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Communication

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Development of an Efficient and Practical Route for the Multikilogram Manufacture of Ethyl 5-Cyano-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate and Ethyl 6-Chloro-5-cyano-2-methylnicotinate, Key Intermediates in the Preparation of P2Y12 Antagonists

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ABSTRACT: Elucidation of the mechanism of formation of two major impurities in the synthetic route towards key intermediate ethyl 5-cyano-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate **1**, led directly to the development of a route with significant process improvements in terms of yield, purity, and operability. The overall process yield increased from 15% to 73% without the need for extra purification steps, giving the key intermediate ethyl 6-chloro-5-cyano-2-methylnicotinate, **2**, in excess of 80 kg to support clinical development.

INTRODUCTION

Ethyl 5-cyano-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate, **1** (cyanopyridone), and ethyl 6-chloro-5-cyano-2-methylnicotinate, **2** (chloropyridine), were key intermediates to an AstraZeneca development candidate[1] (Figure 1). The initial kilogram-scale route to these compounds was problematic, and the development of a more robust and scaleable route to multikilogram quantities was needed.

This kilogram-scale route (Scheme 1), a three-step synthesis, involved a condensation of ethyl acetoacetate **3**, and *N*,*N*-dimethylformamide dimethylacetal (DMFDMA) **4**, to give the enaminone **5**, followed by a condensation with cyanoacetamide **6** to afford **1**, and a final chlorination to produce **2**. The process involved lengthy workups and low yields for both steps 2 and 3, mainly due to the instability of enaminone **5** in step 1. Furthermore, formation of a thick slurry during step 2 reaction made agitation difficult, causing the isolation of impurities with the step 2 product. The colour of step 3 material (caused by impurities) and the compatibility of the thionyl chloride/DMF reagent-pair in step 3 also needed attention.

The major concerns were safety, poor yield and difficult isolations experienced with the original route. The work plan was to carry out a comprehensive literature review to investigate any potential alternative routes to **1** and **2**, followed by testing in the laboratory of the most promising alternatives. Finally, the preferred method of choice was to be developed to give a process suitable for 400−600 L scale. Literature[2] showed that the vast majority of pyridinones such as **1** are synthesized using a similar chemistry approach to the above route. Thus, a better understanding of the reaction and the generation of the process impurities was believed to be of fundamental importance. The results of this investigation are discussed in this report.

RESULTS AND DISCUSSION

Two main impurities were observed in the preparation of **1**, and these are shown in Figure 2. We started our work by trying to understand how these impurities were formed.

Impurity **7** was initially believed to be the acid from ester hydrolysis of the ester product, due to residual water. However, the revised assignment of **7** to **8** as the methyl ketone, supported by the carbonyl peak at 192 ppm in the ^{13}C NMR spectrum, made this impurity the product of an alternate cyclisation (Scheme 2). The condensation of the amide nitrogen with the carbonyl of the ester in intermediate **10** accounts for the formation of ketone **8**. Thus, the required mode of condensation to afford **1** is that between the amide nitrogen and the carbonyl of the ketone in **10**.

Impurity **9**, the formal product of nitrile hydrolysis, was initially believed also to be due to water. However, the higher concentration of impurity **9** formed at both lower temperatures or when the weaker base K_2CO_3 was used, was inconsistent with a simple nitrile hydrolysis of **1**. Rationally, a different mechanism must be operating to afford impurity **9**. A proposed mechanism[3] for the competing pathway to form impurity **9** is outlined in Scheme 3. Under mildly basic conditions the enolate **10b** is formed, use of a stronger base enables deprotonation of **10b** to give the dianion **10a** which gave the desired product **1**. The intramolecular condensation between the enolate and the cyano group of **10b** results in the pyran intermediate **11**. Ring-opening of the pyran intermediate **11** can be easily accomplished by a nucleophile. Dimethylamine, still present in the reaction mixture, could attack the pyran ring to undergo ring-opening and generate the diamide intermediate **12**. The final ring closure is then achieved by an intramolecular *Michael addition*-type reaction, which affords impurity **9**.

