difference would be even larger, making hydroxide a much weaker base compared to *tert*-amylate.

Substrate and Product. The last point of the *in silico* investigation was to assess the basicity of monofluoroanilide **7** and AZD0530 **1**, as both species possess a relatively acidic anilide proton. The calculations showed that the anilide protons of **7** and **1** are more acidic than the OH proton of alcohol **8**. Deprotonation of **7** with hydroxide is 20.6 kcal/mol exergonic in toluene at 363 K; while under the same conditions deprotonation of **8** is 6.7 kcal/mol exergonic (including the chelate effect). As expected, the anilide proton of **1** is less readily available than that of **7**, due to the different substitution pattern (the electron-withdrawing F-substituent of **7** has been replaced by an electron-donating alkoxy group in **1**). Practically, this means that 1 equiv of base is consumed by deprotonation of the substrate, before deprotonation of alcohol **8** is possible. This is in accordance with the FED observation that at least 2 mol equiv of base are required for acceptable reaction rates.

These results suggested to us that *in the absence of water* NaOH should be a valid substitute for sodium *tert*-amylate as a base for this process, especially considering that the aforementioned

chelate effect makes the deprotonation of **8** more favored than that for a normal primary alcohol. Removal of the water formed during the deprotonation of **7** and **8** by NaOH may also be beneficial to reactivity. The relative pK_a values resulting from these *in silico* calculations are summarized in Figure 2.

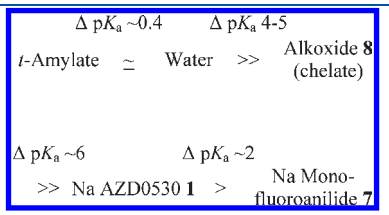


Figure 2. Relative basicities in toluene at 363 K with approximate ΔpK_a values.

The learning from the theoretical study of this reaction is summarized below:

- Both sodium *tert*-amylate and NaOH are basic enough to deprotonate alcohol **8** in anhydrous toluene at 363 K (90 °C).
- The internal chelation of the Na^+ cation in the alkoxide of **8** makes a large contribution to the enhanced acidity of **8** relative to a normal primary alcohol.
- At least 2 equiv of base are required for the transformation as both **7** and **1** are more acidic than **8** and therefore consume the first equivalent of base charged.
- The presence of water when using sodium *tert*-amylate will lead to the hydrolysis of the alkoxide to give aqueous NaOH, which is a weaker base and not capable of completely deprotonating **8**.

Given the now considerable understanding we had of the processes involved in the conversion of monofluoroanilide **7** into AZD0530 **1**, both practical and theoretical, we decided to pursue a water-free process using NaOH as base and toluene as solvent for further development.

We quickly established that this system gave a much better reaction profile by HPLC than the existing *tert*-amyl alcohol system and the upper reaction temperature limit of 90 °C was no longer applicable. The reaction was successful even at reflux temperature (approximately 109 °C), though an operating range of 104−106 °C was deemed preferable when energy consumption at a large scale was considered. The increased temperature and the simplified reaction system meant that the charge of alcohol **8** could be more than halved, from 3.2 to 1.5 mol equiv, though the process is typically carried out with a 1.7 mol equiv charge to ensure robustness. The reaction time was also halved, from 18 to 9 h.

As the water-free system had proved to be beneficial to the process, we also explored the continuous removal of the water formed *in situ* by means of a Dean−Stark apparatus. This indeed proved to be advantageous in terms of reaction rate, reducing reaction times to 5 h, as opposed to 9 h, and this may have delivered further reductions in the charge of alcohol **8**. However, we found that, under these "anhydrous" conditions, reaction mixtures were impractically thick, to the point of being immobile. We propose that the mole equivalent of water liberated *in situ* serves to solubilize some of the anionic species present, though we have no evidence as to which or of the precise mechanism.

We were also keen to understand why, if in the original process the charge of "magic water" simply produced NaOH and *tert*-amyl alcohol *in situ*, the reaction profile observed by HPLC was significantly worse than the newly devised process. To this end, we carried out a series of experiments using the new conditions that included a charge of *tert*-amyl alcohol in increasing amounts. These showed that, as the charge of *tert*-amyl alcohol increased, so the HPLC profile deteriorated. Many of the impurities observed were those arising from hydrolysis of the monofluoroanilide **7** and AZD0530 **1**, at several positions. We presume that the alcohol in some way solubilizes the hydroxide ions in toluene, thus promoting hydrolysis pathways, whereas in the alcohol-free system any unreacted hydroxide remains in the solid phase.

