Development of a Safe and Economical Synthesis of Methyl 6-Chloro-5-(trifluoromethyl)nicotinate: Trifluoromethylation on Kilogram Scale

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Supporting Information

ABSTRACT: Reported herein is a safe and economical synthesis of methyl 6-chloro-5-(trifluoromethyl)nicotinate, an intermediate in the synthesis of novel anti-infective agents. The key to this process is the trifluoromethylation of an aryl iodide using an inexpensive methyl chlorodifluoroacetate (MCDFA)/KF/CuI system, with an emphasis on the development work which led to this effective process.

INTRODUCTION

The trifluoromethyl group is a common functional group that possesses advantageous drug-like properties and exhibits good stability.1 There are an increasing number of pharmaceutical agents currently under development which possess this moiety. This has driven the development of practical strategies for installation of the CF3 group, which is a challenging problem in organic synthesis. However, the cost of many trifluoromethylating reagents can be prohibitive for use in commercial pharmaceutical manufacture.2 As part of the development of an alternative economic route to methyl 6-chloro-5-(trifluoromethyl)nicotinate I, several trifluoromethylation strategies were surveyed (Figure 1).

Methyl 6-chloro-5-(trifluoromethyl)nicotinate, I, is a key synthon in the synthesis of anti-infective agents currently under development in our laboratories. In the first-generation synthesis of I, the sourced raw material hydroxypyridine I was a major contributor to the final drug cost, (>800/kg at 100 kg scale). Alternatively, a strategy involving trifluoromethylation of an aryl halide II could result in a substantial cost reduction if an economical [CF3] source could be used. Herein is reported an efficient and cost-effective process for the synthesis of I, including a description of the process development and scale-up work.

RESULTS AND DISCUSSION

Development of the Substrate for Trifluoromethylation. The raw material 6-hydroxynicotinic acid (2) is an attractive precursor for I (Scheme 1); (<70/kg at 1 MT). A process which involves the substitution of a halide at the 5-position of compound 5 with CF3 would be a potentially cost-effective alternative to purchasing an expensive precursor (such as 1) that already contains the CF3 moiety.

Iodide 5 could be readily obtained via two methods (Scheme 2). In the first strategy (Route A), 6-hydroxynicotinic acid 2 was iodinated with N-iodosuccinimide (NIS) in THF to give iodo acid 4; the iodination was slow, and the addition of 0.5 equiv of sulfuric acid was necessary to drive the iodination to >95% conversion. The product iodo acid 4 was then converted to the acid chloride 6 by bis-chlorination of the carboxyl and hydroxypyridine moieties using oxalyl chloride and DMF. The resulting acyl chloride was not isolated, and instead the methyl ester was formed directly by charging methanol to the reaction mixture. The most notable issue observed with Route A was formation of dimeric impurities, which were difficult to remove. Alternatively, the order of reactions could be interchanged (Route B, Scheme 2), whereby 6-hydroxynicotinic acid 2 was iodinated with N-iodosuccinimide (NIS) in THF to give iodo acid 4; the iodination was slow, and the addition of 0.5 equiv of sulfuric acid was necessary to drive the iodination to >95% conversion. The product iodo acid 4 was then converted to the acid chloride 6 by bis-chlorination of the carboxyl and hydroxypyridine moieties using oxalyl chloride and DMF. The resulting acyl chloride was not isolated, and instead the methyl ester was formed directly by charging methanol to the reaction mixture. The most notable issue observed with Route A was formation of dimeric impurities, which were difficult to remove.

Alternatively, the order of reactions could be interchanged (Route B, Scheme 2), whereby 6-hydroxynicotinic acid 2 was converted to 3 via esterification and iodination in one pot.3 Accordingly, a slurry of 2 was esterified in methanol with sulfuric acid. This esterification consistently gave high conversion (~95%) and was followed by iodination with NIS. A small amount (5%) of starting acid remained, but fortunately, the remaining 2 was eventually converted to 6-chloro-5-
iodonicotinic acid, which was removed in the subsequent chlorination step during the isolation of 5. The product 3 was obtained in 87% yield and contained 3−5% (HPLC area) of the iodinated acid 4.