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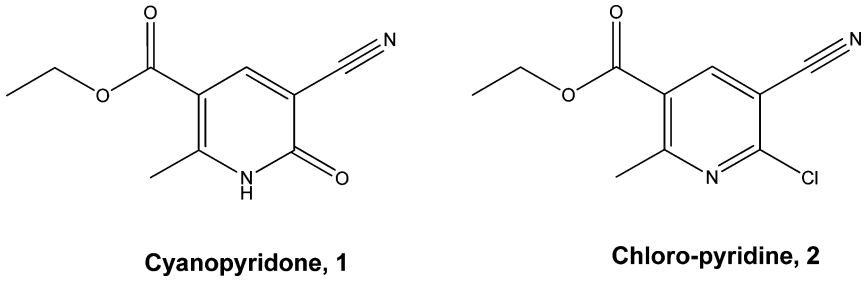
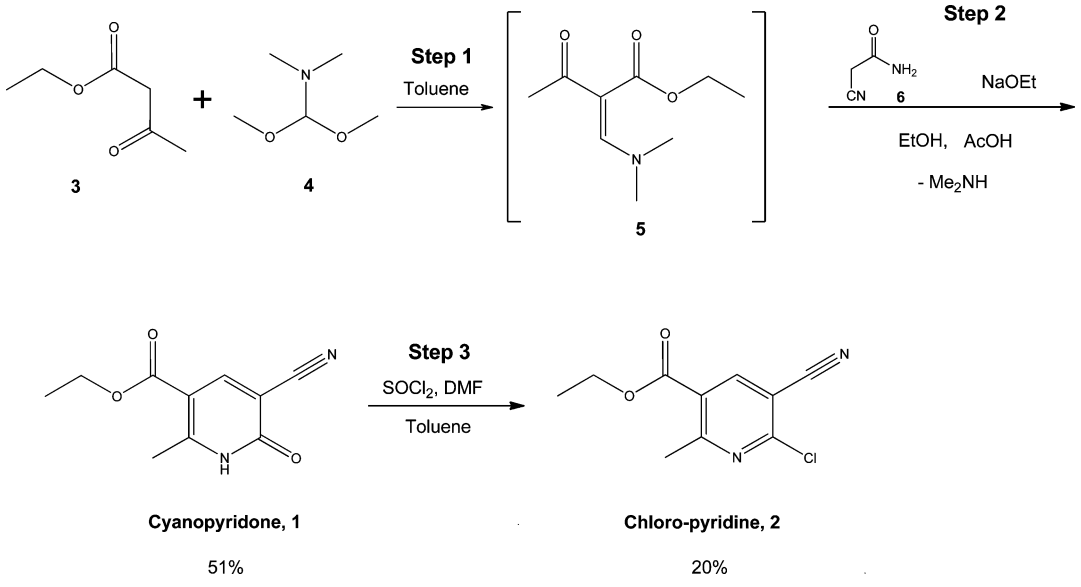


Figure 1. Key intermediates.

Scheme 1. Original route



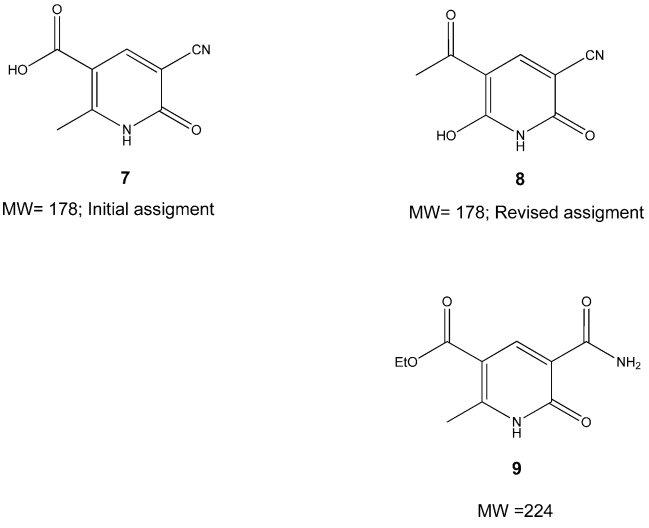


Figure 2. Impurities of original route.