We proved very early in this phase of development that the trihydrate form of AZD0530 **1** could be crystallized from the toluene reaction mixture, albeit after a significant quantity of water (e.g., 2 relative volumes) was charged. As discussed in the Introduction, however, this morphology was problematic in terms of processing. A short investigation showed that a new, anhydrous form of AZD0530 **1** could easily be isolated from the toluene mixture, providing it was dried azeotropically prior to crystallization. We also showed that seeding the mixture at saturation point and subsequent slow addition of heptane antisolvent gave excellent control of the crystallization process. This anhydrate of **1** proved stable up to 95% relative humidity.

The changes discussed above combined to make a robust, much-simplified process. These improvements also saw a significant increase in isolated yield from 63% to ≥80%, with the losses to liquors being ≤1% of theoretical. The process is also now much simpler from an accommodation perspective, with a reduced number of operations. The process flow is outlined in the schematic below (Figure 3)

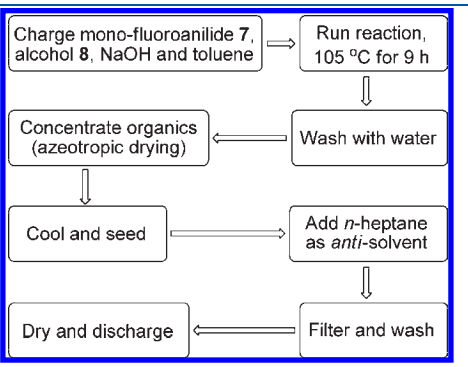
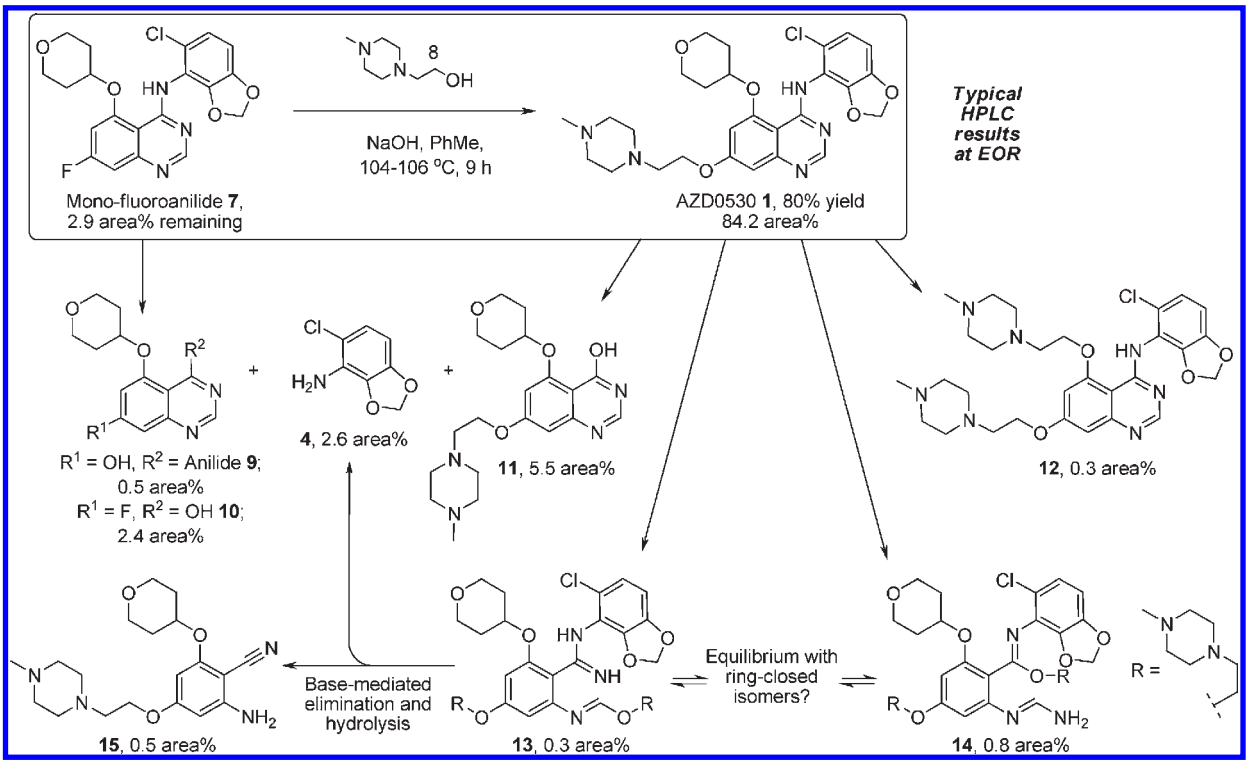


Figure 3. A schematic outline of the new process.