A solvent screen for the chlorination of 3 produced several options that led to high conversion (best results shown in Table 1). Anisole and DMF did not provide 100% conversion during screening (entry 1), failed to give complete conversion to product on gram scale (entry 2). Ethereal solvents 1,4-dioxane, DEE, and DME (entries 4–6) gave the best results, all providing complete conversion. 4,1-Dioxane, although not the most preferred solvent for scale-up (ICH class 2 due to toxicity), was the best option at this stage of development and was chosen to fulfill the immediate scale-up needs.

Diisopropylethylamine provided the best results among several bases screened (including triethylamine, morpholine, and DBU). Thus, intermediate 3 underwent uneventful chlorination using POCl3 with diisopropylethylamine in 1,4-dioxane to give the desired product 5 in 93% yield.

Route B (via intermediate 3) was selected for scale-up because the quality of 5 obtained was superior and the material from this route provided more consistent results and higher yields in the following trifluoromethylation step. A pilot-plant campaign produced ∼100 kg of iodide 3 in two batches in 87% yield.

Development of Trifluoromethylation Conditions.

With iodide 5 in hand, all attention shifted to the trifluoromethylation reaction. There has been an abundance of literature published on trifluoromethylation in recent years. Applications of Ruppert’s reagent (R3SiCF3, R = alkyl) are most prominent.5−9 However, the large-scale availability of CF3SiMe3 and produced several small impurities which could not be easily removed (entries 6, 7). The neat reaction with POCl3 with diethylaniline (entry 8) gave full conversion but also more impurities (30% HPLC area). Acetonitrile, while promising during screening (entry 1), failed to give complete conversion to product on gram scale (entry 2). Ethereal solvents 1,4-dioxane, DEE, and DME (entries 4–6) gave the best results, all providing complete conversion. 4,1-Dioxane, although not the most preferred solvent for scale-up (ICH class 2 due to toxicity), was the best option at this stage of development and was chosen to fulfill the immediate scale-up needs. Disopropylethylamine provided the best results among several bases screened (including triethylamine, morpholine, and DBU). Thus, intermediate 3 underwent uneventful chlorination using POCl3 with disopropylethylamine in 1,4-dioxane to give the desired product 5 in 93% yield.

Route B (via intermediate 3) was selected for scale-up because the quality of 5 obtained was superior and the material from this route provided more consistent results and higher yields in the following trifluoromethylation step. A pilot-plant campaign produced ∼100 kg of iodide 3 in two batches in 87% yield.

Table 1. Solvent screen for chlorination of 3 to produce 5

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>T (°C)</th>
<th>conv. (%)</th>
<th>HPLC area % $^b$</th>
<th>assay yield (wt % $^c$)</th>
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<tbody>
<tr>
<td>1</td>
<td>ACN</td>
<td>80</td>
<td>&gt;99</td>
<td>99.3</td>
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</tr>
<tr>
<td>2</td>
<td>ACN$^a$</td>
<td>80</td>
<td>90</td>
<td>75.0</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>1,4-dioxane</td>
<td>100</td>
<td>100</td>
<td>100.0</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>DEE</td>
<td>105</td>
<td>&gt;99</td>
<td>99.0</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>DME</td>
<td>85</td>
<td>&gt;99</td>
<td>98.3</td>
<td>99</td>
</tr>
<tr>
<td>6</td>
<td>anisole</td>
<td>100</td>
<td>99</td>
<td>97.9</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td>DMF</td>
<td>100</td>
<td>95</td>
<td>89.0</td>
<td>84</td>
</tr>
<tr>
<td>8</td>
<td>none$^d$</td>
<td>100</td>
<td>100</td>
<td>70.0</td>
<td>–</td>
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</tbody>
</table>

$^a$0.2 g scale, POCl3 2 equiv, DIPEA 2 equiv, solvent 10 vols, 12–14 h.

$^b$HPLC 220 nm.

$^c$HPLC wt % assay.

$^d$Diethylaniline as base.