Assuming that the formation of impurity **9** follows the pathway in Scheme 3, then the replacement of cyanoacetamide **6** (Scheme 1) by malononitrile **13** would still afford **1** via **14**, **15**, and **16** (Scheme 4). This pathway was demonstrated by an experiment using malononitrile in place of cyanoacetamide under the initial reaction conditions.

Not only did this support the proposed mechanism of formation of impurity **9** but also gratifyingly formed product **1** with a substantially reduced level of impurity **8** still present due to reaction between deprotonated amide and the ester group in intermediate **16**. The information obtained from the increased understanding of the reaction process led directly to the development of the new conditions for target **1**.

The development work examined the use of a weaker base and a change in the order of addition so that the malononitrile was added slowly over time due to concerns of self-condensation when strong bases in combination with malononitrile are used. This work showed that triethylamine could be used in place of stronger alkoxide bases, and since dimethylamine is liberated as the reaction proceeds, only a catalytic quantity was required. It was observed that the use of the catalytic amounts of weaker base, triethylamine, gave an easily stirred and almost homogeneous mixture up to the quench with acetic acid. Ethanol was the solvent of choice for steps 1 and 2, allowing the process to be telescoped with the product of step 2 isolated by crystallisation simply on addition of water.

With step 2 product in hand, the chlorination of **1** to afford **2** was found to proceed cleanly in both neat $POCl_3$ and $POCl_3$/acetonitrile, avoiding any concerns with the potential genotoxic dimethylcarbamoyl chloride (DMCC).[4] The optimised conditions were 1.6 equiv of $POCl_3$ in 3 vol of acetonitrile; an easily stirred mixture was obtained, and when 1.6 equiv of $POCl_3$ was used, a clear solution was obtained after approximately 2 h. Full conversion (<1% area by HPLC of **1**) was observed after 20 h. The reaction did not go to completion when 1.2 equiv of $POCl_3$ was used.

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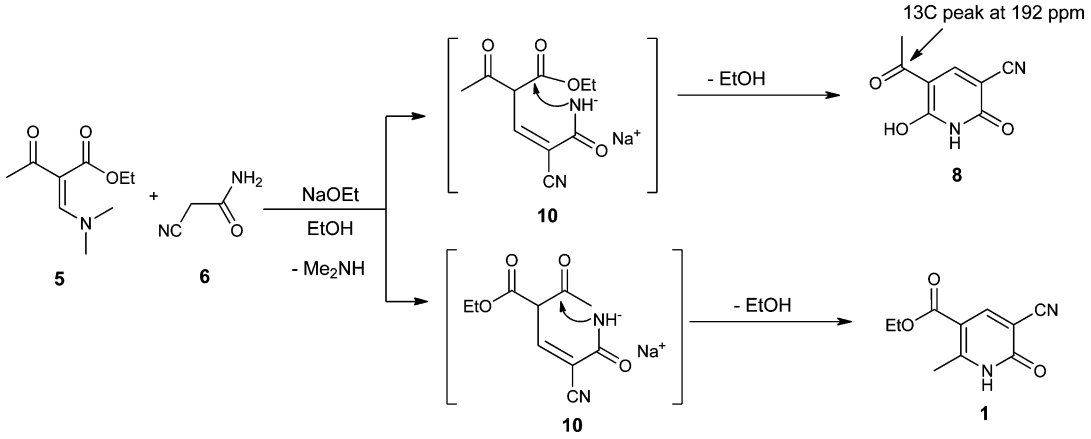
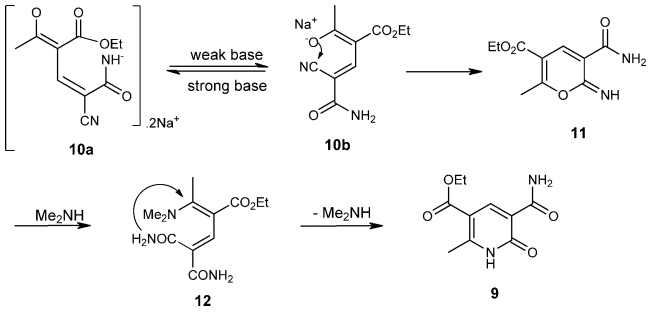
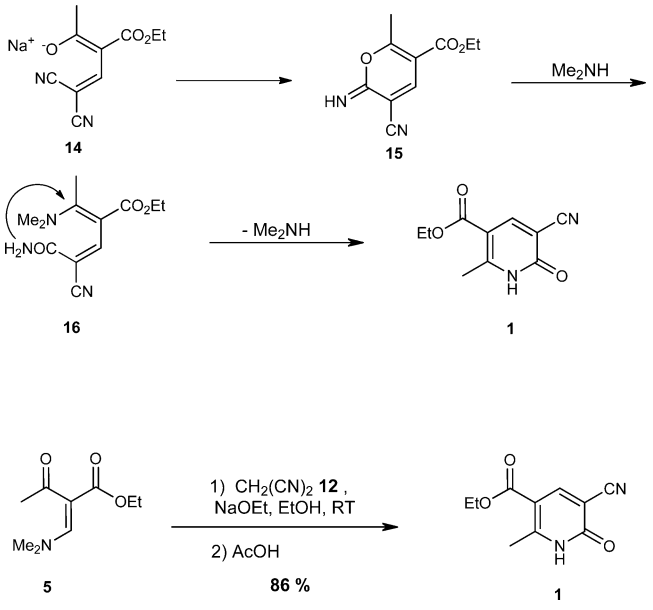
Scheme 2. Mechanism for the formation of impurity 8