In the final phases of development, our focus turned to identification of the byproducts from this S_NAr reaction, in an effort to gain a full understanding of the process. We succeeded in this, with all significant byproducts being characterized (by LCMS at least) and many being synthesized independently (**9**, **10**, **11**, and **15**). We believe that these identified species account for the remaining mass balance of the reaction (Scheme 2). Furthermore, a good understanding of the identity of these byproducts allowed us to make a thorough evaluation of the process against structural alerts for mutagenicity,[6] an important consideration given AZD0530 **1** is the API. In the event, only cyanoaniline **15** gave a structural alert, but this was proven to be non-genotoxic by subsequent synthesis and 5-strain GLP Ames testing (in the presence and absence of S9) using the plate incorporation method.[7]

The majority of these byproducts (**9**, **10**, **11**, **13**, and **14**) are removed by water washes once the reaction is complete, as are

Scheme 2. Typical reaction outcome in the synthesis of AZD0530 1



unreacted alcohol **8** and the inorganic salts. The subsequent crystallization rejects the remainder (**12** and **15**). A small amount of monofluoroanilide **7** persists in the isolated AZD0530 **1**, but this is totally rejected in a subsequent crystallization process in which the difumarate salt of AZD0530 **1** is formed.[1]

CONCLUSIONS

By the effective integration of learning from factorial experimental design studies, *in silico* theoretical analyses, and subsequent focused laboratory experimentation, we have rapidly developed an operationally simple, robust process for the conversion of monofluoroanilide **7** into AZD0530 **1**. We have addressed all of the issues associated with the anteceding processes and, concurrently, gained an excellent understanding of the current process. The improved process has been employed in a pilot plant campaign of AZD0530 **1**, delivering 300 kg of material over four batches in an overall yield of 80%.

EXPERIMENTAL SECTION

Reactants and reagents were purchased from standard chemical suppliers. Quinazolone **2** was purchased from Ube Industries (Fine Chemicals), Ube City, Yamaguchi, Japan.

To a 1150 L hastelloy vessel equipped with a baffle and flat-bladed turbine agitator under an atmosphere of nitrogen were charged sequentially monofluoroanilide **7** (72.5 kg, 173.5 mols), 20−40 mesh sodium hydroxide (25.0 kg, 625 mol), and toluene (399 L). The agitator was started, and the vessel contents were adjusted to 20 °C. To the mixture was then charged side chain **8** (43.8 kg, 303.7 mols), followed by a line wash of toluene (73 L). The resulting slurry was warmed to 104−106 °C over 2 h and then held at this temperature for 9 h. The vessel contents were then adjusted to 70 °C over 30 min, and a sample was taken for analysis to confirm satisfactory conversion.

In a separate 1500 L glass-lined mild-steel vessel, equipped with a baffle and retreat curve agitator, water (510 L) was warmed to 75 °C, ready for use. 290 L of this warm water were charged to the reaction mixture, causing an exotherm of 6 °C. The mixture was stirred at 70 °C for 30 min, and then the agitator stopped. The mixture was allowed to equilibrate for 30 min, and then the lower, aqueous phase was removed and discarded. This washing procedure was repeated twice more with the remainder of the warm water, first with 145 L and last with 75 L. The upper organic phase was retained in the reactor and concentrated by distillation (at a pressure of 1 bar) to a volume of 250 ± 20 L.

The resulting solution was then cooled to 90 °C and transferred from the reactor to the crystallizer, a 1000 L glass-lined mild-steel vessel, equipped with a baffle and retreat curve agitator, followed by a line wash of toluene (50 L). The contents of the crystallizer were adjusted to 65 °C, and AZD0530 **1** seed material (0.363 kg, 0.5 wt %) was added. The batch was allowed to equilibrate for 3 h, and then heptane (288 L) was charged *via* an orifice plate over 2 h, maintaining the temperature at 63−67 °C. The resulting slurry was held for 1 h and then cooled from 65 to 17 °C over 3 h. The mixture was transferred to a 750 L pressure filter, and the liquors were removed by application of nitrogen pressure. To the crystallizer was charged heptane (177 L) and toluene (120 L), and the agitator was restarted. The wash mixture was then transferred to the pressure filter and passed through the cake by nitrogen pressure. This displacement wash procedure was repeated once more. The cake was then dried by a flow of hot nitrogen (40 °C) to a constant weight and discharged to give AZD0530 **1** (81.5 kg, 100 wt/wt%, 86.7% yield), as a highly crystalline, colourless solid.[8]

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COMPUTATIONAL DETAILS

All geometry optimizations and corresponding frequency calculations were carried out at the B3LYP/6-31G* level of theory using the Gaussian 03 suite of programs.[9] Accurate electronic energies were computed as B3LYP/6-31+G** single points on the B3LYP/6-31G* geometries. Scaled zero-point potential energies were used in the calculation of free energies, using a scaling factor of 0.9806.[10] Solvation energies were obtained from single-point calculations on the gas-phase optimized geometries, using the IEF-PCM model[11] and the UAKS set of radii.

AUTHOR INFORMATION

Corresponding Author

*To whom correspondence should be addressed. Email: steven.raw@astrazeneca.com.

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