Table 2. Reagent screen for trifluoromethylation of iodide 5

<table>
<thead>
<tr>
<th>entry</th>
<th>copper source</th>
<th>ligand</th>
<th>CF3 reagent</th>
<th>conv. (%)</th>
<th>des-I $^b$</th>
<th>HPLC area %</th>
<th>assay wt % $^c$</th>
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<tbody>
<tr>
<td>1</td>
<td>CuI (1.5 equiv)</td>
<td>none</td>
<td>MCDFA</td>
<td>98</td>
<td>7</td>
<td>82</td>
<td>71</td>
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<tr>
<td>2</td>
<td>CuI</td>
<td>1,10-phen</td>
<td>MCDFA</td>
<td>91</td>
<td>6</td>
<td>68</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>CuI</td>
<td>2,2′-bipyridine</td>
<td>MCDFA</td>
<td>84</td>
<td>2</td>
<td>70</td>
<td>64</td>
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<tr>
<td>4</td>
<td>CuBr2</td>
<td>1,10-phen</td>
<td>MCDFA</td>
<td>55</td>
<td>12</td>
<td>34</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>CuBr2</td>
<td>2,2′-bipyridine</td>
<td>MCDFA</td>
<td>94</td>
<td>7</td>
<td>70</td>
<td>69</td>
</tr>
<tr>
<td>6</td>
<td>Cu<a href="(ACN)$_2$">I</a>(PF$_6$)</td>
<td>1,10-phen</td>
<td>MCDFA</td>
<td>95</td>
<td>5</td>
<td>75</td>
<td>73</td>
</tr>
<tr>
<td>7</td>
<td>Cu<a href="(ACN)$_2$">I</a>(PF$_6$)</td>
<td>1,10-phen</td>
<td>FSO$_2$CF$_2$CO$_2$Me</td>
<td>99</td>
<td>1</td>
<td>76</td>
<td>72</td>
</tr>
<tr>
<td>8</td>
<td>Cu(acac)$_2$</td>
<td>1,10-phen</td>
<td>MCDFA</td>
<td>100</td>
<td>5</td>
<td>86</td>
<td>76</td>
</tr>
<tr>
<td>9</td>
<td>Cu(acac)$_2$</td>
<td>2,2′-bipyridine</td>
<td>MCDFA</td>
<td>94</td>
<td>2</td>
<td>83</td>
<td>74</td>
</tr>
<tr>
<td>10</td>
<td>Cu(TC)</td>
<td>1,10-phen</td>
<td>MCDFA</td>
<td>100</td>
<td>6</td>
<td>71</td>
<td>63</td>
</tr>
<tr>
<td>11</td>
<td>Cu(TC)</td>
<td>2,2′-bipyridine</td>
<td>MCDFA</td>
<td>92</td>
<td>4</td>
<td>72</td>
<td>58</td>
</tr>
<tr>
<td>12</td>
<td>Cu(OAc)$_2$</td>
<td>1,10-phen</td>
<td>MCDFA</td>
<td>99</td>
<td>2</td>
<td>84</td>
<td>71</td>
</tr>
</tbody>
</table>

$^a$0.5 g scale; 10 vols DMAC; 80 °C for 18 h (120 °C for entry 1); [Cu] and ligand 20 mol %, KF, 2 equiv; CF3 reagent, 3 equiv; HPLC area % (230 nm). $^b$des-I = hydrodeiodinated (reduced) 5. $^c$HPLC wt % assay.
and higher alkyl variants is still limited, and their cost can be prohibitive for use in commercial pharmaceutical manufacture.\(^5\) In addition, CF\(_3\)SiMe\(_3\) also has a low boiling point (55 \(^\circ\)C) which can limit its synthetic utility in transformations where higher temperatures are required.

On the opposite end of the cost spectrum, reagents of the type F\(_3\)CCO\(_2\)R (R = Me, Na, K, etc.) have also been used in trifluoromethylation reactions.\(^6\)\(^11\) However, their utility is limited by the high reaction temperatures that are required (140–180 \(^\circ\)C) to overcome the energy barrier for decarboxylation of the copper carboxylate, which has been proposed to be the rate-limiting step in these transformations.\(^11\)

A modification of the decarboxylative chemistry was developed by Chen and co-workers.\(^12\) MCDFA (methyl chlorodifluoroacetate or CF\(_3\)CCO\(_2\)Me) may be used in combination with a fluoride source (typically KF or CsF) and a copper(I) salt (typically CuI). Under these reaction conditions MCDFA appears to have a lower barrier for decarboxylation and allows more practical reaction temperatures of 80–120 \(^\circ\)C to be used. MCDFA is made on industrial scale and costs ~85% less than Ruppert's reagent.\(^2\) On the basis of the cost benefit, it was determined that a practical application of these conditions for large scale was worth pursuing.