Scheme 3. Mechanism for the formation of impurity 9

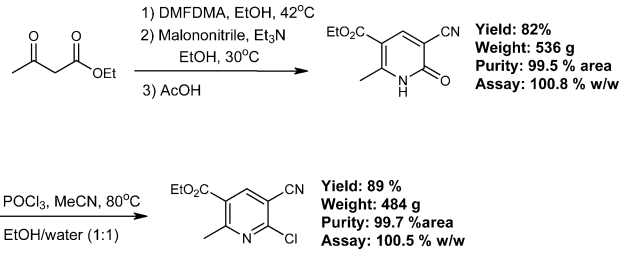


Scheme 4. New process to compound 1



The workup was initially performed by concentrating to dryness. Addition of ice and water was followed by neutralisation with K_2CO_3 or NaOH. Extraction into either MTBE or DCM resulted in the isolation of crude brown material of **2** in 90−95% yield. However, compound **2**, even under strongly acidic conditions (pH <1), is easily extracted into an organic phase such as MTBE or ethyl acetate. Consequently, the neutralisation with a vast amount of base could be avoided and **2** easily obtained in a MTBE solution. The optimised process included the addition of 6 vol of MTBE at 0−15 °C and slow addition of 6 vol of water.[5] The water phase was back-extracted with MTBE and the combined organic phases were subsequently washed with 4 vol of water, 2 × 5% K_2CO_3 solution and water. Crystallisation was found to be excellent from either methanol, ethanol or isopropanol in 1:1 ratio with water. The recovery of **2** was found to be approximately 90% in all three experiments. It was found that a solvent exchange to ethanol proceeded very efficiently. Concentrating the MTBE to approximately 2−3 vol and charging 6 vol of ethanol and concentrating to 5 vol resulted in <1% (by ^{1}H NMR) of MTBE and acetonitrile in the solution. The precipitation of **2** was completed by addition of 5 vol of water at 5−10 °C. The filtration was also found to proceed very efficiently. Under optimised conditions (Scheme 5), **2** was afforded in 89% in 500 g scale.

Scheme 5. Developed process



The first scale-up campaign (1 kg) was performed in a combination of 30 and 50 L vessels to test the chemistry at scale. The formation of the pyridinone behaved as expected with 1.25 kg (79%) of the pyridone obtained after crystallisation from the reaction mixture via the addition of water. However, the step 3 product from the chlorination reaction, while pure by ^{1}H NMR spectroscopy, was much darker than usual (brown vs pale yellow). Following a brief investigation, this was found to be due to charring of the material on the jacket of the reactor. The temperature was thus lowered in subsequent batches from acetonitrile at reflux to 70−75 °C. Although the reaction took longer to reach completion (typically 20 h), the reaction profile remained unchanged, and more importantly the colour of the isolated chloropyridine was more acceptable. Thus, for the manufacturing plant campaign, the jacket temperature was controlled (set to 80−85 °C and contents of reactor monitored) during the

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formation of the chloropyridine. A check of the colour of the product solution at the end of the aqueous workup was also introduced prior to the solvent exchange into ethanol as a final check prior to isolation of the chloropyridine where a charcoal treatment on the solution could be performed in the event of problems with colour. A total of 80.5 kg of chloropyridine **2** was manufactured in three independent batches with consistent yields and purities obtained.[6]

■ CONCLUSION

The new process to the key intermediate cyanopyridone **1** has led to significant process improvements in terms of yield, purity, and operability. The overall yield of chloropyridine **2** from ethyl acetoacetate increased from 15% to 73% without the need for extra purifications post-isolation. The successful characterisation of the key impurities in the original route and the drive to understand the mechanism of their formation led directly to the development of the new route. These processes scaled well into our manufacturing plant, enabling us to produce >80 kg of chloropyridine **2** to the required purity specification. This process was successfully applied to the manufacture of P2Y12 inhibitors development candidate.[1c]

■ EXPERIMENTAL SECTION

All materials were purchased from commercial suppliers and were used as supplied by manufactures. NMR spectra of intermediates were recorded on a Bruker 500 MHz. HPLC analysis results are described as area %. The analysis of intermediates and reaction monitoring was performed by GC for step 1 and HPLC for steps 2 and 3. GC analysis was performed in an Agilent 6890 series or equivalent with FID equipped with a Zebron ZB-5 ms, 30 m × 0.32 mm ID, 0.5 μm FT. The method started with an initial temperature of 100 °C and temperature ramp of 10 °C/min to 300 °C, run time 35 min, carrier gas He with a flow 2.0 mL/min. The FID detector parameters were temperature 300 °C, hydrogen flow 45 mL/min., air 450 mL/min, nitrogen 45 mL/min (make up gas) with an injection volume of 1 μL. HPLC analysis was carried out on a system with a binary/quaternary pump with a variable wavelength or photodiode array detector equipped with a C-18 Onyx Monolithic 100 mm × 4.6 mm column. It used a gradient method of 100% mobile phase A (20 mM sodium phosphate pH 6.0) to 50:50 mobile phase A/mobile phase B (70:30 acetonitrile: mobile phase A), flow rate 2 mL/min injection volume 10 μL.

Ethyl 5-cyano-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (1). To a clean dry reactor equipped with overheaded mechanical stirrer and condenser, ethyl acetoacetate (0.4 L, 1 equiv), ethanol (0.82 L, 2 vol) and DMFDMA (0.46 L, 1.03 equiv) were charged. The mixture was warmed to an internal temperature of 41−43 °C for 5 to 6 h until ≤2% of ethyl acetoacetate remained by GC. The reaction mixture was cooled to 20−25 °C and triethylamine (44.4 mL, 0.1 equiv) was added followed by slow addition of a solution of malononitrile (235 g in 1.77 L of ethanol, 1.1 equiv), cautiously maintaining the temperature between 25 and 36 °C. The mixture was stirred for 16 h at 20 °C until less than 5% area of enaminone **5** remained by HPLC (315 nm). Acetic acid (217 mL, 1.2 equiv) was added slowly at 20−25 °C to pH 4−5, and a dense precipitate was formed. The mixture was warmed to 70−75 °C, and water (5.6 L) was charged. The suspension was cooled down to 10 °C over 3 h and stirred for 15 min at 0 °C. The product was filtered, washed three times with water (3 × 1.25 L), and dried at 50 °C under vacuum to afford 539 g (82% yield) of the desired product **1** as an orange solid pure by HPLC at 99.5% and 100.8% w/w NMR assay (maleic acid standard); ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.0 (s, 1H), 8.44 (s, 1H), 4.21−4.25 (q, 2H, J = 5 Hz), 2.61 (s, 3H), 1.28−1.31 (t, 3H, J = 5 Hz).