**Catalytic Copper Trifluoromethylation.** After first verifying that the stoichiometric trifluoromethylation of iodide \(5\)\(^13\) was viable (Table 2, entry 1), the catalytic reaction was pursued. The use of catalytic copper is attractive because of reduced reagent cost and simplified workup (i.e. reduced burden for removal of copper salts). Copper-catalyzed trifluoromethylation has been reported. In a recent report by Amii and co-workers, the authors utilized 1,10-phenanthroline as the ligand. Extensive screening was conducted investigating variables which included a variety of copper(I) and (II) salts, ligands, trifluoromethyl-generating reagents (CF\(_3\), or :CF\(_3\)\(_2\)), fluoride sources, solvents, reagent loadings, and reaction temperatures.

The best screening results are shown in Table 2. Polar aprotic solvents such as DMF, NMP, and DMAc are best, with DMAc being preferred. These solvents are known to be favored for trifluoromethylation reactions\(^14\) as they solubilize copper salts effectively and also exhibit some solubility for the notoriously insoluble potassium fluoride.\(^15\)

In the absence of a ligand, the copper provided only one turnover (20% copper gave \(\leq 20\%\) conversion).\(^16\) The conditions which provided high conversion and a good assay yield of 1 (entries 2, 5, 6, 8, 10, and 12) were further investigated at larger scale. The MeCO\(_2\)CF\(_3\)SO\(_2\)F reagent\(^17\) (entry 7) was effective; however, it was excluded from further development due its high cost and limited availability. In the scale-up experiments, only CuI and the more soluble CuTC (copper thiophene-2-carboxylate) consistently gave conversion >95%. CuTC was preferred as it provided the most consistent results; most critically, CuTC provided higher conversion than Cu when tested with representative batches of 5.

The ligand 1,10-phenanthroline was slightly preferred over 2,2'-bipyridine. A wide variety of other ligands which were screened gave inferior results.\(^18\) The catalyst system of CuTC/1,10-phenanthroline in NMP or DMAc provided a 60% assay yield of 1 on 50–100 g scale. The byproduct resulting from reduction (hydrodeiodination) of 5 (denoted des-I) is typically formed in ~5%, this impurity is removed efficiently in the isolation of 1.

For the catalytic reaction, slow addition of an excess of the MCDFA over a period of 3–4 h was necessary to avoid foaming due to CO\(_2\) gas formation. In addition, the catalytic reaction could be run at temperatures as low as 80 \(^\circ\)C (compared with ~120 \(^\circ\)C for the stoichiometric conditions). However, the formation of impurities containing perfluorinated alkyl groups (7) plagued this catalytic process (Scheme 3). Other byproducts (8 and 9) resulting from substitution of the activated chloride were formed to a lesser extent (typically <5% HPLC area).

The formation of byproduct 7 is a known problem using MCDFA.\(^19\) This problem is more prevalent when the substrate is less activated, where the increased lifetime of [CuCF\(_3\)]\(^+\) in the system favors chain elongation.\(^20\) Formation of these by-products is also exacerbated by the lack of available copper, which causes them to be more prevalent under catalytic conditions. It has been proposed by Chen that CF\(_3\)\(^+\) is in equilibrium with the carbene :CF\(_3\) Copper can push the equilibrium to [CuCF\(_3\)]\(^+\) which reacts on the productive path

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**Table 3. Kilogram-scale trifluoromethylation batch results**

<table>
<thead>
<tr>
<th>entry</th>
<th>input 5 (kg)</th>
<th>conditions</th>
<th>workup</th>
<th>output 1 (kg)</th>
<th>NMR wt %</th>
<th>HPLC area % (isolated)</th>
<th>assay yield wt %</th>
<th>isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.2</td>
<td>catalytic(^c)</td>
<td>NH(_4)OH</td>
<td>0.81</td>
<td>73(^d)</td>
<td>67(^f) (88)(^g)</td>
<td>ND</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>stoichiometric(^c)</td>
<td>thiacetamide</td>
<td>2.57</td>
<td>96</td>
<td>78 (92)</td>
<td>68</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>stoichiometric(^c)</td>
<td>oxalic acid</td>
<td>3.73</td>
<td>N/A(^d)</td>
<td>92</td>
<td>68</td>
<td>N/A(^d)</td>
</tr>
</tbody>
</table>

\(^a\) MTBE solution assay yield, HPLC wt % based on pure standard of 1. \(^b\) Isolated 1 crystallized from EtOH/water. \(^c\) CuTC/1,10-phen/KF/MCDFA (0.1:0.1:1.5:3.0 equiv) in NMP. \(^d\) Solution of crude 1 after workup. \(^e\) CuI/KF/MCDFA (1.5:1:1:3.0) in DMAc. \(^f\) Conditions same as those of entry 2 in NMP. \(^g\) Not isolated.
with the aryl halide. Unfortunately, in this case the products of chain elongation (7) from \( n = 1 \) to \( n > 10 \) were formed (observed by GC/MS) and combined to account for >20% (GC area) of the product mixture.

Notably, some solids, which appeared to be highly fluorinated polymeric compounds, were observed floating in the crude reaction mixture. This observation helped explain why a minimum of 3 equiv of MDCFA was required for this reaction. These polymeric byproducts were observed to a small extent on lab scale but had minimal impact. However, during the kilo-lab scale-up of the catalytic trifluoromethylation (Table 3, entry 1), these insoluble polymeric impurities made the workup tedious by complicating phase separations and by causing foaming during the reaction and distillation steps.

Ultimately a modest 34% yield (70 wt %) of 1 was isolated on 2.2 kg scale. This low yield was due in part to the instability of 1 toward ammonia used in the workup (vide infra). However, the catalytic system was ultimately abandoned because of chain-elongated impurity (7) formation. Despite great effort, these impurities could not be sufficiently suppressed. Being very similar to the desired product in structure and physical characteristics, these impurities were also very difficult to remove by crystallization at this process stage and downstream. Because of these issues, the stoichiometric copper conditions were pursued for scale-up.

**Development of the Final Process Using Stoichiometric Copper.** The trifluoromethylation using Chen’s conditions with stoichiometric copper, MDCFA/KF/Cul (3:1.5:1.5 equiv), produced 1 in consistently higher isolated yield (65–70% vs 35–60%) and in higher HPLC product purity (75–90+% vs 60–70% for crude 1) than in the catalytic reaction. These conditions also provided a substantial reduction in chain elongation and polymeric impurities. As a result, the foaming problems seen previously were also minimized.

As noted above and shown in Scheme 3, two process impurities were identified as the 5-trifluoromethyl-6-fluoroproduct (8) and the bis-trifluoromethylated product (9). Compound 9 likely results from substitution at the 6-position of the chloride or the more activated fluoride (8). A study of KF loading revealed that 1.0 equiv was insufficient to achieve high conversion (85%) and 2.0 equiv led to unacceptable levels of 8 (23% HPLC area) and 9 (8% HPLC area). A balance between high conversion (97%) and impurity formation (7% 8 + 9 combined HPLC area) was found with a loading of 1.1 equiv of KF.

While investigating the safety profile of the stoichiometric trifluoromethylation batch process (all reagents combined) (Scheme 4) prior to the kilo-lab scale-up, a significant adiabatic temperature rise and a production of a large volume of noncondensable gas (likely due to decomposition of the MDCFA) occurred. While the temperature and pressure increases posed only a moderate safety risk, reactor overflow was very likely based on the combination of pressure rise and the reaction mixture’s tendency to foam. Thus, this batch process was deemed inappropriate for scale-up.

Lowering of the reaction temperature was deleterious to the reaction, and a decrease of the overall reaction concentration also had minimal impact on the safety profile. The semibatch reaction was then investigated, using slow addition of MCDFA to the reaction mixture at the reaction temperature. Due to the slower reaction rate observed in the aforementioned catalytic reaction, a slow addition of MCDFA over 4 h was used to maintain the level of :CF₂ generated throughout the course of catalytic reaction. This also served to reduce foaming caused by formation of polymeric species. This dosing technique also helped with the safety issues mentioned above for the stoichiometric reaction by providing dose control which significantly reduced the peak rates of gas evolution and adiabatic temperature rise. The trifluoromethylation remained efficient with slow addition of MCDFA, albeit not quite as clean as the batch reaction. If the addition time of MCDFA was extended to 3–4 h, more impurities formed. An addition time of 1.5 h kept the temperature rise and gas generation under control and also provided product 1 in good yield with 92% HPLC purity, which proved acceptable when carried through the downstream chemistry. This semibatch strategy was applied successfully on 5.0 kg scale (see Table 3, entry 2).