Ethyl 6-Chloro-5-cyano-2-methylnicotinate (2). Cyanopyridinone **1** (500 g, 1 equiv), acetonitrile (1.5 L, 3 vol), and $POCl_3$ (361 mL, 1.6 equiv) were charged in 20 L round-bottom flask with an overhead mechanical stirrer and condenser, heated to 80−85 °C (external temperature), and stirred for 20 h under nitrogen until less than 1% area of cyanopyridinone **1** was observed by HPLC (260 nm). The reaction mixture was cooled to 0−5 °C, and MTBE (3 L, 6 vol) was charged; then purified water (3 L, 6 vol) was charged over 1.5 h at a temperature between 0 and 15 °C. *CAUTION: Exothermic quench of* $POCl_3$. Layers were stirred for 30 min at 10−20 °C and settled for 10 min. The layers were separated, the remaining aqueous layer was recharged, and MTBE (1 L) was added to this layer. It was stirred for 5 min and settled for 5 min at 20 °C. The layers were separated, and the remaining organic layer was combined with the previous one. Water (2 L) was charged to the combined organic layer, stirred for 5 min, and settled for 5 min at 20 °C. The layers were separated. A solution of potassium carbonate 5% w/w in water (2 L, 4 vol) was charged, stirred for 5 min, and settled for 5 min at 20 °C; the layers were separated. The previous wash was repeated a second time. Purified water (2 L) was charged, stirred for 5 min, settled for 5 min and the layers were separated. The remaining organic layer was concentrated under vacuum at 40 °C to 2−3 volumes of solvent (∼1 L of solvent, ∼2 mL of solvent/g of pyridinone). Ethanol (3 L) was added and distilled under vacuum at 40 °C up to 5 volumes (∼2.5 L). The previous operation was repeated until residual MTBE and acetonitrile was below 1 mol % by ^{1}H NMR relative to ethanol. The mixture was stirred and cooled down to 5−10 °C. Purified water was charged (2.5 L) over 20 min and stirred for 30 min at 5−10 °C. The product was filtered and washed twice with purified water (2 × 1 L) to give 484 g (yield 89%) of the desired product **2** as a yellow solid pure by HPLC at 99.7% and 100.5% w/w NMR assay (maleic acid standard); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (s, 1H), 4.40−4.44 (q, 2H, J = 5 Hz), 2.90 (s, 3H), 1.41−1.44 (t, 3H, J = 5 Hz).

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Notes

The authors declare no competing financial interest.

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(5) ARSST analysis of the reaction and quench mixtures was used to establish the basis of safety for the process.
(6) Analytical information: NMR spectra of intermediates were recorded on a Bruker 500 MHz. HPLC analysis results are described as area %. The analysis of intermediates and reaction monitoring was performed by GC for step 1 and HPLC for steps 2 and 3. GC analysis was performed in an Agilent 6890 series or equivalent with F.I.D equipped with a Zebron ZB-5 ms, 30 m × 0.32 mm ID, 0.5 μm FT. The method started with an initial temperature of 100 °C and temperature ramp of 10 °C/min to 300 °C, run time 35 min, carrier gas He with a flow 2.0 mL/min. The FID detector parameters were temperature 300 °C, hydrogen flow 45 mL/min, air 450 mL/min, nitrogen 45 mL/min (make up gas), with an injection volume of 1 μL. HPLC analysis was carried out on a system with a binary/quaternary pump with a variable wavelength or photodiode array detector equipped with a C-18 Onyx Monolithic 100 mm × 4.6 mm column. It used a gradient method of 100% mobile phase A (20 mM sodium phosphate pH 6.0) to 50:50 mobile phase A/mobile phase B (70:30 acetonitrile/mobile phase A), flow rate 2 mL/min, injection volume 10 μL.

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