**Trifluoromethylation Workup Optimization.** Initially, an ammonium hydroxide workup was used in the first kilogram batch (catalytic copper conditions) (Table 3, entry 1). This workup involved dissolution of the product in MTBE and was followed by multiple aqueous \( \text{NH}_4\text{OH} \) washes to remove copper salts. This workup was very tedious and required a large volume of both solvent and ammonium hydroxide in order to remove all of the copper salts. In addition, following the aqueous workup, the crude product had to be recrystallized from aqueous ethanol to upgrade the purity. However, the most critical problem for the \( \text{NH}_4\text{OH} \) workup was product decompostion, which contributed to the disappointing 34% yield for this batch. The activated chlorine at the 6-position proved unstable to extended contact with the ammonia used in the workup. This amine byproduct was observed in lab runs at low levels and was efficiently removed in the aqueous layers. However, the extended addition time (exothermic addition) and longer contact time required on kilogram scale led to an increase in the 6-amino byproduct formation.

Alternative workup conditions were investigated in order to avoid impurity formation. Aqueous thioacetamide was used on 5.0-kg scale to remove copper species from the organic layer (Table 3, entry 2), giving 68% assay yield and allowing a 40% reduction in the reaction \( V_{\text{max}} \) (15 L/kg 5). The crude product required a subsequent recrystallization from aqueous ethanol to upgrade the purity. Unfortunately, the process using thioacetamide also led to an unacceptable stench in the waste streams and the isolated product.

Oxalic acid is an attractive alternative reagent for copper removal due to its low cost, low molecular weight, and unlikely propensity to cause stench. Accordingly, a 7.0 kg batch was processed (Table 3, entry 3) using the slow addition of MCDFA mentioned above. Following the reaction, the controlled addition of aqueous oxalic acid to the NMP reaction mixture provided a slurry and facilitated the isolation of the crude product directly by filtration. The majority of the organic impurities were retained in the NMP/water filtrate with less than 5% product loss. Because of this effective impurity removal, the crude product from this process did not require an
additional crystallization. This was required in all previous processes to obtain sufficient purity. While the HPLC purity was high, the crude product contained residual copper salts. The salts could be removed by filtration of a simple MTBE slurry of I; the resulting filtrate was used directly in the subsequent process step. This workup procedure was a significant improvement for all process factors and is the preferred process.

**CONCLUSION**

In conclusion, a safe, efficient, and scalable process for the synthesis of methyl 6-chloro-5-((trifluoromethyl)nicotinate 1 was developed. This new process enabled the production of kilogram quantities of this intermediate beginning from readily available and inexpensive 6-hydroxynicotinic acid. The key step involved a copper-promoted trifluromethylation of 5 to give 1 using MCDFA; this was demonstrated using catalytic as well as stoichiometric copper conditions, the latter of which was ultimately preferred for scale-up. This reaction provided a cost-effective and efficient solution for installing the trifluoromethyl group to make this versatile pyridyl intermediate on kilogram scale.

**EXPERIMENTAL SECTION**

**General.** Spray-dried KF was purchased from Aldrich and was used for all experiments. Reported assay yields are based on HPLC integration compared to a standard of high purity or by NMR assay compared to an internal standard (dimethyl amine (12.05 kg, 93.1 mol), and 1,4-dioxane (134.4 kg) (added last) were charged to a reactor. (The addition of DIPEA prior to 1,4-dioxane minimizes potential caking.) POCl₃ (2.90 kg, 18.6 mol, 0.2 equiv) was charged, and a slight exotherm (~5 °C) was observed. The batch was stirred and heated to 95 °C. At 95 °C the remaining POCl₃ (26.25 kg, 171.4, 1.85 equiv) was charged, and a minimal exotherm was observed. The batch was heated at 100 °C for 7 h and then cooled to 20 °C.

**Reverse Quench.** To a second vessel was charged water (260 kg) which was cooled to 10 °C. The chlorination reaction mixture was then transferred to the second vessel (with agitation) over 2 h, maintaining a batch temperature of 10–15 °C. After a rinse of 1,4-dioxane (4 kg) the batch was stirred for 10 h at 10 °C. The resulting solid was collected by filtration in a centrifuge. The cake was washed with water (52 kg) and the product spun for 1 h. The product was then dried in a vacuum oven (80 Torr) at 35 °C for 24 h to afford 27.44 kg of 5 as a tan solid (97.1 wt %, 96.2% yield, 98.9% purity by HPLC, Rₚ = 8.39 min). Vₘₐₓ = 17.2 (L/kg 2) and E-factor = 17.1 (kg waste/kg 5).¹ H NMR (400 MHz, DMSO-d₆) δ 3.92 (s, 3H), 8.68 (d, J = 2.0 Hz, 1H), 8.86 (d, J = 2.0 Hz, 1H);¹³C NMR (100.6 MHz, DMSO-d₆) δ 164.2, 158.4, 150.2, 150.0, 126.6, 97.1, 53.7; LC/MS for C₇H₅ClINO₂ calcd 296.9, (M + H⁺) = 297.9.

**Methyl 6-Chloro-5-(trifluoromethyl)nicotinate (1).** Iodide 5 (7.0 kg, 97 wt %, 22.8 mol), Cul (6.65 kg, 98 wt %, 34.2 mol, 1.5 equiv), and KF (1.47 kg, 25.1 mol, 1.1 equiv) were charged to a 50-L hastelloy reactor. After the reactor was evacuated and purged with nitrogen, NMP (36 L) was charged. The batch was sparged with nitrogen for 15 min and then was heated to 120 °C. To the batch was charged pre-sparged Cl₂C₃CO₂Me (12.45 kg, 84.5 mol, 3.7 equiv) at a constant rate over 1 h at 120 °C (an additional 0.7 equiv of MCDFA was added due to distillation equipment hold-up). Subsequently, the mixture was stirred for approximately 2 h. The reaction was cooled to 15 °C.

**Workup.** A solution of oxalic acid dihydrate (4.4 kg, 34.2 mol, 1.5 equiv) in water (35 kg) held at 50 °C was added over 1 h to the reaction mixture, maintaining temperature at 30–40 °C. Upon complete addition, the slurry was heated to 40 °C, stirred for 30 min, and then cooled to 20 °C over 30 min and stirred for 1 h at 20 °C. The resulting solid was collected by filtration, and the cake was rinsed with 2:3 NMP/water (NMP 3.4 kg/water 5 kg) and then water (2 × 5.6 kg). Then it was air-dried in the filter funnel (suction) for 2 h and then dried at <35 °C for 24–48 h. The crude solid, which contains residual copper, was dissolved in MTBE (42 L) and heated to 45 °C for 1 h, cooled to 30 °C over 1 h, and filtered to remove copper solids, regulating the filtrate which contains the product. The filter cake was rinsed with MTBE (16 L), and this was combined with the filtrate to yield a pale-orange MTBE solution of 1 (68% assay yield, 92.3% purity by HPLC, Rₚ = 8.30 min). Vₘₐₓ = 11 (L/kg 5) and E-factor = 32 (kg waste/kg 5). The MTBE solution may be used directly in the subsequent reaction:¹ H NMR (400 MHz, CDCI₃) δ 3.97 (s, 3H), 8.59 (d, J = 2.0 Hz, 1H), 9.17, J = 2.0 Hz, 1 H);¹³C NMR (100.6 MHz, DMSO-d₆) δ 164.3, 154.6, 152.0, 138.7 (q, J = 2.0 Hz, 1H); LC/MS for C₇H₅ClINO₂ calcd 296.9, (M + H⁺) = 297.9.

**ASSOCIATED CONTENT**

S Supporting Information

¹H and ¹³C NMR data for compounds 1, 3, 4, and 5; chlorination and trifluoromethylation screening results; and
trifluoromethylation calorimetry data. 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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**REFERENCES**

(1) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. 


(4) THF and 2-MeTHF gave insufficient conversion. See Supporting Information for a more extensive solvent table.


(13) The trifluoromethylation of 3 and 4 (Scheme 2) failed under catalytic and stoichiometric copper conditions. This result was anticipated, as this reaction involves a nucleophilic trifluoromethyl species, likely incompatible with hydroxypyridines 3 and 4. The 5-chloro and 5-bromo analogues of 5 were also investigated; however, the trifluoromethylation was ineffective with the chloride and very slow with the bromide.


(15) The spray-dried variant of KF was used; it is more easily suspended and was found to provide more reproducible results on large scale.

(16) For Cul/1,10-phen. < 10 mol% catalyst was insufficient to provide good conversion regardless of other reagent stoichiometries, 10–20 mol% was preferred and gave nearly identical results; 50% or 150% were both inferior to 20 mol%. A ligand/Cu ratio of >1:1 was also not beneficial.


(18) See Supporting Information for additional screening data.